http://www.cjmb.org doi 10.34172/cjmb.2025.5039

Open Access Review

Crescent Journal of Medical and Biological Sciences
Vol. xx, No. x, xx 2025, x–x
eISSN 2148-9696

Improving Sperm Quality and Hormonal Receptor Expression: N-acetylcysteine Treatment in Testicular Hypoxia

Majid Shokoohi[1], Zahra Shojaei[2], Gilda Ghazi Soltani[1], Saba Vaezi[1], Vahideh Kianmarz Bonab[3*], Amir Afshin Khaki[4], Kian Keyhan[3], Alireza Alihemmati[2*]

Abstract

Testicular hypoxia, defined as insufficient oxygen supply to the testes, is a critical factor in male infertility and reproductive health issues. N-acetylcysteine (NAC), through its antioxidant properties and role as a glutathione (GSH) precursor, has been proposed as a protective agent against testicular hypoxia. This review evaluates whether NAC improves sperm quality and hormonal receptor regulation by reducing oxidative stress and modulating redox balance. We also summarize NAC's effects on androgen receptors (ARs), estrogen receptors (ERs), and follicle-stimulating hormone receptors (FSHRs), highlighting its potential to influence spermatogenesis and endocrine function. Evidence from experimental studies and clinical trials suggests that NAC may improve sperm concentration, motility, morphology, and DNA integrity, though results on morphology remain inconsistent. Clinical findings indicate improvements in sperm parameters and oxidative stress biomarkers; however, effect sizes vary, and study limitations must be considered. This narrative review supports NAC as a potential therapy for hypoxia-related male infertility, while emphasizing the need for further clinical trials to clarify optimal dosing, treatment duration, and long-term safety.

Keywords: N-acetylcysteine, Sperm quality, Hormonal receptor, Testicular hypoxia

Introduction

Testicular hypoxia, characterized by insufficient oxygen supply to testicular tissue, negatively impacts male reproductive function, particularly sperm quality and hormonal receptor expression. Causes include testicular torsion, varicocele, and ischemia/reperfusion (I/R) injury, leading to disrupted spermatogenesis and hormonal dysregulation. Sperm quality encompasses density, motility, morphology, and DNA integrity, all essential for fertility. Androgen receptor (AR), estrogen receptor (ER) expression in the testes regulates spermatogenesis and steroidogenesis. Dysregulation of these pathways during hypoxia contributes to infertility (1,2).

N-acetylcysteine (NAC), a glutathione precursor and potent antioxidant, has shown protective effects against hypoxia-induced testicular damage. In experimental models, NAC reduced oxidative stress, inflammation, and apoptosis, thereby preserving testicular function. Preclinical evidence indicates beneficial effects on sperm parameters, though some results remain inconsistent (3,4).

This narrative review explores the pathophysiology of testicular hypoxia, NAC's mechanisms of action, its effects on sperm characteristics and hormonal receptor expression, and clinical implications for infertility management. We also highlight limitations in current evidence and directions for future research. Ultimately, by determining the molecular mechanisms by which NAC may reverse the effects of hypoxia on sperm quality and hormonal receptors, we hope that this review could serve as a basis for the exploration of novel therapeutic approaches in protecting male fertility in the setting of testicular hypoxia.

Testicular Hypoxia: Pathophysiology and Consequences

Reduced oxygen supply to the testes, termed testicular hypoxia, disrupts spermatogenesis and steroidogenesis (Figure 1). Causes include torsion, varicocele, ischemia/reperfusion injury, and systemic vascular diseases. Hypoxia induces oxidative stress, mitochondrial dysfunction, and inflammation. Hypoxia-inducible factors (HIFs) activate genes that promote angiogenesis, glycolysis, and cell survival, helping restore oxygen balance (5-8).

Testicular hypoxia was reported to be a multifactorial disorder whose pathogenesis is rooted in vascular, cellular, and molecular mechanisms. Decreased blood flow rates imply a decrease in oxygen delivery to the testicular tissue and a consequent state of ischemia and hypoxia. Sustained through the progressive induction of oxidative stress and inflammation, impaired mitochondrial function

Received 20 September 2024, **Accepted** 9 July 2024, **Available online** 29 September 2025

[1]Clinical Research Development Unit of Tabriz Valiasr Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Department of Exercise Physiology and Sport Science, Payam Noor University, Tehran, Iran
[4]Department of Anatomical Sciences, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
***Corresponding Authors:** Alireza Alihemmati, Email: Hemmatti@yahoo.com; Vahideh Kianmarz Bonab, Email: vkianmarz@pnu.ac.ir

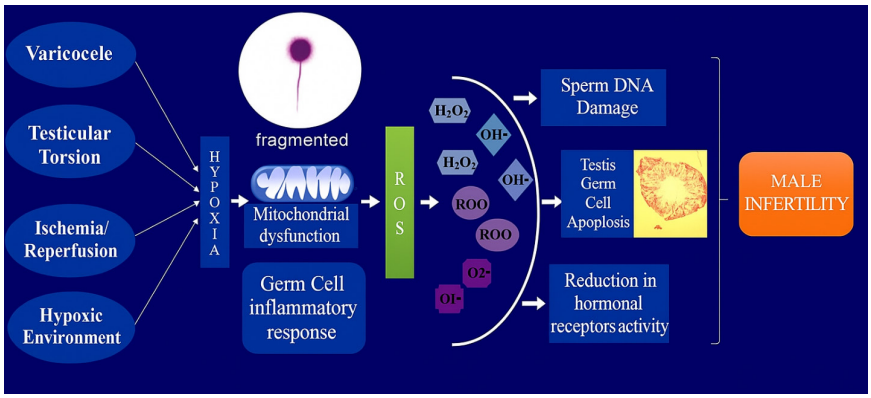

Figure 1. The Molecular Mechanisms Leading to Male Infertility. Conditions such as varicocele, testicular torsion, ischemia/reperfusion, and hypoxic environments induce testicular hypoxia. Hypoxia triggers mitochondrial dysfunction and germ cell inflammatory responses, resulting in excessive production of reactive oxygen species (ROS). Elevated ROS levels cause sperm DNA damage, testicular germ cell apoptosis, and reduced hormonal receptor activity, ultimately contributing to impaired spermatogenesis and the development of male infertility.

following ischemia adds to the existing tissue injury. HIFs are a group of soluble hypoxia-inducible nuclear factors that govern testicular hypoxia and the cellular reactions triggered by close oxygen limitation. HIF activation leads to the synthesis of genes that contribute to angiogenesis, glycolysis, and cell survival, thereby replenishing oxygen homeostasis during tissue repair (1,9-11).

Testicular hypoxia reduces sperm count, alters morphology, and decreases motility. It also disrupts AR and ER signaling, impairing hormonal regulation essential for fertility. In clinical practice, conditions such as varicocele and torsion require early detection and intervention to prevent infertility. Furthermore, hypoxia changes the quantity and function of the receptors to hormones such as ARs and ERs; due to changes in hormone signaling that are paramount in an organ such as the testis. Hormone receptor yellow was also found to be deregulated in relation to testicular dysfunction, as well as hormonal abnormalities and impaired fertility in affected males (12-16).

In clinical practice, testicular hypoxia causatively relates to male sterility and reproductive disorders. Circulatory disruptions in the testis, like testicular torsion and varicocele, should be identified early and treated to prevent hypoxic changes in the testicular tissue, which can impair spermatogenesis and lead to infertility. Extensive knowledge about the mechanisms of testicular hypoxia and its effects on the male reproductive organs is crucial for designing effective cellular and molecular treatments and diagnostic approaches. These strategies aim to minimize tissue injury and improve spermatogenic potential and general reproductive function in men with impaired oxygen supply to the testes. Effective therapeutic strategies and targets for hypoxic testis are still scarce in the literature, and future studies should expand on the understanding of hypoxia at the molecular level and testicular tissue, as well as on the development of possible therapeutic options tailored to address the issue of infertility management in male patients (17-19).

Sperm Quality: Assessment and Importance

Sperm quality is evaluated based on sperm concentration, motility, morphology, and DNA integrity. Abnormalities such as oligozoospermia, asthenozoospermia, or high DNA fragmentation are associated with reduced fertility and poor outcomes in assisted reproduction. These parameters are crucial for infertility assessment and treatment decisions (11,21,22).

Sperm count: In more precise terms, sperm count is known as sperm concentration, the number of spermatozoa per milliliter of ejaculate. This is usually expressed in terms of concentration per milliliter (mL) of semen and gives the number of sperm available for fertilization. When the number of sperm significantly decreases, it is termed oligozoospermia, which certainly affects fertility since there would be few sperm available to make it to the egg and attempt fertilization (23,24).

Sperm motility: Sperm motility, therefore, is the ability of the spermatozoa to swim actively and in a coordinated pattern through the female reproductive system with a view to getting to the site of fertilization. Motility can therefore be divided into various categories depending on the nature of the movement, which can be described as progressive motility (smooth and likely to move forward), non-progressive motility (indistinct and irregular movement), and immotility (no movement). Reduced sperm motility, or asthenozoospermia, affects sperm movement, preventing it from reaching the egg and thus affecting fertility chances (25-27).

Sperm morphology: Sperm morphology is a measure of the size and shape of sperm coupled with the structural characteristics of spermatozoa, which are viewed and determined through microscopy. The effects of shapes or irregularities in spermatozoon design impact sperm motility, viability, and potential to score through the oviductal lining and fertilize the egg; thus, normal sperm morphology is crucial for sperm functions. The morphology of human sperm is assessed with the help of a microscope, following the general guidelines mentioned in

the WHO or any other norms established internationally.

DNA Integrity: Sperm DNA integrity can be defined as the physical and chemical stability of sperm chromatin that has not been exposed to DNA fragmentation or otherwise contains any damage. Preserving and safely conveying chromosomes to the offspring and other developmental processes in an embryonic formation is significant. The abnormality found in sperm samples includes DNA fragmentation or strand breaks, which have been shown to have negative implications in fertility, pregnancy rate, and pregnancy complications (28,29).

Sperm analysis is crucial for the identification of the infertile male, for evaluating the prognosis in patients who are being managed, and for decisions concerning treatment that has to be instituted either for the correction of the disease or before subjecting the couple to ART such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). These findings highlight the relevance of sperm quality and its contribution to reproductive health, and therefore affirm the role of appropriate sperm analysis in the evaluation of male infertility and management. Consequently, it can be seen that, to enhance fertility treatments, clinician often depends on abnormalities in the sperm parameters and try to treat the reasons that lead to poor sperm quality, which are sometimes instrumental in providing fertility to the couple who are experiencing difficulties in conceiving (30-32).

Hormonal Receptor Expression in Testicular Hypoxia

Testicular hypoxia, a state of relative or absolute deprivation of oxygen at the testicular level, contributes significantly to various pathological states of male fertility. Some studies indicate that obstruction of blood flow in the testes can result in hypoxia within the tissue and changes in levels and density of androgen receptors, affecting fertility and reproductive capacity. Many of the examined hormonal receptors are disturbed in case of testicular hypoxia, but one of the most prominent is the AR. Testosterone, therefore, has been noted to facilitate spermatogenesis, sperm maturation, and involvement in male republican health. Research has pointed to a reduced level of AR expression, particularly in the testis when the O2 level is low. This could mean reduced sensitivity to androgens and thus top-down spermatogenesis and fertility (9,33,34).

Other hormonal receptors revealed to be affected by hypoxia include the ERs and the follicle-stimulating hormone receptors (FSHRs). It is thus imperative to establish the estrogen receptors and their role in testicular spermatogenesis and steroidogenesis. These include changes in ER expression during hypoxia that added to the disturbance in these processes and thus, reproduction. In addition, hypoxia can influence FSHRs that support spermatogenic activity since they stimulate the Sertoli cells located in the testes. As previously mentioned, Sertoli cells are specialized cells that nourish and impose structural organization on developing sperm cells. Reduced FSHR signaling and responsiveness to hypoxic conditions might directly affect Sertoli cell function and efficiency in spermatogenesis and sperm maturation (35,36).

ARs: The dominating androgen, testosterone, is essential to spermatogenesis, spermiation, and male sexual functions. Testicular cells contain ARs in their cytoplasm. Testicular Leydig cells, Sertoli cells, and germ cells are responsible for impacting target tissues with androgens. Under the circumstances of reduced oxygen levels in the testes, changes in AR copy numbers or the functional rate of the proteins may interfere with the androgen-signaling pathways, thus affecting the spermatogenic process, production of testosterone, and hormonal balance disturbances (37,38).

ERs: These include the ability of estrogens, particularly estradiol, to influence various factors such as germ cells, Sertoli cells, and the process of steroidogenesis in the testes. Some of the diverse actions of estrogens are exerted through ERs localized in different testicular cell types, such as Leydig cells, Sertoli cells, and germ cells. Disruption in either ER expression or signaling in conditions as testicular hypoxia would undermine the function of estrogen on processes such as spermatogenesis and steroidogenesis, and could be part of the reason for testicular dysfunction and impaired fertility (39,40).

There could be many ways the hormonal receptor was dysregulated in testicular hypoxia, including the effects of oxidative stress, inflammation, and changes in signaling pathways. Cytokine signaling can also be disrupted by hypoxia-induced oxidative stress through post-translational modifications like nitration, oxidation, or carbonylation of proteins, which can affect receptor stability and ligand-binding properties or alter the production of specific cytokines. Moreover, the inflammation-induced cytokine signaling may still affect the variations of hormonal receptors and their activity and competitively enhance testicular dysfunction under hypoxic conditions (41-43).

The assessment of hormonal receptors considering testicular hypoxia is of significant importance in determining the pathophysiology of hypoxia-induced thermal stress disorder and testicular failure. Hence, there is an excellent value in targeting the indicated molecular pathways, such as AR and ER signaling, to prevent or reverse the effects of testicular hypoxia on testicular function. It was described earlier that testicular hypoxia led to dysregulated expression of hormonal receptors (20,40-42), and more work should be done to delineate the molecular basis of the hormonal receptor disturbances and to identify new targets for enhancing the reproductive potential in patients affected by testicular hypoxia (44,45).

N-acetylcysteine: Mechanisms of Action and Therapeutic Potential

NAC is an analog of L-cysteine but has different

pharmacological properties; NAC is an essential precursor of glutathione (GSH), which plays a significant role in maintaining redox balance. Thus, interest in NAC has been much deserved because of its multi-target, multifunctional nature and potential anxiolytic and therapeutic applications in diseases based on oxidative stress, some respiratory disorders, and some neurological diseases and disorders. There are various ways through which NAC functions and hence plays the therapeutic role; NAC functions as an antioxidant to decrease the level of ROS in the body, anti-inflammatory, which acts to reduce the inflammatory processes in the body, and even cytoprotective, where NAC may function to spare the cells from cell death (46-48) (Figure 2).

Antioxidant activity: The primary source of NAC benefit is as a prodrug for GSH synthesis, wherein it also demonstrates antioxidant function. GSH is a fundamental antioxidant in the cells, protecting against oxidative stress by neutralizing ROS and free radicals to balance cellular oxidation-reduction. NAC is known to revive the depleted GSH levels inside the cells by donating cysteine, a fundamental amino acid required to manufacture GSH. Higher GSH concentrations promote antioxidant intracellular activity, reduce ROS levels, and thus release cells from oxidative insult of biomolecules like lipids, proteins, and DNA (48-50).

Anti-inflammatory effects: NAC also possesses anti-inflammatory actions and interacts with inflammatory signals and cytokines. It also inhibits the nuclear factor-kappa B (NF-κB), the critical transcription factor for controlling inflammatory genes. NAC suppresses NF-κB activation with the assistance of MAPK and IKK; this in turn reduces the synthesis of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β); and the subsequent dampening of inflammation and tissue damage (51-53).

Mucolytic activity: This work confirms that NAC has mucolytic properties due to its capacity to cleave disulfide bonds within mucin glycoproteins. This results in the lowering of mucus viscosity and improvement in the clearance of mucus in pulmonary diseases, such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis. NAC enhances respiratory function and prevents attacks and infections in chronic bronchitis by increasing mucus expectoration and airway clearance (54-56).

Cytoprotective effects: NAC has, therefore, been proven to have cytoprotective properties that can guard cells against several forms of stress, including oxidative stress, inflammation, and apoptosis. NAC has antioxidant action, which counteracts oxidative stress, promotes antioxidant activity and capability, neutralizes free radicals, and inhibits lipid peroxidation. Furthermore, NAC influences apoptotic signals and the overall balance of life and death within cells by suppressing apoptotic parameters in the stressed cell (54,57,58).

Therapeutic potential: Due to its multifaceted antioxidant and anti-inflammatory characteristics, NAC holds promising candidacy as a therapeutic agent for various diseases and ailments, including respiratory diseases, cardiovascular diseases, neurodegenerative disorders, and liver diseases. In respiratory diseases and conditions, including COPD and cystic fibrosis, NAC promotes mucus clearance, decreases inflammation, and has a more noticeable effect on lung capacity. Furthermore, NAC has been researched in the context of several models of neurological disorders, including Alzheimer's disease, Parkinson's disease, and traumatic brain injury, because it appears to possess antioxidant and anti-inflammatory functions (47,48,59,60).

Nevertheless, NAC impacts on several fronts, as an antioxidant, anti-inflammatory, mucolytic, and cell protectant with potential applications for treating various disease states. More studies are needed to capture the complete pharmacological profile of NAC and understand other areas where it can be used in the treatment of human diseases (48,61,62) (Figure 2).

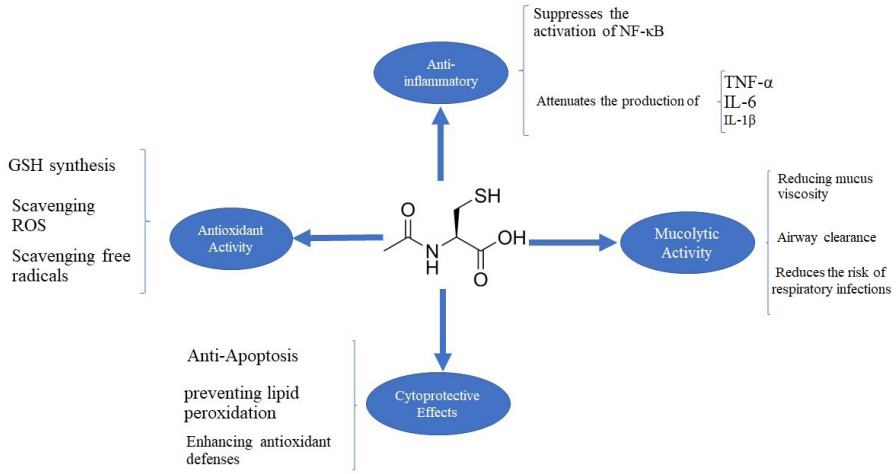

Figure 2. Summary of NAC's antioxidant, anti-inflammatory, cytoprotective, and therapeutic mechanisms.

Experimental Models of Testicular Hypoxia

Hypoxia-modeled testicular tissues are valuable in the context of studying hypoxic effects on the testis and identifying therapeutic targets for hypoxia–induced testicular toxicity. These models are designed to mimic situations involving a decrease in the supply of oxygen to the testicular tissue, which appear in clinical practice as testicular torsion, varicocele, or ischemia/reperfusion. The testicular hypoxia has been modeled in various ways in animal models to understand the systemically damaging effects of hypoxia at the molecular level and to assess the anti-therapeutic interventions in this model (63).

Testicular torsion models: Testicular torsion occurs when the spermatic cord rotates, hindering the blood supply to the testes, resulting in ischemia. The animal models of testicular torsion in rats and rabbits are based on the surgical establishment of torsion in testicular vessels to replicate the clinical ischemic finding. One can alter the cycle duration and degree of torsion to adjust the degree of testicular hypoxia and study its impact on testicular functions (64-66).

Varicocele models: Varicocele, then, is the condition manifesting as dilated veins in a testis, which may negatively affect testicular perfusion and vascular hypoxia, in conjunction with impaired testicular function. Experimental varicocele has been best generated by surgically standardizing the ligation or sectioning of various testicular veins necessary to cause the hemodynamic changes seen in varicocele, and generate testicular hypoxia. These models enable scientists to draw the consequences of chronic hypoxia on the testicular tissue structure, sterility, and gene regulation (8,67-69).

Ischemia/reperfusion (I/R) models: I/R refers to a situation or a process whereby testicular blood supply is occluded (ischemia) for some time, then later restored (reperfusion), resulting in cell damage due to secreted free radicals, inflammation, and impaired mitochondrial activity. Testicular ischemia/reperfusion models of injury can be performed on animals by manipulating the oxygen supply to the testicular tissue by clamping blood vessels for fixed intervals and then releasing the clamp to allow reperfusion. These models also enable investigators to address how ischemia/reperfusion testicular toxicity occurs and whether antioxidant or anti-inflammatory agents are effective (70).

Hypoxia chamber models: There are hypoxia chamber models in which animals can be exposed to low O2 concentrations, which, though producing more widespread hypoxic effects, lack the rapid onset required for some experimental purposes. Animals are housed in chambers where oxygen concentrations can be controlled for the periodic induction of hypoxia. Standard hypoxia chamber models enable researchers to expose the whole body to hypoxia, thus facilitating studies on hypoxia-induced changes in different organs and organ systems, including the testicular tissue, as well as the evaluation of the body's adaptation to low oxygen availability (71-73).

Since hypoxia is thought to contribute to testicular dysfunction, the HIF-1α-mediated experimental models of testicular hypoxia help understand the underlying mechanisms of hypoxia and assess the efficacy of potential treatments. These models are helpful as they mimic the clinical situation associated with testicular torsion, varicocele, ischemia, and reperfusion. Thus, they help to determine the molecular pathways that cause hypoxic damage to the testis and develop potential methods to prevent loss of testicular function and fertility (72,74).

Effects of NAC Treatment on Sperm Characteristics

NAC has been used in many experimental and clinical studies for its impact on sperm quality to determine its therapeutic virtues in enhancing fertility in males. S-NAC is an antioxidant and a precursor of GSH, and it has a protective action against cells by preventing cell damage through inhibiting the formation of ROS, depressing the level of oxidative stress, and maintaining cell structure. In this section of the article, we present the effect of NAC on sperm parameters such as sperm concentration, motility, morphology, and DNA fragmentation using data from preclinical and clinical studies (75,76).

Sperm count: Other studies have shown that treatment with NAC improves sperm count in both experimental animals and humans. The improvements in the concentration and motility of the sperms, the significant reduction of oxidative stress in germ cells, and the subsequent support of spermatogonia viability and proliferation are the mechanisms by which NAC has been demonstrated to convey beneficial effects on spermatogenesis (76-78).

Sperm motility: Different experiments have shown that sperm motility can be enhanced through NAC treatment, particularly in male models of varicocele-induced testicular incompetence and in models involving oxidative stress-induced abnormalities in sperm. NAC alleviates the damage of ROS on the sperm, thus improving the swimming and progressive motility and augmenting the probability of fertilization (76,78).

Sperm morphology: The existing literature on the impacts of NAC on sperm morphology has been inconclusive, although some articles with mammalian models have noted enhancement of sperm morphology

metrics like the head and the acrosome following NAC treatment; on the other hand, the rest of the articles have failed to note significant changes in sperm morphology after taking NAC. More studies are required to determine the effects of NAC on sperm morphology smear and to examine how NAC may exert its effects (76).

DNA integrity: Earlier experiments established NAC's ability to prevent oxidative stress on sperm DNA integrity in experimental models of injury that negatively affected sperm integrity. Having elucidated the cytotoxicity potential, ROS-scavenging, and anti-oxidative DNA

protection roles of NAC, we can conclude that it helps maintain sperm chromatin integrity, consequently minimizing DNA fragmentation and improving sperm quality and fertility (61,76).

The potential of NAC administration as a therapeutic approach for altering sperm attributes, thus impacting the fertility of males, is highly significant. An improvement in sperm oxidative state, combined with the preservation of sperm functions and DNA integrity, can be considerable for couples experiencing infertility, mainly due to an imbalance in sperm morphology and movement. However, future experimental, clinical, and interventional studies using better-designed trials with more participants and rigorous controls are required to substantiate the potential of NAC intervention in enhancing sperm characteristics and human fertility outcomes (61,78).

Effects of NAC Treatment on Hormonal Receptor Expression

Thus, the role of NAC treatment in relation to hormonal receptor changes in testicular hypoxic contexts has become a focal issue in reproductive science. ARs and ERs are essential for controlling testicular functions, spermatogenesis, and the synthesis of steroids and other androgens. Here are the findings of the effect of NAC treatment in subjects based on a review of pre-clinical investigations and clinical observation (79-82).

AR expression: From various experimental studies, it was evident that NAC treatment could effectively alter AR expression and abundance in the testicular cells under stressed conditions, such as oxidative stress and hypoxia. L-arginine administration has previously been documented to increase AR levels in experimentally induced testicular injury in animals, including varicocele impacting on spermatogenesis and testicular ischemia/reperfusion injury. Thus, the upregulation of AR by NAC could presumably reinforce androgen/AR target pathways and stimulate the Leydig cell work, spermatogenesis, testosterone synthesis, and secretion (83-85).

ER expression: Insufficient information is currently available to determine the impact of NAC administered to the testes on the expression of estrogen receptors. However, previous studies concerning the regulation of estrogen receptors by NAC show other interactions between NAC and ER activity in other tissues. It has been demonstrated that NAC influences both ER levels and activity in different cells, including breast cancer and endothelial cells, and impacts oestrogen-dependent gene expression and cell division. It is also necessary to carry out further studies that focus on the position of NAC in the concentration of ER and the manifestation of testicular activity (86,87).

In general, NAC therapy has provided encouraging outcomes in hormonal receptor density, especially AR density, in various experimental testicular hypoxic and oxidative settings. As shown, NAC could improve AR signaling pathways and, therefore, affect the activity of ERs and, consequently, protective effects on testicular function, spermatogenesis, and steroidogenesis. However, more comprehensive investigations in well-controlled clinical trials should be conducted to elaborate more on the underlying NAC modulation of hormonal receptors in the testis and its potential use towards male infertility and other related reproductive diseases (87,88) (Figure 3).

Clinical Implications of NAC Treatment in Testicular Hypoxia

The further understanding implies that apart from the antioxidant efficacy of NAC treatment in testicular hypoxia, there might be additional therapeutic applications related to male fertility and reproductive health. Reduced blood circulation in the testicular tissue is known as testicular hypoxia, and its effects are negative impacts on spermatogenesis and hormonal balance issues, eventually causing infertility. In the following section, the clinical benefits of NAC when used in testicular hypoxia are analyzed comprehensively while relying on clinical trials and experimental studies (76,78).

Reservation of testicular function: These findings provide evidence for using NAC treatment as a therapeutic strategy to prevent hypoxic injury to testicular tissue, peritubular steroidogenesis, and Sertoli cells' function. As a scavenger of ROS and reducing the oxidative stress on the testicular tissue, NAC could help to maintain the germ cells, Leydig cells, and Sertoli cells from hypoxic damage and thereby maintain testicular function and potential fertility (80).

Improvement of sperm quality: Several clinical trials have provided evidence that NAC may enhance the indicators of sperm quality in idiopathic infertility or oxidative stress-compromised male participants through increasing sperm concentration, motility, and morphology, and decreasing sperm DNA fragmentation. NAC treatment may improve sperm quality and reduce the fertility deficit in affected individuals due to the effects of NAC on reducing oxidative stress and boosting the capacity of antioxidants in the seminal microenvironment (61).

Enhancement of male fertility: NAC has therefore been evaluated as an add-on intervention that can enhance ART success rates in couples with infertility, specifically those who desire IVF or ICSI procedures. Namely, NAC supplementation could positively impact the sperm characteristics and pregnancy/chance for fertilization in patients with MF owing to oxidative stress-induced sperm abnormalities and/or testicular failure (61,89).

Management of oxidative stress-related disorders: Apart from the beneficial impacts on male fertility, further studies involving NAC treatment may provide indications for managing other conditions connected with oxidative stress, such as cardiovascular diseases, respiratory diseases, or neurodegenerative disorders. These facts prove that

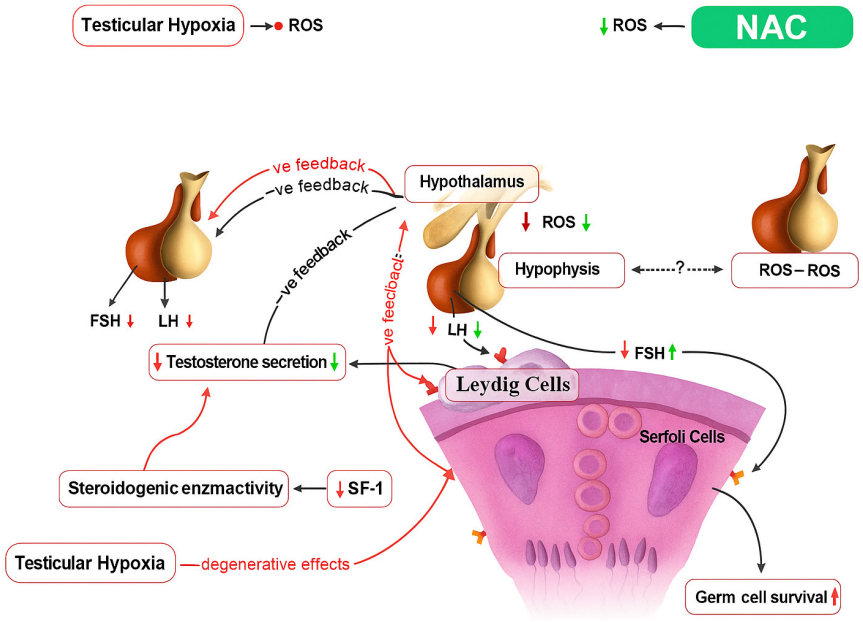

Figure 3. NAC's Potential Modulation of Hormonal Receptor Expression in Testicular Hypoxia.

NAC has potential for use as a therapeutic agent in treating diseases associated with oxidative stress and inflammation because of its effective antioxidant and anti-inflammatory effects in protecting tissue and preserving organ function (54,61,90).

Clinical studies indicate NAC supplementation can improve sperm count, motility, morphology, and DNA integrity in men with idiopathic infertility or oxidative stress. Meta-analyses show moderate but significant improvements, though variability across trials and small sample sizes limit conclusions. Some trials suggest NAC may improve ART outcomes, but evidence remains preliminary (54,61).

While NAC shows promise, clinical recommendations require larger, well-controlled studies to define dosage, treatment duration, and long-term safety.

Challenges and Future Directions

Although experimental studies have shown possible therapeutic uses of NAC in alleviating testicular hypoxia, a few limitations and strategies could be undertaken in the future to enhance the efficiency and applicability of NAC treatment. These issues comprise many factors, such as study weaknesses and limitations in clinical applications and treatments (61,76).

Research limitations: The studies that define the molecular adjustments mediated through NAC in testicular hypoxia need further investigation. Although the previous in vitro and in vivo studies have offered valuable information regarding the antioxidant and cytoprotective nature of NAC and its potential to ameliorate male infertility, further investigations should be conducted to explore the mechanisms by which NAC may interact with hormonal signaling pathways, redox signaling, and gene expression of the testicular cells in greater detail. Therefore, randomized controlled trials that are designed adequately and that incorporate long-term follow-up data with confirmed testicular hypoxia are required to investigate the appropriate doses of NAC therapy for patients with testicular hypoxia-related infertility.

Clinical considerations: Clinically, the result is that patient populations and the mechanisms of testicular hypoxia vary, which complicates the identification of candidates who might benefit most from NAC treatment. For future investigations, the emphasis should be placed on the further enhancement of the criteria for patient selection and formation of the individual treatment strategy according to the degree of testicular torsion, occurrence of oxidative stress, as well as other clinical characteristics that may be important for the outcome of the treatment. Lastly, more systematic approaches regarding NAC dosing regimens, withdrawal schedules from the current experimental intervention, and more straightforward guidelines for assessing drug effectiveness and patient outcomes are necessary for successive practical trials in treating various diseases (61).

Therapeutic optimization: In addition to NAC supplementation, various combination therapies, including the use of NAC in conjunction with other antioxidants, anti-inflammatory agents, or hormones, should be further explored in re-establishing optimal testicular function and fertility indices in patients with testicular hypoxia. Additionally, design and synthesis of new generations of NAC or design of appropriate drug delivery systems like polymeric micelles, liposomes, or nanosomes, or developing sustained-release formulations and controlled release formulations may further increase the bioavailability of the drug, tissue affinity, and

therapeutic activity of NAC with less undesirable side effects (61).

Translation into practice: It is crucial to identify the approaches and strategies that would make the transfer of NAC treatment into clinical practice possible and sustainable, participatory in engaging the clinicians, researchers, and pharmaceutical companies across different institutions to support the translation process from laboratory bench to clinic bedside, and develop plans to integrate the effective evidence-based treatment into routine clinical practice. It should also be noted that to increase the adoption and use of NAC treatment for infertile patients with testicular hypoxic dysfunction, it is necessary to conduct health education aimed at improving the awareness level of healthcare providers and patients about the opportunities and effectiveness of NAC therapy among fertility clinics and reproductive medicine service providers.

Besides the challenges and future directions mentioned above, they provide a robust framework and basis for improving current and future NAC treatment for testicular hypoxic conditions and their overall utility for enhancing male fertility results. By minimizing some of these research limitations, improving clinical methodologies, and encouraging interprofessional collaboration and synergy, NAC's trophic and therapeutic value has been optimally tapped in treating testicular hypoxia-associated infertility and improving reproductive health in affected patients.

Discussion and Conclusion

NAC shows considerable potential as a therapeutic option for testicular hypoxia–related infertility. By acting as a glutathione precursor and a potent antioxidant, NAC reduces oxidative stress, prevents cellular damage, and modulates signaling pathways that regulate redox balance. Experimental studies demonstrate that NAC can preserve testicular function, support spermatogenesis, and improve key sperm parameters such as concentration, motility, morphology, and DNA integrity. Clinical trials in men with idiopathic infertility or oxidative stress–related abnormalities also report improvements in semen quality, and NAC has been evaluated as an adjunct therapy to enhance outcomes in assisted reproductive techniques such as IVF and ICSI.

Despite these promising findings, essential limitations remain. Current clinical studies are few, often with small sample sizes and inconsistent methodologies. The molecular mechanisms underlying NAC's effects on hormonal receptors and the blood–testis barrier require further clarification. In addition, patient selection criteria, optimal dosage, treatment duration, and long-term safety have not yet been firmly established.

In summary, NAC appears to be a promising supportive therapy for protecting testicular function and improving male fertility under hypoxic conditions. However, well-designed basic and clinical studies are essential to validate its efficacy, define clinical indications, and optimize treatment strategies for testicular hypoxia–related infertility.

Authors' Contribution

Conceptualization: Majid Shokoohi, Amir Afshin Khaki, Alireza Alihemmati.
Data curation: Majid Shokoohi, Zahra Shojaei, Kian Keyhan.
Formal analysis: Gilda Ghazi Soltani, Kian Keyhan.
Funding acquisition: Alireza Alihemmati, Amir Afshin Khaki.
Investigation: Majid Shokoohi, Zahra Shojaei.
Methodology: Alireza Alihemmati, Majid Shokoohi, Gilda Ghazi Soltani.
Project administration: Amir Afshin Khaki, Alireza Alihemmati.
Resources: Alireza Alihemmati.
Software: Majid Shokoohi, Gilda Ghazi Soltani, Saba Vaezi.
Supervision: Alireza Alihemmati.
Validation: Majid Shokoohi, Zahra Shojaei, Kian Keyhan, Gilda Ghazi Soltani, Amir Afshin Khaki, Alireza Alihemmati.
Visualization: Majid Shokoohi, Gilda Ghazi Soltani, Amir Afshin Khaki, Alireza Alihemmati.
Writing–original draft: Majid Shokoohi, Kian Keyhan, Vahideh Kianmarz Bonab, Gilda Ghazi Soltani, Amir Afshin Khaki, Alireza Alihemmati, Saba Vaezi.
Writing–review & editing: Majid Shokoohi, Zahra Shojaei, Gilda Ghazi Soltani, Amir Afshin Khaki, Alireza Alihemmati.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

Not applicable.

Financial Support

Nil.

Acknowledgments

We sincerely acknowledge the "Clinical Research Development Unit of Tabriz Valiasr Hospital" at Tabriz University of Medical Sciences, Tabriz, Iran, for their valuable assistance in this research.

References

1. Li Z, Wang S, Gong C, et al. Effects of environmental and pathological hypoxia on male fertility. Front Cell Dev Biol. 2021;9:725933. doi:10.3389/fcell.2021.725933
2. Rizzoto G, Kastelic J. A new paradigm regarding testicular thermoregulation in ruminants? Theriogenology. 2020;147:166-175. doi:10.1016/j.theriogenology.2020.02.030
3. Farias JG, Herrera EA, Carrasco-Pozo C, et al. Pharmacological models and approaches for pathophysiological conditions associated with hypoxia and oxidative stress. Pharmacol Ther. 2016;158:1-23. doi:10.1016/j.pharmthera.2015.11.006
4. Kazaz I, Demir S, Yulug E, et al. N-acetylcysteine protects testicular tissue against ischemia/reperfusion injury via inhibiting endoplasmic reticulum stress and apoptosis. J Pediatr Urol. 2019;15(3):253.e1-e8. doi:10.1016/j.jpurol.2019.02.005
5. Li S, Yang Q-E. Hypobaric hypoxia exposure alters transcriptome in mouse testis and impairs spermatogenesis in offspring. Gene. 2022;823:146390. doi:10.1016/j.gene.2022.146390
6. Rizzoto G, Hall C, Tyberg J, Thundathil J, Caulkett N, Kastelic J. Increased testicular blood flow maintains oxygen delivery and avoids testicular hypoxia in response to reduced oxygen content in inspired air. Sci Rep. 2018;8(1):10905. doi:10.1038/s41598-018-29286-7
7. Lai KP, Li JW, Wang SY, et al. Transcriptomic analysis reveals

transgenerational effect of hypoxia on the neural control of testicular functions. Aquat Toxicol. 2018;195:41-48. doi:10.1016/j.aquatox.2017.12.005
8. Shokoohi M, Khaki A, Roudi Rasht Abadi A, et al. Minocycline can reduce testicular apoptosis related to varicocele in male rats. Andrologia. 2022;54(4):e14375. doi:10.1111/and.14375
9. Oyedokun P, Akhigbe R, Ajayi L, Ajayi A. Impact of hypoxia on male reproductive functions. Mol Cell Biochem. 2023;478(4):875-885. doi:10.1007/s11010-022-04563-4
10. Su JS, Farber NJ, Vij SC. Pathophysiology and treatment options of varicocele: an overview. Andrologia. 2021;53(1):e13576. doi:10.1111/and.13576
11. Ameli M, Moghimian M, Saeb F, et al. The effect of clomiphene citrate and human chorionic gonadotropin on the expression of CatSper1, CatSper2, LHCGR, and SF1 genes, as well as the structural changes in testicular tissue of adult rats. Mol Reprod Dev. 2019;86(6):738-748. doi:10.1002/mrd.23144
12. Ye L, Huang W, Liu S, et al. Impacts of immunometabolism on male reproduction. Front Immunol. 2021;12:658432. doi:10.3389/fimmu.2021.658432
13. Gille A, Givelet M, Pehlic D, et al. Impact of the hypoxic microenvironment on spermatogonial stem cells in culture. Front Cell Dev Biol. 2023;11:1339385. doi:10.3389/fcell.2023.1339385
14. Samir H, ElSayed MI, Radwan F, et al. An updated insight on testicular hemodynamics: environmental, physiological, and technical perspectives in farm and companion animals. Vet Res Commun. 2023;47(2):323-345. doi:10.1007/s11259-022-09975-9
15. Raut S, Kumar AV, Deshpande S, Khambata K, Balasinor NH. Sex hormones regulate lipid metabolism in adult Sertoli cells: a genome-wide study of estrogen and androgen receptor binding sites. J Steroid Biochem Mol Biol. 2021;211:105898. doi:10.1016/j.jsbmb.2021.105898
16. Dolatkhah MA, Khezri S, Shokoohi M, Alihemmati A. The effect of Fumaria parviflora on the expression of sexual hormones along with their receptors in testicles of adult rats induced by varicocele. Andrologia. 2022;54(9):e14512. doi:10.1111/and.14512
17. Palatova TV, Bucharskaya AB, Medvedeva AV, Voronina ES, Pakhomy SS, Maslyakova GN. The effect of intrauterine hypoxia on testicular reproductive function. Russ Open Med J. 2021;10(2):204. doi:10.15275/rusomj.2021.0204
18. Hazrati A, Salimnejad R, Alipour M, Mirzaei Bavil F, Alihemmati A. Protective effect of ghrelin on testicular damages caused by chronic hypoxia in rats: a histopathological study. Andrologia. 2018;50(4):e12989. doi:10.1111/and.12989
19. Akin AT, Kaymak E, Ceylan T, et al. Chloroquine attenuates chronic hypoxia-induced testicular damage via suppressing endoplasmic reticulum stress and apoptosis in experimental rat model. Clin Exp Pharmacol Physiol. 2022;49(8):813-823. doi:10.1111/1440-1681.13665
20. Li Z, Wang S, Gong C, et al. Effects of environmental and pathological hypoxia on male fertility. Front Cell Dev Biol. 2021;9:725933. doi:10.3389/fcell.2021.725933
21. Halimi M, Pourlak T, Kalarestaghi H, et al. Effects of Syzygium aromaticum (clove) extract on male fertility factors and oxidative stress after torsion/detorsion in adult male rats using intrauterine insemination method. Int J Womens Health Reprod Sci. 2022;10(3):131-138. doi:10.15296/ijwhr.2022.23
22. Tanga BM, Qamar AY, Raza S, et al. Semen evaluation: methodological advancements in sperm quality-specific fertility assessment—a review. Anim Biosci. 2021;34(8):1253-1270. doi:10.5713/ab.2020.0087
23. Levine H, Jørgensen N, Martino-Andrade A, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. Hum Reprod Update. 2023;29(2):157-176. doi:10.1093/humupd/dmac035
24. Jørgensen N, Lamb DJ, Levine H, et al. Are worldwide sperm counts declining? Fertil Steril. 2021;116(6):1457-1463. doi:10.1016/j.fertnstert.2021.10.008
25. Sayed MA, Abd Elhafeez HH, Rutland CS, El-Sherry TM. The relationship of sperm motility pattern and its ability to agglutinate with vaginal sperm selection, uptake in sperm storage tubules and competitiveness. In: Poultry Farming-New Perspectives and Applications. IntechOpen; 2023. doi:10.5772/intechopen.100370
26. Waberski D, Suarez SS, Henning H. Assessment of sperm motility in livestock: perspectives based on sperm swimming conditions in vivo. Anim Reprod Sci. 2022;246:106849. doi:10.1016/j.anireprosci.2022.106849
27. Chakraborty S, Saha S. Understanding sperm motility mechanisms and the implication of sperm surface molecules in promoting motility. Middle East Fertil Soc J. 2022;27(1):1-12. doi:10.1186/s43043-022-00094-7
28. Danis RB, Samplaski MK. Sperm morphology: history, challenges, and impact on natural and assisted fertility. Curr Urol Rep. 2019;20(8):46. doi:10.1007/s11934-019-0911-7
29. Jakubik-Uljasz J, Gill K, Rosiak-Gill A, Piasecka M. Relationship between sperm morphology and sperm DNA dispersion. Transl Androl Urol. 2020;9(2):405-415. doi:10.21037/tau.2020.03.09
30. Khatun A, Rahman MS, Pang M-G. Clinical assessment of the male fertility. Obstet Gynecol Sci. 2018;61(2):179-191. doi:10.5468/ogs.2018.61.2.179
31. Barbăroșie C, Agarwal A, Henkel R. Diagnostic value of advanced semen analysis in evaluation of male infertility. Andrologia. 2021;53(2):e13625. doi:10.1111/and.13625
32. Del Giudice F, Belladelli F, Chen T, et al. The association of impaired semen quality and pregnancy rates in assisted reproduction technology cycles: systematic review and meta-analysis. Andrologia. 2022;54(6):e14409. doi:10.1111/and.14409
33. Konkal P, Ganesh C. Exposure to hypoxia inhibits pituitary-testicular activity in the fish Oreochromis mossambicus. Aquaculture. 2020;515:734552. doi:10.1016/j.aquaculture.2019.734552
34. Cho Y-M, Chou J-C, Fang C-M, et al. Chronic intermittent hypoxia stimulates testosterone production in rat Leydig cells. Life Sci. 2019;233:116694. doi:10.1016/j.lfs.2019.116694
35. Antonuccio P, Pallio G, Marini HR, et al. Involvement of hypoxia-inducible factor 1-α in experimental testicular ischemia and reperfusion: effects of polydeoxyribonucleotide and selenium. Int J Mol Sci. 2022;23(21):13144. doi:10.3390/ijms232113144
36. Qamar AY, Hussain T, Rafique MK, et al. The role of stem cells and their derived extracellular vesicles in restoring female and male fertility. Cells. 2021;10(9):2460. doi:10.3390/cells10092460
37. Christin-Maitre S, Young J, eds. Androgens and spermatogenesis. Ann Endocrinol (Paris). 2022;83(3):156-162. doi:10.1016/j.ando.2022.06.002
38. Wang J-M, Li Z-F, Yang W-X. What does androgen receptor signaling pathway in Sertoli cells during normal spermatogenesis tell us? Front Endocrinol (Lausanne). 2022;13:838858. doi:10.3389/fendo.2022.838858
39. Shah W, Khan R, Shah B, et al. The molecular mechanism of sex hormones on Sertoli cell development and proliferation. Front Endocrinol (Lausanne). 2021;12:648141. doi:10.3389/fendo.2021.648141
40. Verderame M, Scudiero R. A comparative review on estrogen receptors in the reproductive male tract of non mammalian vertebrates. Steroids. 2018;134:1-8. doi:10.1016/j.steroids.2018.03.001
41. Darbandi M, Darbandi S, Agarwal A, et al. Reactive oxygen species and male reproductive hormones. Reprod Biol Endocrinol. 2018;16(1):87. doi:10.1186/s12958-018-0406-2
42. Agarwal A, Leisegang K, Sengupta P. Oxidative stress in pathologies of male reproductive disorders. In: Agarwal A, Dutta S, Sengupta P, eds. Pathology. Elsevier; 2020:15-27. doi:10.1016/B978-0-12-815972-9.00002-0
43. Dutta S, Sengupta P, Chakravarthi S. Oxidant-sensitive inflammatory pathways and male reproductive functions. In: Dutta S, Sengupta P, Nandi A, eds. Oxidative Stress and Toxicity in Reproductive Biology and Medicine: A Comprehensive

Update on Male Infertility-Volume One. Springer; 2022:165-180. doi:10.1007/978-3-030-89340-8_10
44. Matsuyama S, DeFalco T. Steroid hormone signaling: multifaceted support of testicular function. Front Cell Dev Biol. 2023;11:1339385. doi:10.3389/fcell.2023.1339385
45. Espinosa-Sánchez A, Suárez-Martínez E, Sánchez-Díaz L, Carnero A. Therapeutic targeting of signaling pathways related to cancer stemness. Front Oncol. 2020;10:1533. doi:10.3389/fonc.2020.01533
46. Poe FL, Corn J. N-acetylcysteine: a potential therapeutic agent for SARS-CoV-2. Med Hypotheses. 2020;143:109862. doi:10.1016/j.mehy.2020.109862
47. Tenório MCdS, Graciliano NG, Moura FA, Oliveira ACMd, Goulart MOF. N-acetylcysteine (NAC): impacts on human health. Antioxid (Basel). 2021;10(6):967. doi:10.3390/antiox10060967
48. Raghu G, Berk M, Campochiaro PA, et al. The multifaceted therapeutic role of N-acetylcysteine (NAC) in disorders characterized by oxidative stress. Curr Neuropharmacol. 2021;19(8):1202-1224. doi:10.2174/1570159X19666201230144109
49. Ezeriņa D, Takano Y, Hanaoka K, Urano Y, Dick TP. N-acetyl cysteine functions as a fast-acting antioxidant by triggering intracellular H(2)S and sulfane sulfur production. Cell Chem Biol. 2018;25(4):447-459.e4. doi:10.1016/j.chembiol.2018.01.011
50. Pedre B, Barayeu U, Ezeriňa D, Dick TP. The mechanism of action of N-acetylcysteine (NAC): the emerging role of H2S and sulfane sulfur species. Pharmacol Ther. 2021;228:107916. doi:10.1016/j.pharmthera.2021.107916
51. Abdel-Fattah MM, Salama AAA, Messiha BAS. Immunomodulatory and anti-inflammatory effects of N-acetylcysteine in ovalbumin-sensitized rats. Beni Suef Univ J Basic Appl Sci. 2022;11(1):2. doi:10.1186/s43088-021-00196-6
52. Mokra D, Mokry J, Barosova R, Hanusrichterova J. Advances in the use of N-acetylcysteine in chronic respiratory diseases. Antioxid (Basel). 2023;12(9):1713. doi:10.3390/antiox12091713
53. Faghfouri AH, Zarezadeh M, Tavakoli-Rouzbehani OM, et al. The effects of N-acetylcysteine on inflammatory and oxidative stress biomarkers: a systematic review and meta-analysis of controlled clinical trials. Eur J Pharmacol. 2020;884:173368. doi:10.1016/j.ejphar.2020.173368
54. Tieu S, Charchoglyan A, Paulsen L, et al. N-acetylcysteine and its immunomodulatory properties in humans and domesticated animals. Antioxid (Basel). 2023;12(10):1867. doi:10.3390/antiox12101867
55. Otu A, Langridge P, Denning DW. Nebulised N-acetylcysteine for unresponsive bronchial obstruction in allergic bronchopulmonary aspergillosis: a case series and review of the literature. J Fungi (Basel). 2018;4(4):117. doi:10.3390/jof4040117
56. Liao Y, Wu Y, Zi K, et al. The effect of N-acetylcysteine in patients with non-cystic fibrosis bronchiectasis (NINCFB): study protocol for a multicentre, double-blind, randomised, placebo-controlled trial. BMC Pulm Med. 2022;22(1):401. doi:10.1186/s12890-022-02199-7
57. Ranasinghe R, Mathai M, Zulli A. Cytoprotective remedies for ameliorating nephrotoxicity induced by renal oxidative stress. Life Sci. 2023;318:121466. doi:10.1016/j.lfs.2023.121466
58. Mehta J, Rayalam S, Wang X. Cytoprotective effects of natural compounds against oxidative stress. Antioxid (Basel). 2018;7(10):147. doi:10.3390/antiox7100147
59. Tardiolo G, Bramanti P, Mazzon E. Overview on the effects of N-acetylcysteine in neurodegenerative diseases. Molecules. 2018;23(12):3305. doi:10.3390/molecules23123305
60. Hoffer BJ, Pick CG, Hoffer ME, Becker RE, Chiang YH, Greig NH. Repositioning drugs for traumatic brain injury - N-acetyl cysteine and Phenserine. J Biomed Sci. 2017;24(1):71. doi:10.1186/s12929-017-0378-4
61. Tenório MCdS, Graciliano NG, Moura FA, Oliveira ACMd, Goulart MOF. N-acetylcysteine (NAC): impacts on human health. Antioxid (Basel). 2021;10(6):967. doi:10.3390/antiox10060967
62. Ghaderi A, Bussu A, Tsang C, Jafarnejad S. Effect of N-acetylcysteine on positive and negative syndrome scale associated with schizophrenia: a meta-analysis. Rev Clin Med. 2020;7(3):134-144. doi:10.22088/rcm.7.3.134
63. Katz MJ, Najari BB, Li PS, Goldstein M. The role of animal models in the study of varicocele. Transl Androl Urol. 2014;3(1):59-63. doi:10.3978/j.issn.2223-4683.2014.01.08
64. Minas A, Mahmoudabadi S, Gamchi NS, Antoniassi MP, Alizadeh A, Bertolla RP. Testicular torsion in vivo models: mechanisms and treatments. Andrology. 2023;11(7):1267-1285. doi:10.1111/andr.13411
65. Abadi ARR, Boukani LM, Shokoohi M, et al. The flavonoid chrysin protects against testicular apoptosis induced by torsion/detorsion in adult rats. Andrologia. 2023;2023:5736601. doi:10.1155/2023/5736601
66. Ameli M, Hashemi MS, Moghimian M, Shokoohi M. Protective effect of tadalafil and verapamil on testicular function and oxidative stress after torsion/detorsion in adult male rat. Andrologia. 2018;50(8):e13068. doi:10.1111/and.13068
67. Shokoohi M, Khaki A, Shoorei H, Khaki A, Moghimian M, Abtahi-Eivary SH. Hesperidin attenuated apoptotic-related genes in testicle of a male rat model of varicocele. Andrology. 2020;8(1):249-258. doi:10.1111/andr.12681
68. Cho CL, Esteves SC, Agarwal A. Novel insights into the pathophysiology of varicocele and its association with reactive oxygen species and sperm DNA fragmentation. Asian J Androl. 2016;18(2):186-193. doi:10.4103/1008-682X.170441
69. Tadros NN, Sabanegh E. Varicocele. In: Henkel R, Samanta L, Agarwal A, eds. Oxidants, Antioxidants and Impact of the Oxidative Status in Male Reproduction. Academic Press; 2019:105-115. doi:10.1016/B978-0-12-812501-4.00011-8
70. Trujillo-Rangel WÁ, García-Valdés L, Méndez-del Villar M, Castañeda-Arellano R, Totsuka-Sutto SE, García-Benavides L. Therapeutic targets for regulating oxidative damage induced by ischemia-reperfusion injury: a study from a pharmacological perspective. Oxid Med Cell Longev. 2022;2022:8624318. doi:10.1155/2022/8624318
71. Hillman TC, Idnani R, Wilson CG. An inexpensive open-source chamber for controlled hypoxia/hyperoxia exposure. Front Physiol. 2022;13:891005. doi:10.3389/fphys.2022.891005
72. Salyha N, Oliynyk I. Hypoxia modeling techniques: a review. Heliyon. 2023;9(2):e13238. doi:10.1016/j.heliyon.2023.e13238
73. Ziliotto M, Rodrigues RM, Chies JAB. Controlled hypobaric hypoxia increases immunological tolerance by modifying HLA-G expression, a potential therapy to inflammatory diseases. Med Hypotheses. 2020;140:109664. doi:10.1016/j.mehy.2020.109664
74. Reyes JG, Farias JG, Henríquez-Olavarrieta S, et al. The hypoxic testicle: physiology and pathophysiology. Oxid Med Cell Longev. 2012;2012:929285. doi:10.1155/2012/929285
75. Jannatifar R, Parivar K, Roodbari NH, Nasr-Esfahani MH. Effects of N-acetyl-cysteine supplementation on sperm quality, chromatin integrity and level of oxidative stress in infertile men. Reprod Biol Endocrinol. 2019;17(1):24. doi:10.1186/s12958-019-0468-9
76. Baetas J, Rabaça A, Gonçalves A, Barros A, Sousa M, Sá R. Protective role of N-acetylcysteine (NAC) on human sperm exposed to etoposide. Basic Clin Androl. 2019;29:3. doi:10.1186/s12610-019-0091-8
77. Jannatifar R, Parivar K, Roodbari NH, Nasr-Esfahani MH. Effects of N-acetyl-cysteine supplementation on sperm quality, chromatin integrity and level of oxidative stress in infertile men. Reprod Biol Endocrinol. 2019;17(1):24. doi:10.1186/s12958-019-0468-9
78. Zhou Z, Cui Y, Zhang X, Zhang Y. The role of N-acetyl-cysteine (NAC) orally daily on the sperm parameters and serum hormones in idiopathic infertile men: a systematic review and meta-analysis of randomised controlled trials. Andrologia. 2021;53(2):e13953. doi:10.1111/and.13953
79. Kowalczyk A. The role of the natural antioxidant mechanism in sperm cells. Reprod Sci. 2022;29(5):1387-1394. doi:10.1007/s43032-021-00740-2
80. Avdatek F, TÜrkmen R, DemİRel HH, BİRdane YO. Protective effect of N-acetylcysteine on testicular oxidative damage, spermatological parameters and DNA damage in glyphosate-

based herbicide-exposed rats. Kocatepe Vet J. 2018;11(3):292-300. doi:10.29185/kvj.434141
81. Hashim AR, Bashir DW, Yasin NAE, Rashad MM, El-Gharbawy SM. Ameliorative effect of N-acetylcysteine on the testicular tissue of adult male albino rats after glyphosate-based herbicide exposure. J Biochem Mol Toxicol. 2022;36(4):e22997. doi:10.1002/jbt.22997
82. Ventura RD, Chaves AS, Magalhães NS, et al. Activation of PPARγ reduces N-acetyl-cysteine -induced hypercorticoidism by down-regulating MC2R expression into adrenal glands. Free Radic Biol Med. 2020;156:137-143. doi:10.1016/j.freeradbiomed.2020.06.023
83. Ding H, Yang Y, Wei S, et al. Influence of N-acetylcysteine on steroidogenesis and gene expression in porcine placental trophoblast cells. Theriogenology. 2021;161:49-56. doi:10.1016/j.theriogenology.2020.11.020
84. Liu YX, Zhang KJ, Tang LL. Clinical significance of androgen receptor expression in triple negative breast cancer-an immunohistochemistry study. Oncol Lett. 2018;15(6):10008-10016. doi:10.3892/ol.2018.8532
85. Liu YX, Zhang KJ, Tang LL. Clinical significance of androgen receptor expression in triple negative breast cancer-an immunohistochemistry study. Oncol Lett. 2018;15(6):10008-10016. doi:10.3892/ol.2018.8532
86. Lan A, Jin Y, Wang Y, et al. Association of serum reproductive hormones changes after neoadjuvant chemotherapy with hormone receptors expression alterations and survival outcomes in breast cancer. Front Surg. 2022;9:947218. doi:10.3389/fsurg.2022.947218
87. Lan A, Jin Y, Wang Y, et al. Association of serum reproductive hormones changes after neoadjuvant chemotherapy with hormone receptors expression alterations and survival outcomes in breast cancer. Front Surg. 2022;9:947218. doi:10.3389/fsurg.2022.947218
88. Shi Z, Liu Y, Zhang S, et al. Evaluation of predictive and prognostic value of androgen receptor expression in breast cancer subtypes treated with neoadjuvant chemotherapy. Discov Oncol. 2023;14(1):49. doi:10.1007/s12672-023-00680-7
89. Ciftci H, Verit A, Savas M, Yeni E, Erel O. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. Urology. 2009;74(1):73-76. doi:10.1016/j.urology.2008.12.064
90. Agarwal A, Majzoub A. Role of antioxidants in assisted reproductive techniques. World J Mens Health. 2017;35(2):77-93. doi:10.5534/wjmh.2017.35.2.77

Copyright © 2025 The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.