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RESEARCH ARTICLE

A MOLECULAR UNDERSTANDING OF THE DETRIMENTAL IMPACT OF OXIDATIVE STRESS ON MALE FERTILITY

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Abstract

Male infertility is a widely discussed issue globally, involving various intricate processes. Oxidative stress stands out as a key culprit, where an overabundance of free radicals exerts a significant influence on both the quantity and quality of sperm. The body's antioxidant defense system struggles to effectively regulate the surplus reactive oxygen species (ROS), leading to potential disruptions in male fertility and adverse impacts on sperm quality metrics. Mitochondria, the powerhouses of sperm motility, play a pivotal role. Aberrations in their function can trigger apoptosis, alterations in signaling systems, and ultimately, diminished fertility. Moreover, research indicates that the presence of inflammation can impede sperm activity, with cytokine synthesis being triggered by an excess of reactive oxygen species. This complex interplay of factors underscores the multifaceted nature of male infertility, shedding light on the intricate mechanisms at play. Moreover, the interplay between seminal plasma proteomes, which significantly influence male fertility and oxidative stress, is a crucial aspect. Elevated production of reactive oxygen species (ROS) poses a threat by causing damage to essential biological components, such as DNA, and hindering the sperm's ability to fertilize the ovum. In this examination, we delve into the latest research to enhance our comprehension of the intricate relationship between oxidative stress and male infertility. The role of mitochondria, the cellular response mechanisms, inflammation's impact on fertility, and the intricate interactions of seminal plasma proteomes with oxidative stress are also scrutinized. Additionally, we underscore the noteworthy influence of oxidative stress on hormonal regulation. Collectively, these elements are deemed crucial in the intricate control of male infertility. This article aims to contribute valuable insights to our understanding of male infertility and potential preventive measures.

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Introduction:-

When a guy is unable to successfully conceive a female, it is known as male infertility (1). It is a global problem that accounts for 50% of instances of infertility (2). It can arise for a variety of causes, including pituitary or hypothalamic dysfunction, testicular blockage or inflammation, or other disorders that can lead to infertility. In addition, a number of other disorders, including erectile dysfunction, hypogonadism, epididymitis, congenital bilateral absence of the vas deferens, and Sertoli cell syndrome, have been linked to male infertility (3). There are idiopathic causes for most male infertility (2). These elements are all thought to play a role, either directly or indirectly, in the development of oxidative stress. Male infertility is largely caused by reactive oxygen species (ROS), which are the active oxidative metabolites that produce oxidative stress (4, 5). Semen characteristics including motility, morphology, and sperm concentration can all be impacted by excessive oxidative stress, which can worsen the quality of the semen and lower the chance of conception (6). Research has indicated that oxidative stress has a role in disorders that impact the reproductive status of men (7).Spermatozoa gradually lose their ability to fertilise because the sperm plasma membrane includes polyunsaturated fatty acids, which render it more fragile and prone to oxidative damage.

In addition, broken DNA might hinder the genetic potential of the father to create embryos (5). The unpaired electrons that make up ROS have the ability to harm amino acids, fats, carbohydrates, and DNA (8). The three types of ROS are primary, secondary, and tertiary, which is interesting to note. Free radicals are not the only kind of ROS (5, 9); hyperactivation, sperm capacitation, and other acrosomal alterations are significantly influenced by the physiological concentration of ROS (10). According to available data, ROS-induced sperm destruction accounts for 30–80% of male-related reproductive problems (11–13).

Prostate-level obstacles to male fertility can be predicted by using advanced proteomic technologies that enable the characterisation of semen patterns through the use of mechanistic approaches and aid in the detection of proteins and their underlying biological processes (13). With further understanding in this field, it is now possible to distinguish between men who are fertile and those who are not (14). Seminal plasma and sperm proteins can now be easily understood. Previous studies have demonstrated the connection between the sperm and seminal plasma protein composition and oxidative stress-potentiated male infertility; changes in protein expression and function may be visible during sperm maturation. To determine the diseases connected to male infertility at the molecular and proteome levels, more research is required. There is little research on the connection between oxidative stress and the proteomic profile of human ejaculation, despite the fact that the effects of oxidative stress on male infertility have been extensively studied. The correlation between oxidative stress and the proteomic profile is evident in the research currently available on human infertility (15–17). Furthermore, oxidative stress has an impact on poor semen quality, as evidenced by further research based on proteomic profiles (18, 19).

The diagnosis of male infertility can be made by analysing fundamental semen properties, including motility, morphological traits, sperm viability, liquefaction time, and sperm count. For the purpose of determining the reproductive status of both people and animals, the World Health Organisation has established reference values or standards for sperm abnormalities, alterations in sperm concentration, motility, and morphology (20, 21). In order to determine the potential reasons of infertility, a variety of sophisticated techniques may be used, including DNA compaction, sperm DNA oxidation, antioxidant capacity analysis, apoptosis, the presence of anti-sperm antibodies, and genetic testing (22). It has been documented that infertile human patients with unstable chromatin packing and DNA damage have elevated ROS concentrations (5). Many people believe that sperm DNA damage is the cause of infertility because it is a biomarker for cellular integrity loss, which is linked to a decrease in semen quality (23, 24). The use of fragmented DNA spermatozoa in assisted reproductive technologies increases the risk of miscarriage, congenital abnormalities, and other childhood malformations, as well as decreased rates of fertilisation and pregnancy, aberrant embryonic development, and other complications (25, 26). For idiopathic infertile couples, the degree of DNA fragmentation is a reliable predictor of assisted reproductive outcomes. Nonetheless, after IVF therapy, reduced birth weight has been linked to increased sperm DNA fragmentation (24). The primary goal of this review was to clarify the function of mitochondria, the cellular response in issues linked to fertility, the relationship between oxidative stress and seminal plasma proteomes, and the impact of oxidative stress on hormones.

Ros and The Role Of Mitochondria

Oxidative stress brought on by oxidants is brought on in germ cells by an increase in ROS. Redox equilibrium is maintained by ROS, which are essential organelles at low quantities. Acrolein, malondialdehyde, and 4-hydroxynonenal (4-HNE) are examples of tiny molecules of aldehydes that are inhibited by lipid peroxidation

processes, which are heightened by large amounts of ROS. The targeted proteins' histidine, lysine, and cysteine residues are vulnerable to binding by these compounds at protein sites (27). These proteins' activities result in free radicals, which are in charge of producing additional aldehyde products, and they also hinder electron flow towards the mitochondrial electron transport chain (27). Oxidant cascades can be caused by any stimulus that affects germ cells by oxidatively phosphorylating them and producing oxidants. Numerous factors, including a deficiency in antioxidants, ionising radiation, leukocytes, obesity, smoking, reproductive tract infections, and pesticides, can lead to oxidative stress. It is generally known that polyunsaturated fatty acid-containing spermatozoa and free radicals have a beneficial association.

The generation of ROS by mitochondria is a necessary step in the induction of intrinsic apoptosis. The few spermatozoa that survive ultimately go through apoptosis, and their survival is essential to the fertilisation process continuing successfully. A bacterial endotoxin called lipopolysaccharide (LPS) has been shown to cause apoptosis in a significant proportion of spermatozoa (28). As dead spermatozoa are seldom removed by phagocytosis by neutrophils and macrophages, apoptosis is a necessary mechanism for life to continue. It has been observed that the completion of the apoptotic process can occur even in the presence of cytokines, ROS generation, and inflammation. Nevertheless, the existence of an inflammatory reaction that recurs following a vasectomy or during a sexual act makes leukocyte infiltration detrimental. The sperms trigger a reaction in gametes that leads to phagocytosis, although this reaction can be counteracted if phosphatidylserine (a hallmark of apoptosis) is present. Figure 1 shows the essential ROS and RNS mechanism for spermatozoa's fundamental development correction and functional activity.

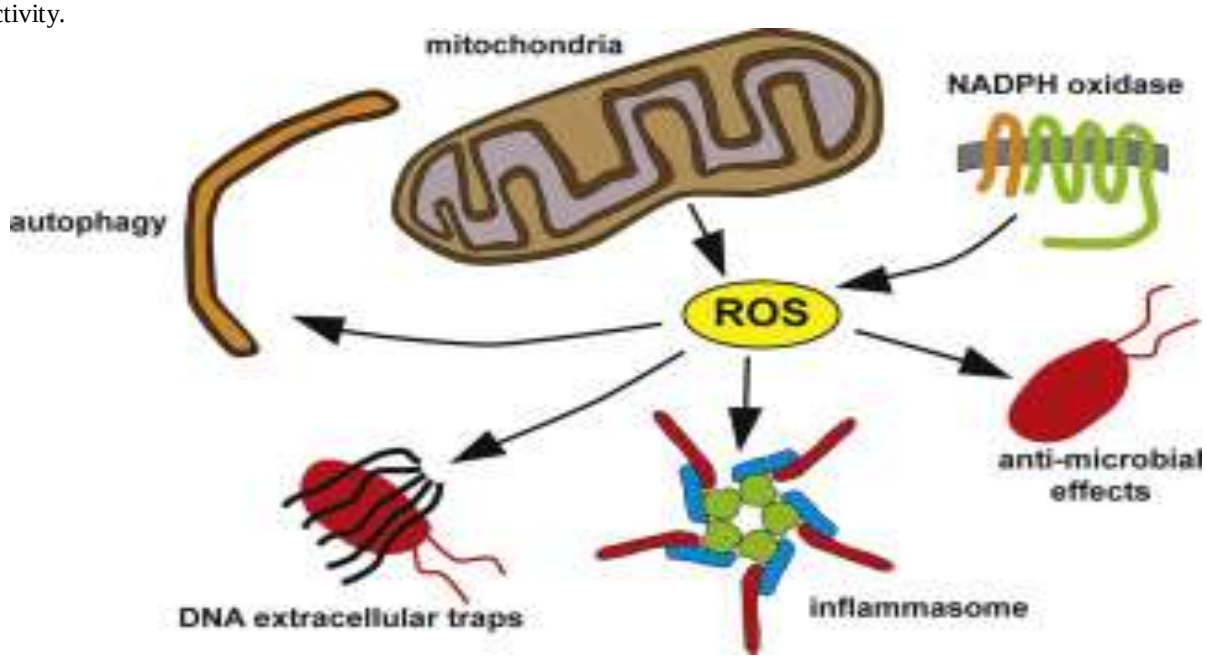

Figure 1:- Understanding of the Reactive oxygen species and mitochondria.

Phospholipase 4,5-bisphosphate 3-kinase (PI3K), an enzyme that cells need for survival, is realistically the cause of spermatozoa's death (29). By phosphorylating downstream kinases like AKT (protein kinase B), the PI3K signalling cascade is activated, which renders gametes viable and active. AKT affects downstream proteins such BCL2-related death promoter (BAD), which when dephosphorylated creates mitochondrial membrane holes that induce apoptosis and encourage the creation of pores with BAK/BAX (30). Understanding the fundamental process of sperm apoptotic genesis is the first step towards comprehending the underlying mechanism that stimulates PI3K activity. Notably, spermatozoa have a number of prosurvival hormonal receptors that, when activated by its corresponding ligands, enable sustained survival. Examples of these receptors include prolactin (31) and insulin. On the other hand, gametes quickly increase mitochondrial ROS production when the PI3K inhibitor wortmanin is administered, increasing the susceptibility of cells to apoptosis (29).

ROS As Well As The Process Of Capping

There are many pathways that trigger ROS, all of which rely on adenylyl cyclase activity activation (32), which then triggers protein kinase A (33, 34). It has been extensively documented that H202 is essential for regulating the phosphorylation and capacitation processes during capacitation in suspensions of human, bovine, and hamster sperm (32). Similarly, when spermatozoa are exposed to artificially oxidised circumstances, the capacitation process begins and extracellular ROS production is induced by the glucose oxidase or xanthine oxidase systems. In certain species, catalase may be induced, which reduces tyrosine phosphorylation (32). Though they may reverse in the presence of seminal plasma antioxidants, ROS-generated leucocytes contribute to human sperm capacitation (35). Catalase is a prime example of the profound function of H202; it reduces processes like hyperactivation, acrosomal exocytosis, and sperm-egg fusion, all of which occur after capacitation, by restoring the spontaneous induction of tyrosine phosphorylation in capacitating mammalian spermatozoa (36). A range of reactive oxygen species (ROS) sources, including superoxide anion, nitric oxide, and peroxynitrite, has been employed to initiate capacitation processes 39. Research has shown that during sperm capacitation, there is a significant interconversion of ROS that can involve any ROS. The regulators will be H2O2 and peroxynitrite if the potential of oxidative metabolites shows a critical function in capacitation. Many characteristics of capacitating spermatozoa, such as the inhibition of tyrosine phosphate activity, are produced by peroxynitriate (38).

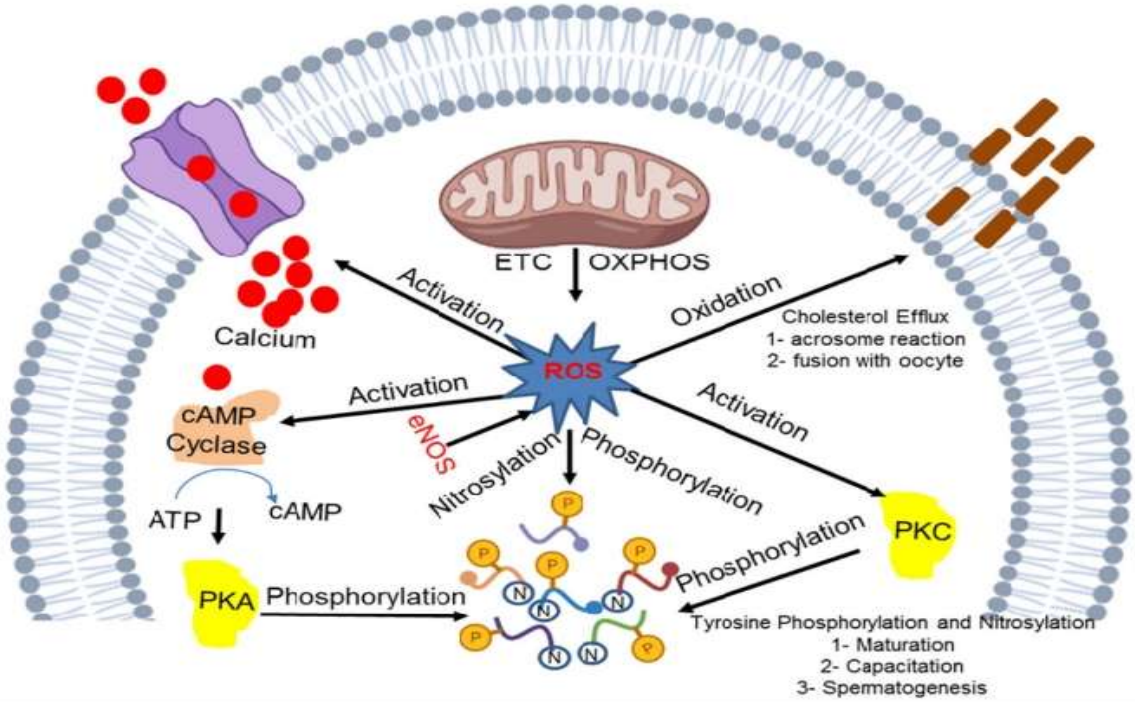

Figure 2:- Understanding of the molecular role of ROS and RNS in spermatozoa formation and function.

There have been reports of the female reproductive tract benefiting from ROS production and capacitation. Only when the oviductal epithelium releases spermatozoa, right before the site of fertilisation, can they create excessive ROS. In this case, each spermatozoon gets a brief exposure to ROS in order to get ready for fertilisation. Should there be no spermatozoa fertilisation, the generation of free radicals on their own causes overcapacitation, which in turn causes oxidative stress. As a result, lipid aldehydes are eventually produced, which start ROS-mediated peroxidation and eventually cause apoptosis (39, 40). In order to maintain sperm capacitation for a longer amount of time, spermatozoa may benefit from long-term storage through sperm capacitation towards apoptosis. It is a fact that a number of domestic species of spermatozoa experience alterations resembling capacitation, which result in oxidative and stress-related cryopreservation. This might potentially contribute to the gametes' lifespan before insemination (41). The greatest method to reduce oxidative stress in cryopreserved spermatozoa is to add antioxidants, which are frequently utilised because of their large impact. Examples of antioxidants include lycopene, cysteamine, melatonin, vitamin E, and resveratrol (42). Figure 2 shows molecular insights into apoptosis and the spermatozoa capacitation process.

Hormones Produced By Males And Oxidative Injury During Reproduction

Both an excess of reactive oxygen species (ROS) or a reduction in antioxidant levels can cause oxidative stress, which can lead to lipid peroxidation in Leydig cells and germ cells, as well as deleterious effects on lipoproteins, protein aggregation and fragmentation, and the inhibition of steroidogenic enzymes (43). Reduced testosterone production occurs as a result of damage to the Leydig cells or other endocrine organs, including the anterior pituitary, when OS is prevalent in the testicles (44, 45). Remarkably, ROS are also produced during the physiological synthesis of hormones and are primarily produced by mitochondrial respiration and the catalytic activities of steroidogenic cytochrome P450 enzymes (46). Accordingly, the spermatozoa's mitochondrial membranes suffer damage from the generation of ROS, which also significantly reduces the synthesis of steroids (47). A larger quantity of immature spermatozoa is linked to OS through an indirect influence on the synthesis of male hormones, which is linked to spermatogenesis (48, 49).

Hormones have been shown to influence seminal total antioxidant capacity (TAC), including follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, oestrogen (E2), and prolactin (PRL) (50, 51). There is also a link (52) between PRL or free thyroxine T4 (fT4) and TAC that is negatively correlated with gonadotropins or gonadal steroids. Certain hormones, such melatonin (MLT) and testosterone, are thought to boost antioxidant capacity to protect testicular cells, including sperm, from the damaging effects of reactive oxygen species (ROS) (53, 54). Other hormone metabolites, such dehydroepiandrosterone (DHEA), boost antioxidant levels within cells via a precise mechanism that is yet unknown (55). Testosterone and zinc levels have been shown to be correlated both directly and indirectly with antioxidant levels in infertile men (51, 56). Invertase the levels of FSH and LH may be lowered by Q10 (CoQ10) (57). Serum levels of sperm DNA fragmentation, E2, fT4, and testosterone have all shown a negative correlation (58, 59). Antioxidants may be suppressed, which may affect neurotransmitters noradrenaline, thyroxine (T4), triiodothyronine (T3), and increase sperm DNA destruction (60). Sperm DNA damage (62), as well as reactive oxygen species (ROS) generation, are decreased when idiopathic infertile men receive highly pure FSH. The quantity of FSH, testosterone, and inhibin B may be modulated by a prolonged antioxidant action, and it has been discovered that testosterone may cause DNA breakage and germ cell caspase activity in Sertoli cells (63, 64).

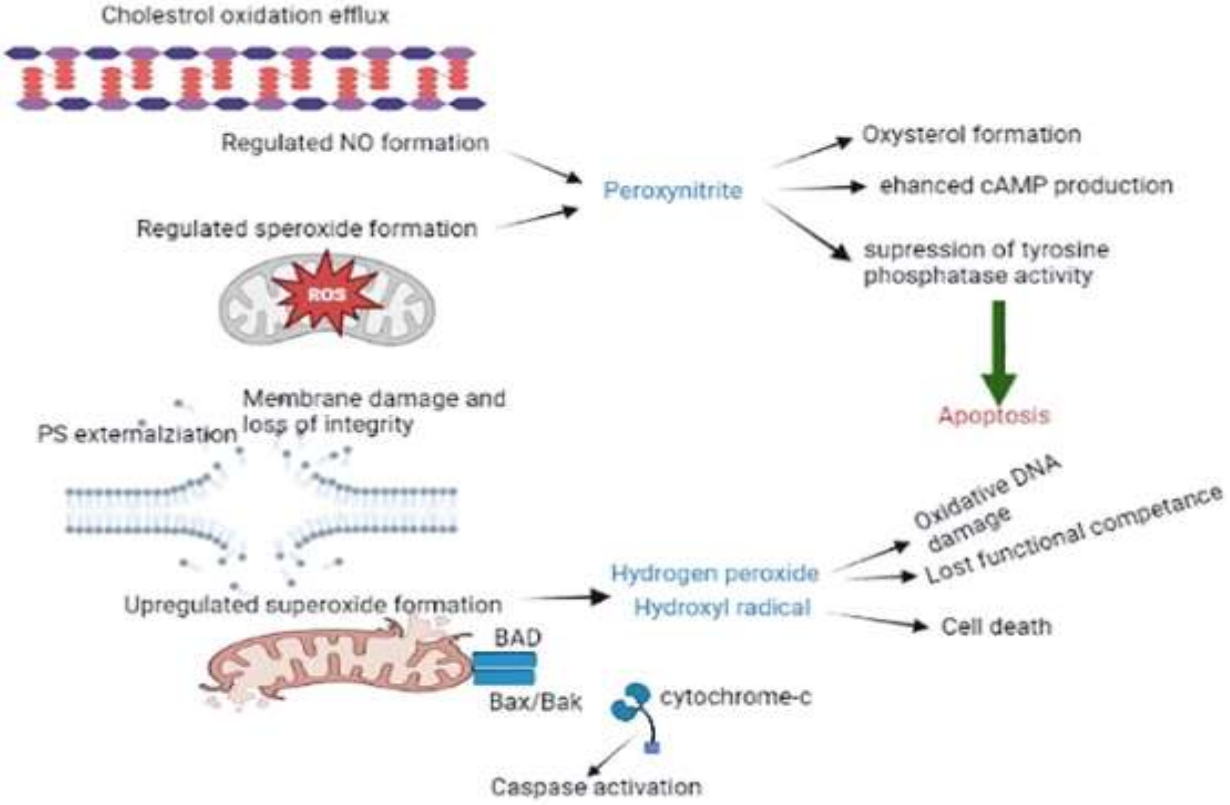

Figure 3:- Apoptotic process and spermatozoa capacitation. The accelerated generation of ROS (primarily ONOO) is depicted in the schematic diagram. This leads to the production of oxysterol, which aids in the removal of

cholesterol from the plasma membrane and promotes membrane fluidity. Other changes include the enhancement of cAMP activity and the suppression of tyrosine phosphatase. Spermatozoa with capacity are ultimately the result of this procedure. In the event of infertility, oxysterol and lipid aldehydes are produced, which set off a cascade of events that culminate in increased production of mitochondrial superoxide, lipid peroxidation, cytochrome c release, activation of caspase, exposure to phosphatidylserine, oxidative DNA fragmentation, and death.

As mentioned previously, high ROS affects the HPA, which causes animals and humans to produce cortisol and corticosterone, which causes stress. Stress hormone release disrupts the anterior pituitary glands ability to produce LH via reducing interaction between the HPG and HPA axes. Leydig cells, which generate testosterone, cannot be activated by low amounts of LH. Decreased FSH causes the Sertoli cells to produce less androgen-binding protein (ABP), which in turn lowers the amount of testosterone in the bloodstream because of an abundance of OS. ROS inhibits the production of T3 and T4 via influencing the HPT axis. Decreased T3 levels of testosterone synthesis, Leydig cell protein, and steroidogenic acute regulatory protein (StAR) mRNA are seen (65). When OS is overproduced, the pancreas produces less insulin, which negatively affects the thyroid glands ability to release T3, which triggers the creation of testosterone. Inhibin and testicular E2 are mostly released during OS synthesis, which inhibits the production of testosterone. Aromatase activity is increased subsequent to OS synthesis, resulting in increased E2 output. Moreover, exposure to ROS increases the anterior pituitary glands PRL release, which lowers the release of GnRH. In conclusion, many mechanisms have been noted for OS to interfere with hormone communication. A major factor in the male reproductive system's operation is hormones. Spermatogenesis is influenced by testosterone production, which is impacted by ROS. OS also interferes with testosterone production, which finally results in infertility and impacts male reproductive behavior

Cellular Reaction To Combat Infertility And Inflammation.

As the body's natural defence against external invaders, inflammation leads to cellular damage and the subsequent restoration of tissue function (66, 67). It has been observed that the overproduction of prostaglandin E2, cytokines, and nitric oxide (NO) by macrophages and other inflammatory cells results in the establishment of an inflammatory response (68). According to certain data, spermatogenesis and steroidogenesis may be impacted by inflammation. Inflammation has also been linked to a rapid drop in blood luteinizing hormones and testosterone (69). A significant decrease in testosterone was seen in a research where lipopolysaccharide (LPS) was utilized to induce an inflammatory response. Steroid acute regulatory StAR proteins, on the other hand, are known to have a reduced sensitivity to steroidogenesis (70). Research has shown that inflammation slows down the development of sperm and promotes spermatogenic arrest (71). Another area targeted by inflammation as a result of testicular assaults is the epididymis. Crucially, leukocytes that invade semen and release anti-sperm antibodies are what cause inflammation. The sperm flagella membrane becomes stiffer due to the inflammatory response, which lowers the membrane's lipid content. Therefore, sperm agglutination and asthenospermia may arise from the suppression of sperm motility. Furthermore, it results in abnormalities in the acrosome reaction, which stops sperm from passing through the oolemma. Additionally, the increasing quantity of apoptotic sperm cells lowers DNA integrity (5).

There is evidence from earlier research linking oxidative stress to inflammation. Men who are infertile have higher amounts of ROS in their semen, which has been shown to cause an inflammatory response (72). Furthermore, it is thought that leukocytes are the primary contributor of seminal ROS, while invasive bacteria produce ROS on their own (8). Leukocytes produce ROS through two mechanisms: direct and indirect. The latter occurs through the release of inflammatory cytokines, which raise the concentration of ROS. The process of phagocytosis activation results in a direct rise in ROS. The spermatozoon membrane is damaged by these oxidants, which causes an oxidative burst that drastically alters the oxidant/antioxidant ratio. This situation also arises when viruses are effectively introduced (69).

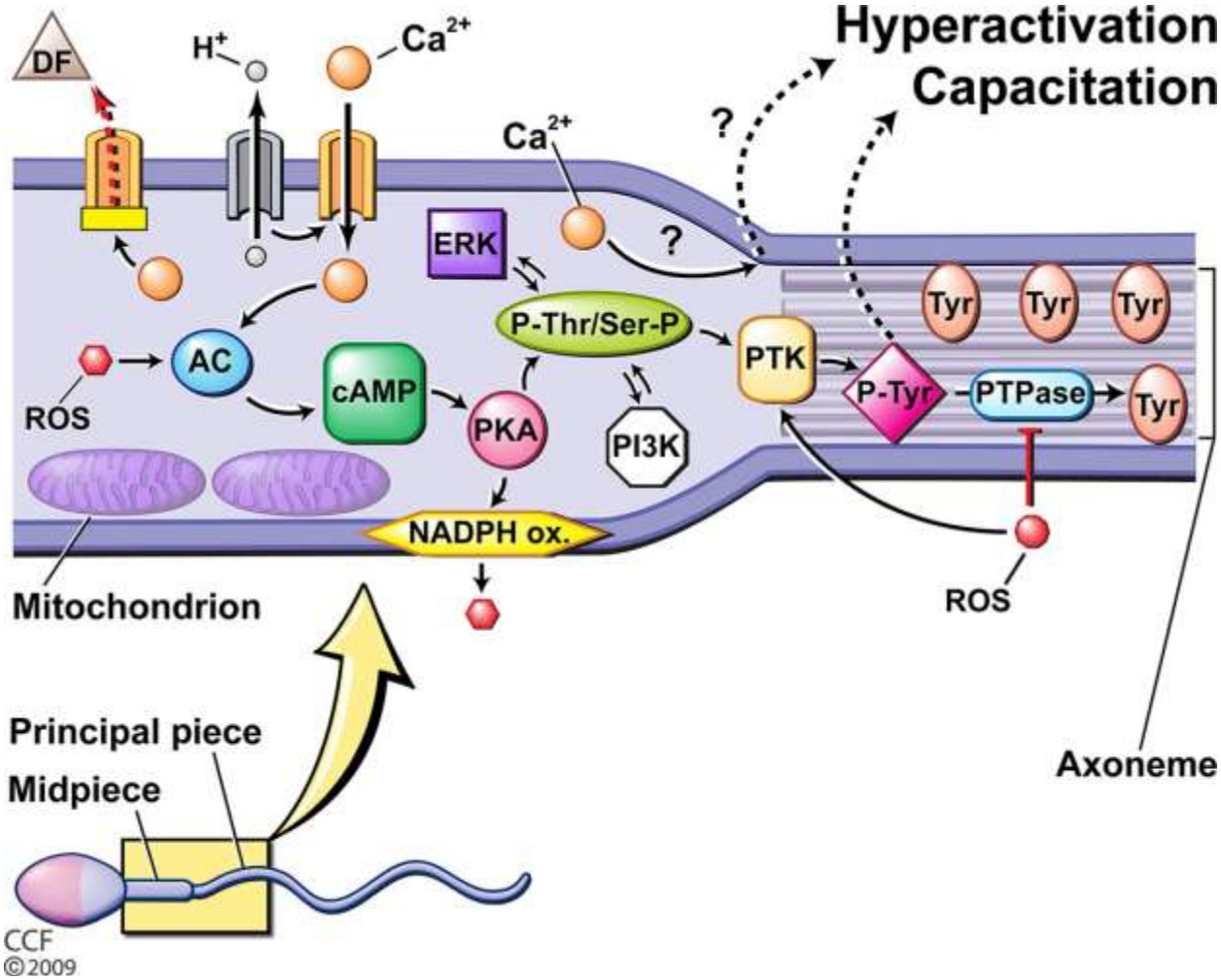

Figure 4:- Understanding the role of Role of oxidative stress, infection and inflammation in male infertility.

Polypeptide proteins called cytokines are linked to several physiological processes such as inflammation, cellular development and differentiation, and immunological response. Cytokines are released by the testes in the male reproductive system, where they play a role in steroid anabolism, mesenchymal cell differentiation, and germ cell proliferation (8, 73). An increasing amount of research has shown that cytokines and ROS interact intricately with one another. While certain cytokines control the pro-oxidant and antioxidant system as well as the formation of ROS, ROS itself increases the production of cytokines (5, 74, and 75). The connection between cytokines and ROS has been the subject of several investigations. For instance, elevated IL-6 and IL-8 concentrations cause the peroxidation process, affecting the functioning of sperm and ultimately leading to infertility during inflammation of the male reproductive tract (5). The function of the male gonad depends on the restricted concentration of cytokines, which appears to be present in seminal plasma (76). Human semen was used to study a wide range of cytokines, chemokines, growth factors, and their soluble receptors and antagonists, among other parameters (76, 77). Additionally, interleukins, IFN-g, and certain of its soluble receptors, which are found in human semen, produce tumour necrosis factor a (TNF-a), immune cells, spermatogonia, mesenchymal cells, and Sertoli cells. There have been reports on the physiological concentrations of TNF-a, IL-6, and IL-8 in human semen (76, 77). While TNF-a, TGF-b2, and TGF-b3, together with testosterone, can control spermatogenesis, cytokines are not directly implicated in apoptosis (78, 79). On the other hand, TGF-b is involved in a number of cellular processes, such as the intensity of spermatogenesis, the biological development of the testes, Leydig cells, and Sertoli cells' secretary function (80). Sperm include a variety of cytokines and immunological factors, as was previously addressed, yet it is debatable how they affect the parameters of sperm function and semen quality (81, 82).

Male Reproduction, Cellular Defence, And Oxidative Assaults.

Increased oxidative stress has been linked to a number of pathogenic diseases, including heat stress, ischemia, and inflammation, which implies it plays a significant role in male infertility (5, 83). Oxidation may readily target spermatozoa. Higher activity may result in male infertility (85), since spermatogenic cells remove oxidative DNA by apoptosis through p53-dependent and -independent processes (84). Redoxsensitive proteins, on the other hand, are thought to be ROS powerful targets during oxidative stress because they are the most vulnerable to ROS. Superoxide anion radicals (ROS), which include glutathione peroxidase (GPX) and superoxide dismutase (SOD), are neutralised by the body's antioxidant defence system. Only the ameliorative effects of ROS in male reproductive abnormalities have been documented in this assessment; a thorough assessment of an antioxidant enzymatic system in male reproduction has been explored (86, 87). The enzyme SOD stops the harmful consequences of a radical chain reaction from the beginning by converting superoxide radicals into hydrogen peroxide (88). The SOD1-encoded copper-zinc sodium dismutase is mostly found in the cytoplasm and is also partially found in mitochondria. While females lacking SOD1 are sterile, SOD1 is not linked to conditions that affect male fertility (89). Additionally, a lack of the SOD1 enzyme might lead to testicular shrinkage and an increased susceptibility to heat stress (90). When comparing aged SOD1-deficient mice to wild-type mice, the amount of sperm after greater frequencies of lipid peroxidation products was lower (91), but the correlation between fertilising capacity and animals was not detected. An isoform of manganese sodium dismutase that is found in mitochondria functions in response to inflammation and oxidative stress. Once the foetus or newborn is delivered, the lack of this enzyme is fatal (92). Additionally, it's possible for transgenic mice to express more SOD2 and become sterile; the underlying cause of this disorder is unclear (93). The SOD3 is a form of extracellular SOD that is low in spermatogenic cells and high in epididymis fluid (94). Although the presence of SOD3 in the penis has been linked to improved erectile performance in elderly mice, SOD3 knockout mice do not exhibit any discernible phenotypic alterations in male reproduction (95). Higher concentrations of SOD3 in blood plasma lengthen the half-life of nitric oxide and facilitate the superoxide radical's fast reaction with nitric oxide to generate peroxinitrite. Finally support the erection process. On the other hand, extreme SOD activity has been connected to abnormalities in human sperm motility (96), which may lead to the elimination of superoxide, indicating that SOD is crucial for sperm movement. Consequently, the question of whether superoxide is good or bad for reproductive function depends on both the source and the underlying mechanism.

Long recognised, there are several ways to produce hydrogen peroxide through enzymatic and non-enzymatic processes, and glutathione is responsible for effectively removing them. catalase, peroxiredoxin (PRDX), and peroxidase (GPX). This is demonstrated by GPX, which transfers electrons from glutathione to catalyse the reduction of several peroxidases (97), even though the roles of the many members of the gene family are diverse and intricate (98). Thioredoxin (Trx), not glutathione, gives one electron (99) and plays a variety of roles in redox processes, including ROS signalling, which is how peroxiredoxins (PRDXs) catalyse the reductive elimination of hydrogen peroxide.

Pollen And Seminal Blood Plasma Exhibit Stress Caused By Oxidation.

Oxygen-based radicals having one or more unpaired electrons are known as free radicals, or ROS (100). Hypochloric acid, singlet oxygen, hydrogen peroxides, lipid peroxide, and ozone are examples of non-radicals, whereas hydroxyl, superoxide, peroxyl, and lipid peroxyl are examples of free radicals (101). Superoxide anion, hydrogen peroxide, and hydroxyl radicals are the three most significant ROS from sperm. Because of their great reactivity in nature, they have very short half-lives (10−9 s for hydroxyl radicals and 10−3 s for superoxide anion); as a result, they react at the site of formation (102, 103). Furthermore, hydrogen peroxide, which is practically a weak free radical, is created when the superoxide anion dismutates (104, 105). Following their production, superoxide and hydrogen peroxide travel through many cellular processes before undergoing the Fenton and Haber-Weiss reaction, which turns them into very potent hydroxyl radical free radicals (106). Furthermore, superoxide anion combines with nitric oxide to generate peroxynitrite. It is also thought of nitric oxide as a reactive free radical with an odd number of particles (105, 107). Leukocytes and immature spermatozoa are the main causes of ROS generation in men (85). Sperm failure has been associated with leukocytes, particularly neutrophils and macrophages, and their overproduction of reactive oxygen species (ROS) (101, 108).

Semen Characteristics And Oxidants.

Extremely common knowledge that spermatogenesis requires low levels of ROS. In the presence of antioxidants, ROS production is essential for spermatogenic activities to take place. Antioxidants, like hydrogen peroxide, aid in the process of sperm capacitation, which facilitates the attachment of spermatozoa to the zona pellucida and

subsequent fertilisation of the egg (9, 83). Notably, catalase keeps sperm motility intact while simultaneously causing H202 to break down (5). Oxidative stress is eliminated and redox status is balanced thanks to the interaction between H202 and catalase. The byproducts of mitochondrial oxidative metabolism are free radicals. In mitochondria, oxygen reduction takes place in response to these events (5). According to research, mitochondria are often found in the sperm's midpiece, and their DNA is more susceptible to mutation than nuclear DNA.Consequently, it increases the formation of ROS from DNA (109). In males with infertility issues, there is a report of increased generation of reactive oxygen species (ROS) which has been linked to the activation of cytochrome-c, a protein implicated in programmed cell death (110). The formation of ROS by mitochondria is a major factor in DNA damage, as previous research has shown (111). In vitro blastocyst development may suffer as a result of ROS-induced DNA damage (112). Furthermore, polyunsaturated fatty acids, which are mostly found in the membrane of sperm, are essential for membrane fusion (9). Seminal fluid, however, is a vital source of antioxidants in semen because there is limited room for antioxidant enzyme translations because to the spermatozoa's lack of cytoplasm and DNA compaction (113). As previously indicated, ROS may readily target the delicate sperm membrane structure, which in turn impacts sperm motility (114). Figure 3 shows the beneficial and detrimental effects of ROS on male infertility.

The Effects Of Oxidative Stress And Seminal Plasma Proteomes.

Numerous proteins have been suggested as potential indicators of oxidative stress (OS) damage. Wang and associates propose that the decrease in DJ-1 protein is a factor in the Endocrine disruptor-induced suppression of OS is a potential indicator of OS in individuals with asthenozoospermia (19). Herwig et al. found that in individuals with idiopathic oligo-astheno-teratozoospermia, tubulin folding cofactor b and increased levels of a-1 chymotrypsin and aldose reductase are related to OS (18). A further investigation revealed elevated prolactin-triggered protein expression, which is connected to sperm quality issues and OS damage (16). Mucin 5B overexpression was linked to higher levels of seminal lipid peroxidation in normozoospermic men, according to research by Intasqui and colleagues. This suggests that Mucin 5B is involved in changes in sperm transport in both sexes and may serve as a marker for lipid peroxidation brought on by OS (115). Notably, infertile individuals seldom experience large-scale OSaugmented modification of the seminal plasma proteome, although it also often occurs in individuals that are reproductive. In a recent study, stress-related proteins such haptoglobin (HP), peroxiredoxin 4 (PRDX4), and protein S100 calcium-binding protein A9 (S100A9) were overexpressed in fertile individuals with increased OS. Particularly, HP and PRDX4 exhibit antioxidant qualities; as a result, it is recognised that their overexpression contributes to the scavenging action against ROS overproduction. Proinflammatory activity is exhibited by the S100A9 protein; its overexpression in conjunction with the C3 complement demonstrates the inflammatory state brought on by OS (116). Table 1 displays the upregulation of seminal plasma proteome in patients as a result of oxidative stress.

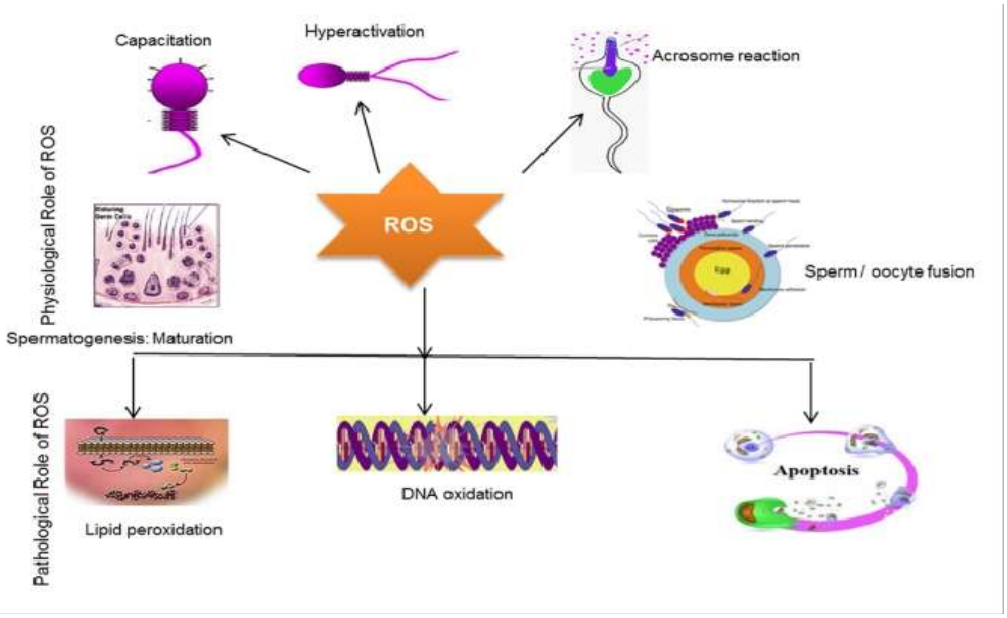

Figure 5:- The beneficial and detrimental effects of ROS on male infertility. Sperm capacitation, sperm hyperactivation, acrosomal response, sperm maturation, and sperm/oocyte fusion processes are all significantly

impacted by a restricted concentration of ROS, as the schematic picture illustrates. On the other hand, an excessive generation of reactive oxygen species (ROS) leads to oxidative stress, which damages the sperm membrane and results in lipid peroxidation and DNA oxidation, which in turn trigger apoptosis and sterility.

Diseases and lifestyle choices can cause seminal plasma OS. Heavy metals, alcoholism, cigarette smoking, and obesity have all been strongly associated with OS. Additionally, environmental elements like heavy Metals are another factor that causes too many ROS. Furthermore, a number of illnesses, including varicocele and accessory gland infection/inflammation (MAGI), can produce ROS (117). Few researchers have found that patients' SP proteomes are altered, regardless of varicocele. Furthermore, few proteins have been proposed as disease indicators, and there is no research on the differential expression of proteins with and without elevated ROS. Nonetheless, asthenozoospermic individuals with OS have been found to overexpress intelectin 1, suggesting the possibility of a genital tract infection. Similarly, overexpression of aminolevulenic acid dehydratase suggested lead exposure, while overexpression of alcohol dehydrogenase led to alcohol metabolism, according to a research. Thus, it demonstrates how sperm quality is negatively impacted by environmental and lifestyle variables because of the overproduction of free radicals (19). Provides excellent illustrations of further in-depth information addressing the role of male infertility issues (118).

Proof Of Oxidative Stress And The Sperm Transcriptome Profile.

Spermatogenic activities are thought to involve RNAs, as sperm cells have an active transcriptional programme (119). Many processes, including fertilisation, are assumed to be mediated by sperm RNAs (119, 120). Furthermore, it has been established that sperm RNAs indicate fertility (120, 124, 125) and the sperm quality index (121–123). Interestingly, coding and non-coding RNAs have been found in sperm (123, 126) and may have an impact on sperm activity. Bulls with limited fertility had dysregulated transcripts in 559 of them, according to a DNA microarray. Notably, transcriptions relating to the oxidation reduction process, MMP mediation, apoptosis, and NOS3, SOD, BAK, and PRDX6 have all been connected to fertility. This work offers a development pathway for indicators associated with male infertility (127). According to the transcriptome profile of bulls, non-coding RNAs (ncRNAs) have a role in controlling sperm motility (128). Male fertility and spermatogenesis are primarily regulated by noncoding RNAs (ncRNAs), yet there is little research on ncRNAs in oligozoospermia in humans. Twelve human normalozoospermia and oligozoospermia samples' sequencing data of lncRNA and mRNA showed that male infertility is associated with altered expression of lncRNAs (DE lncRNAs) and mRNAs (DE mRNAs). To find them and look at their potential roles, the Gaussian graphical model, gene ontology, and Encyclopaedia of Genes and Genomes pathways were utilised. The transcriptome data demonstrated that in individual oligozoospermia participants, PERK-EIF2 pathway-induced ER stress, oxidative stress, and apoptotic sperms were all impacted by the accumulation of unfolded proteins in sperm ER, DE lncRNAs, and DE mRNAs, along with their target genes. This implies that these lncRNAs and pathways may be used as a target for infertility therapy. Regarding the semen transcriptome profile's connections with oxidative stress, there is limited data. To ascertain if oxidative stress has a role in male infertility issues, more research is necessary (129).

Table 1:- Over expressed seminal plasma proteins in patients showing signs of oxidative stress.

S. N.	Seminal Plasma Protein	Functions	References
1	Aldose reductase	Through the polyol pathway (glucose metabolism), transforms glucose into sorbitol.	(18)
2	a1-chymotrypsin	The chymotrypsin-specific substrate N-Succinyl-Ala-Ala-Pro-Phe-p-nitroanilide is the target of proteolytic action, which is thereafter released in granulocytes.	(18)
3	DJ-1	ROS catalysis is caused by DJ-1 activation. After it is triggered, inhibit DJ-1 to eliminate the NFkB signal.	(19)
4	Haptoglobin	Inflammatory protein in the late positive acute phase.	(116)
5	Mucin 5B	Increases SP viscosity and is connected to OS, hypoxia, and inflammation.	(115)
6	Peroxiredoxin 4	Belongs to a family of enzymes that breaks down peroxide and helps regulate the operating system of cells.	(116)
7	Prolactin-induced protein	Protein found in extracellular matrix that may control how tissues react to inflammation.	(16)

8	Protein S100A9	Pivotal in cell differentiation and OS response	(116)
9	Tubulin-folding cofactor b	Plays a role in the formation of a/b-tubulin heterodimers, which are necessary for mammalian cell proliferation. Helps the hypoxic-ischemic damage process to progress.	(18)

NFkB, nuclear factor kappa light chain enhancer; OS, oxidative stress; ROS, reactive oxygen species; SP, seminal plasma; S100A9, S100 calcium binding protein A9.

Many RNA-seq researches have tried to describe the ejaculated spermatozoa's transcriptome in terms of fertility and sperm quality. Seasonal variations exist in the quality of semen. Among the sperm RNA, 4,436 coding genes with moderate to high abundance have been found. Genes related to spermatogenesis, chromatin compaction, and fertility showed an increase in transcript fragmentation. The transcriptome profiles of the summer and winter ejaculates differed considerably, with 34 coding genes and 7 microRNAs exhibiting a different distribution. These genes have been associated with autophagy, DNA damage, and oxidative stress. Pig sperm quality indicators were identified by annotating the boar sperm transcriptome profile (130). The contribution of transcriptome variables to male infertility is displayed in Table 2.

Table 2:- Effect of transcriptomic factors on male infertility.

S.N.	**miRNA/ transcriptomic factors**	**Regulatory influence**	**Outcomes**	**References**
1	miR-196a-2, miR-196a-5p,miR-141, miR-429, and miR-7-1-3p	Upregulation	Idiopathic male infertility	(131, 132)
2	miR-424	Downregulation	Idiopathic male infertility	(133)
3	MiR-371a-3p	Upregulation	Sperm concentration and total sperm count	(134)
4	piR-31068, piR-31098, piR-31925, piR-43771, and piR-43773	Differentially expressed/ downregulation	Asthenozoospermia	(135)
5	miR-19b and let-7a	Upregulation	Idiopathic infertility	(136)
6	miR-192a	Upregulation	Germ cell apoptosis	(137)

The Breakdown Of Dna And Oxidative Damage.

Through interactions with several biological components, the overproduction of ROS may contribute to male infertility by causing damage to sperm (138, 139). Lipid peroxidation and protein oxidation are achieved by the use of many molecular processes in this process. Specifically, OS causes the DNA to produce oxidised DNA adducts, such as 8-hydroxy-2'-deoxyguanosine (8OHdG), which can break the DNA strands single or double (140). Furthermore, ROS induces nucleases and caspases that support apoptotic pathways, which results in indirect sperm DNA damage through premature apoptosis (141). Currently, measurements of total antioxidant capacity (TAC) (143), malondialdehyde (144), intracellular ROS (142), or DNA damage (8-OHdG) (145) are used in research to measure oxidative stress. These parameters have been found to be significant sperm damage markers in infertile patients (146–148) and to be markers of OS. Additionally, damage to sperm DNA has been connected to assisted reproductive technologies and has been shown to reduce sperm fertility as well as embryo development during natural conception (149–151). It's interesting to note that individuals who are infertile may benefit from antioxidant supplements or lifestyle modifications, thus measuring oxidative stress may be relevant (152). These factors highlight the urgent need for novel diagnostic techniques as well as better understanding of the relationship between sperm DNA damage and seminal plasma oxidative stress. Recently, OS was measured using a brand-new galvanostat-based method. The oxidation-reduction potential (ORP) of semen is measured using this method to ascertain the ratio of oxidants to reductants (153).

During their development, spermatozoa acquire an enzyme called one-base excision repair (BER), which is useful for repairing DNA. 8-oxoguanine DNA glycosylase 1 (OGG1) is an enzyme that helps excision of DNA base adducts, which liberates adducts into the extracellular environment (154, 155). APE1 (apurinic endonuclease 1) and XRCC1 (x-ray repair cross-complementing protein 1) are examples of BER enzymes that are absent from spermatozoa. Spermatozoa's sensitive DNA repair capacity is caused by this, and as a result, oxidised DNA base adducts such 8-OHdG may be repaired (155). Additionally, research has shown that 8-OHdG causes germline mutations in human spermatozoa, which in turn damages DNA indirectly (156).

Preventative Measures For Male Infertility.

To better understand the extent and frequency of male infertility, which is a very worrisome issue, not much attention has been paid to it. Numerous idiopathic reasons contribute to male infertility. The necessity to address the issue and look into preventive measures has therefore arisen (157).

To prevent male infertility issues, the following strategies should be taken into consideration:

1. **Maintain a Healthy Lifestyle:** Adopting a healthy lifestyle is crucial for preventing male infertility. This includes maintaining a balanced diet rich in vitamins and minerals, regular exercise, and avoiding excessive consumption of alcohol and tobacco.
2. **Manage Stress Levels:** Chronic stress can negatively impact reproductive health. Engage in stress-reducing activities such as yoga, meditation, or hobbies to help manage stress levels and promote overall well-being.
3. **Avoid Excessive Heat Exposure:** Prolonged exposure to high temperatures, such as hot baths, saunas, or placing laptops directly on the lap, can raise testicular temperatures and affect sperm production. It's advisable to avoid such exposures, especially for extended periods.
4. **Maintain a Healthy Weight:** Obesity can contribute to hormonal imbalances and reduce fertility. Maintaining a healthy weight through proper diet and regular exercise can positively impact reproductive health.
5. **Protect Against Sexually Transmitted Infections (STIs):** Certain STIs, such as chlamydia and gonorrhea, can lead to infertility if left untreated. Practicing safe sex and getting regular screenings are essential preventive measures.
6. **Limit Exposure to Environmental Toxins:** Exposure to environmental toxins, such as pesticides, heavy metals, and industrial chemicals, can affect sperm quality. Minimize exposure to these substances in both personal and occupational settings.
7. **Stay Hydrated:** Dehydration can lead to a concentration of salts and minerals in the semen, affecting sperm motility. Maintaining proper hydration levels is important for overall health and fertility.
8. **Get Regular Exercise**: Moderate, regular exercise can contribute to overall health, including reproductive health. However, excessive exercise, especially endurance training, may have a negative impact on fertility, so balance is key.
9. **Address Hormonal Imbalances:** Hormonal imbalances, such as low testosterone levels, can affect sperm production. Consult with a healthcare professional if there are concerns about hormonal imbalances and explore appropriate treatments.
10. **Seek Early Intervention for Reproductive Issues:** If a couple is having difficulty conceiving, it's important to seek medical advice early. Consulting with a fertility specialist can help identify any underlying issues and explore potential treatments or interventions to improve fertility. Early intervention may increase the chances of successful conception.

Conclusions:-

Finally, we have addressed the role proteomic studies play in male infertility as well as the connection between oxidative stress and infertility in males. We have examined the values of distinct protein profiles in seminal plasma under healthy and oxidative circumstances. In addition to being acknowledged as a potential marker or indication of the prevalence of oxidative stress, the proteomic profile of seminal plasma may be crucial in minimising oxidative stress. The pathway analysis shows how proteins contribute to cellular, metabolic, regulatory, and stress processes while keeping the literature in mind. The reviewed literature in this review will aid in the investigation of the main factors leading to idiopathic male infertility. Ideally, male infertility will be acknowledged at a molecular level, as well as its diagnosis, treatment, and avoidance. Determining which mechanism should be addressed in normozoospermic settings proved to be a challenging task. Nevertheless, this situation remains unfinished, and more investigation is required to create diagnostic tests based on methylation patterns, such as phosphorylation and RNA profiles. We also emphasised the usefulness of intact sperm DNA as a diagnostic for infertility that remains unexplained. Omics technologies are anticipated to be used in the diagnosis of idiopathic fertility in the next years.

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In conclusion, the accomplishment of this project successfully demonstrates the teamwork, commitment, and hard work of a wide range of people and organization. We are appreciative of the chance to enhance our knowledge of the effects of oxidative stress on male fertility and eagerly anticipate more developments in this important area of study.

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