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Insights of Sperm Pathology and Its Association with Infertility

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Abstract

This section considers the structural characteristics of spermatozoon, its assembly, composition, and mechanism behind regulation of their peculiar function. The spermatozoon is tremendously peculiar cell with an arrangement of structural characteristics which furnish it with remarkable capability of carrying the genome of male to the egg. A variety of genes are only expressed in spermatids and result in the formation of proteins that are very crucial and distinctive to spermatozoa. These proteins package the DNA, form the head of sperm, account the component of matrix and enzymes of acrosome, construct the flagellar structure, and work as ion channels that are associated in modulating the motility of sperm and also become adenylyl cyclase which yields cyclic adenosine monophosphate (cAMP) to induce signaling effect which regulates the function of spermatozoon. These proteins are critical essential to sperm and, sometimes, mutation inhibits their synthesis or disrupts their function which leads to male infertility. Researchers are trying to identify those proteins that are significant for proper function of sperm through gene knockout approach in mice that are probable to be necessary in humans as well. However, various questions still persist regarding the spermatozoon composition, organization, and function and need to be answered.

Keywords: sperm, spermatogenesis, ROS, infertility, oxidative stress, motility

1. Introduction

Male reproductive function can be divided into three subdivision: (i) hormonal balance of male reproductive function (ii) spermatogenesis, development of sperm; and (iii) fulfill of male sexual act.

Spermatogenesis begins within the seminiferous tubules of testis through the successive mitotic, meiotic and post meiotic phases which results in the formation of spermatozoon, the end product of this process. To expand the spermatogonial population, the germ line stem cell during the mitotic phase undergo a series of division which culminates into two meiotic division and formation of haploid spermatids without the replication of DNA. For the development of male gametes these two phases are very significant. During this phase the remodeling of spermatids occurs extensively into sperm by acrosome formation, condensation of nucleus, development of flagella and loss of cytoplasm. The head and flagellum are the two-substantial component of sperm. These two components are joined together by a connective piece. The head carries the nucleus, cytoskeleton element and cytoplasm. It comprises various types of enzymes homogeneous to

lysosomes of a typical cell, including hyaluronidase (having the ability to digest proteoglycan filaments of tissue) and powerful proteolytic enzymes which can digest proteins having an important role in the process of oocyte fertilization. The flagellum is divided into three regions: mid piece, principle piece and terminal piece. A central complex of microtubules covered by outer dense forms the axoneme. Mitochondria are present in the mid piece which surrounds the outer dense fibers and neighboring axoneme. The principle part of the flagellum is mostly comprised by the existence of fibrous sheath which surrounds the dense fibers and axoneme. In higher vertebrates these dense fibers and fibrous sheath are developed due to internal fertilization and these are cytoskeletal material of sperm flagellum [1]. The plasma membrane as in sperm head surrounds the flagellum tightly and contains scattered cytoplasm. Invertebrate's sperm usually have an acrosome in the head region and mitochondria and an axoneme in the flagellar region but the accessory or additional cytoskeletal elements are absent [2]. To achieve the fertilization the acrosome, have an enzyme which plays a key role to penetrate into egg. The flagellum of the sperm contains the source of energy that generates sperm motility required to reach the egg. All these characteristics of sperm are necessary to deliver the genetic material exists in sperm nucleus to egg. After that, zygote is formed by the fusion of haploid pronuclei of male and female, and thus development initiates. In most mammals, the nucleus of haploid sperm carries the sex chromosome decides the sex of resulting animals [3]. The genome of both maternal and paternal parents is essentially required to proceed the normal development, generally due to distinctive genes imprinting in males and females during gametogenesis [4, 5].

This chapter gives center of attention on the unique features of mammalian spermatozoa with especial consideration to molecules presently known that enrich to the structure and function of sperm. The main topics contemplated are; physiology of male sexual organ, spermatogenesis, sperm count, heritable effect on human sperm structure, regulation of sperm motility, effect of oxidative stress on male reproductive system, sources of reactive oxygen species in seminal plasma, physiological role of ROS in seminal plasma, consequence of Oxidative Stress on male Reproductive System, management and prevention of oxidative stress, correlation between biology of male reproduction and sleep and role of inflammation in infertility.

2. Physiology of male sexual organ

The favorable outcome of male reproductive system depends mainly upon the cohesive function of vast array of tissues. It comprises of assembly of sperm in the testes, sperm maturation in epididymis, secretion of seminal fluid by addition sex glands, deliver sperm into the reproductive tract of female, erection of penis, emission and final ejaculation. Fertilization of the egg requires the motility of sperm, successful capacitation and acrosomal reaction. These entire needs are dependent directly or indirectly on the secretion of testosterone hormone by the Leydig cells. The testis of male is comprised of up to 900 coiled seminiferous tubules, in which the sperm is formed and each seminiferous tubule exceeds up to 1 meter long in average. The sperm then discharged into one more coiled tube which is about 6-meter long known as epididymis. The epididymis enlarges into vasa deferens that infiltrates into prostate gland. There are two seminal vesicles and the material (Is secreted) from both the ampulla and seminal vesicles. The excretion from both the prostate gland and seminal vesicles enters into the ejaculatory duct through the body of prostate gland and then vacant into the internal urethra. Mucus released

from urethral gland and more from bilateral bulbourethral glands which is located near to urethra is supplied to urethra [6].

3. Spermatogenesis

The process of spermatogenesis takes place in each of the testis tubules. In this process the spermatozoa are produced by the population of germ cells (spermatogonia) through process of mitosis and meiosis. This entire spermatogenesis process starts during the onset of puberty and last till the old age. This process involved various stages starting with germ cells formation in the germinal epithelium and followed by continuous development into primary and secondary spermatocytes. These spermatocytes finally developed into functional spermatozoa. Spermatogenesis is extremely well-ordered process; male germ cells proliferate and differentiate rapidly and the modulation of spermatogenesis occurs at the extra testicular and intra testicular level and can be dispersed ubiquitously. As aforementioned, spermatogonia originated from the primordial germ cells that migrate into the genital ridge of the indifferent gonads, during embryo development and are present in two to three layers in seminiferous tubules. At puberty, the spermatogonia starts mitotic division, proliferate and differentiate continuously to form mature sperm cells [7] (**Figure 1**).

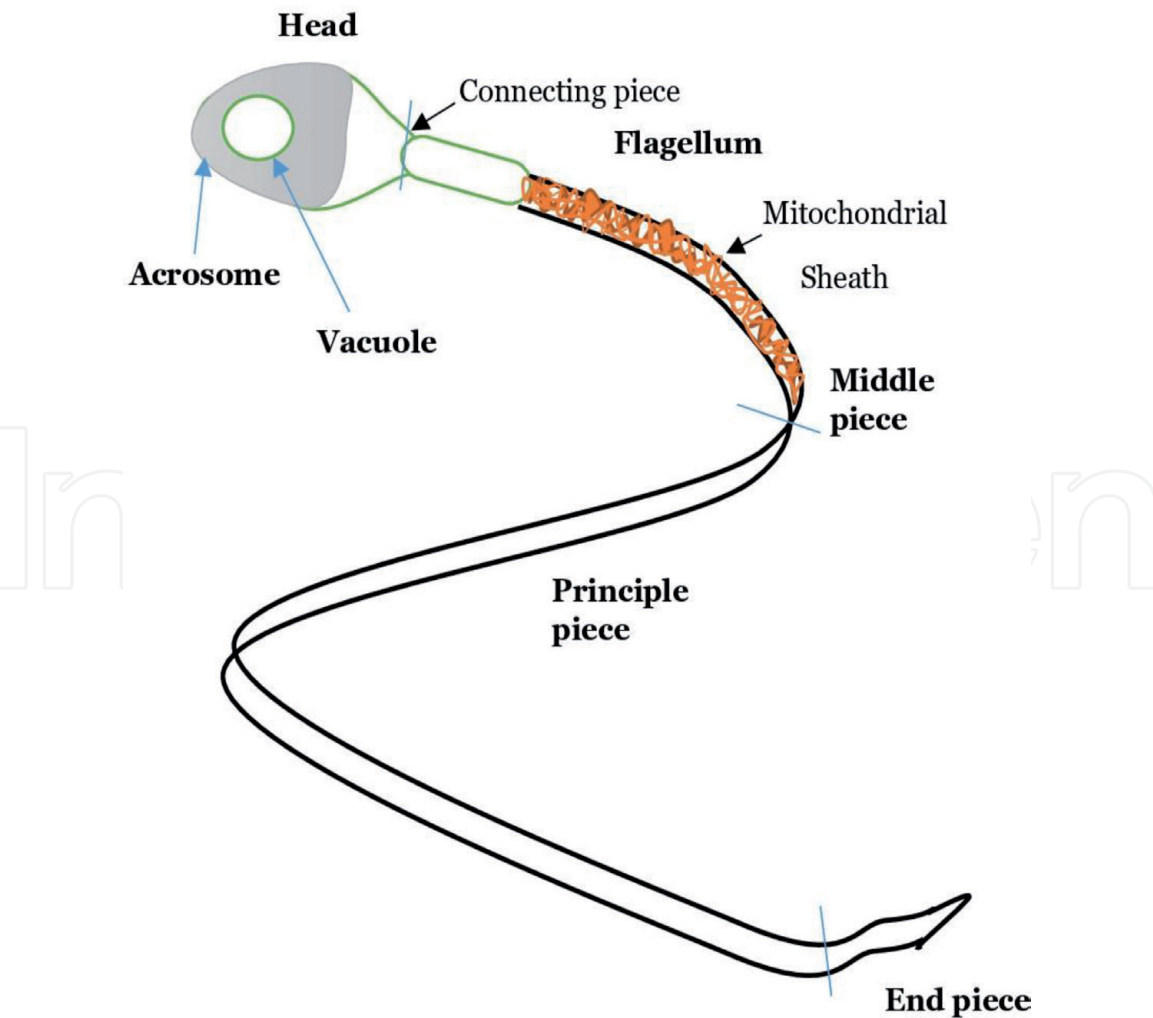


Figure 1.
General characteristics of germ.

3.1 Steps of spermatogenesis

The process of spermatogenesis starts at an average age of 12–13 years, continues throughout the remaining life, and markedly decreases during the older age. During the initial stage of spermatogenesis, the spermatogonia shift toward the central

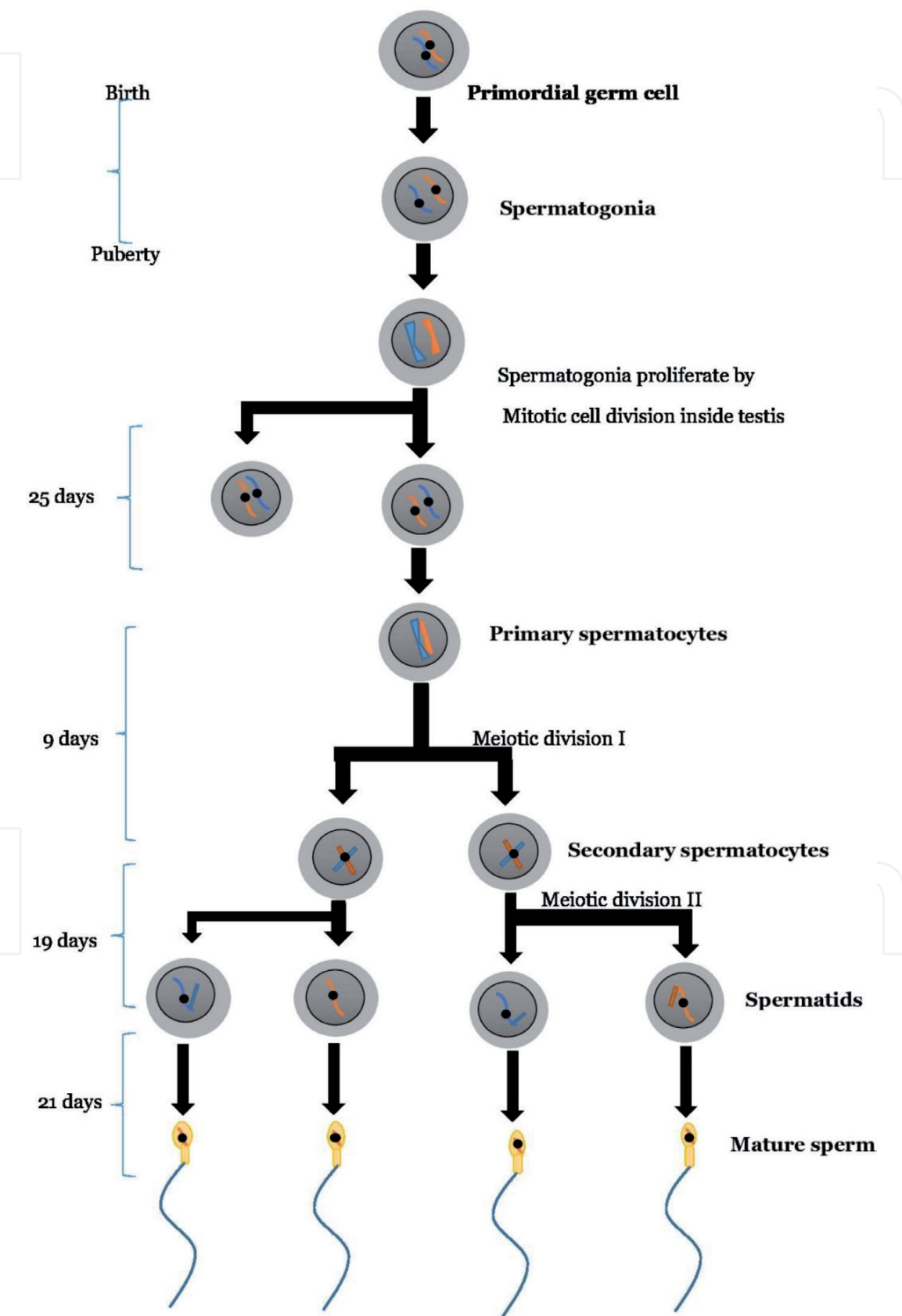


Figure 2.
Steps of spermatogenesis.

lumen of seminiferous tubules. The Sertoli cells are part of a seminiferous tubule and support the process of spermatogenesis. Its main function is to nourish the developing sperm cells throughout the stages of spermatogenesis. Sertoli cells control the entry and exit of nutrients, hormones and other substances into the tubules of the testis. The Sertoli cells are also responsible for establishing and maintaining the spermatogonial stem cell niche, which ensures the renewal of stem cells and the differentiation of spermatogonia into mature germ cells, that progress stepwise through the long process of spermatogenesis, ending in the release of spermatozoa.

3.2 Meiosis

Spermatogonia which are able to pass across Sertoli cell layer change and grow in size progressively into primary spermatocytes. The two secondary spermatocytes are formed by meiotic division from the primary spermatocytes. These secondary spermatocytes, also divide to produce spermatids that transform into sperm after a period of time. During the process of spermatocyte to spermatid stage transformation, the 23 pair of chromosomes (46 chromosome total) of spermatocytes also divides, and as a result, 23 chromosomes go to one spermatid and the rest 23 chromosomes to the other spermatid. It takes about 74 days to complete the entire process of spermatogenesis, from spermatogonia to spermatozoa [6] **Figure 2**. Suggested: Round and elongated spermatids will differentiate into mature spermatozoa, by the process of spermiogenesis.

4. Sperm motility

Motility of sperm cells is provided by the back-and-forth movement of tail and it results from rhythmic longitudinal sliding motion between the anterior and posterior tubules [8]. Different molecular markers of sperm, such as mitochondrial membrane potential (MMP), DNA fragmentations and ROS have presently concluded as reliable estimators of sperm function that can be used to evaluate the quality of the sperm [9]. Due to the overloading of ROS, osmotic stress is increased which in turn decreases the MMP and increases the fragmentation of DNA, affecting the viability of sperm [10]. It is broadly accepted that motility of sperm mainly depends upon ATP which is produced by the mitochondria. The latest is located in mid piece of spermatozoa, which explains the correlation between motility and mitochondrial membrane potential [11, 12].

4.1 Sperm count: how much is considered normal?

The spermatozoon is the cell of male reproductive system. Sperm count, also known as sperm concentration, is the parameter to measure the number of sperm cells in the ejaculate. During each coitus the quantity of ejaculated semen in average, is about 3.5 milliliters, and 120 million sperm might be present in average in each milliliter of semen. However, in normal males this count can vary from 35 to 200 million. In several milliliters of each ejaculated semen, an average of total of 400 million sperms might be present. When the sperm count is less than 20 million in 1 milliliter (ml), it might point to infertility. A relatively high sperm count might elevate the chances of conception [6].

There are several causes of infertility in males such as genetic factors like cryptorchidism, congenital absence of vas deferens, karyotype abnormalities and some acquired factors like trauma, varicocele, medication, urogenital infection, inflammation, testicular torsion and idiopathic factors.

Semen deficiencies are termed as

- a. Oligospermia or oligozoospermia—lower than normal number of spermatozoa in semen.
- b. Aspermia—complete lack of semen.
- c. Azoospermia—absence of sperm cells in semen.
- d. Hypospermia—reduction in the seminal volume.
- e. Teratospermia—abnormal morphology of sperm cells.
- f. Asthenozoospermia—reduced motility of sperm.

4.1.1 Oligospermia

Oligospermia, is one of male infertility causes, defined as low concentration of sperm cells in the ejaculate. Semen with decreased concentration of sperm may often depict considerable abnormalities in morphology and motility of spermatozoa. Low sperm count may be due to an endocrinopathy such as varicocele, prolactinoma or it may be a genetic cause. In about 6 and 15% of patients with severe low sperm count or azoospermia (respectively), microdeletions can be found in azoospermic factor (AZF) region of Y chromosome. AZF refers to one of several proteins or their genes, which are coded from the AZF region located in the human male Y chromosome. Deletions in this region are associated with inability to produce sperm. Subregions within the AZF region are AZFa, AZFb and AZFc, located in the long arm of Y chromosome [13]. By cytogenetic analysis, chromosomal abnormalities were detected in 2% of men having low sperm count and 15–20% with no sperm count. These abnormalities include translocation of nonsex chromosome and Klinefelter syndrome [14].

4.1.2 Asthenozoospermia

Asthenozoospermia, low sperm motility, could be derived due to:

- A.** Inborn metabolic deficiency (such as Kartagener's syndrome or immotile cilia syndrome—ICS).
- B.** Abnormal ultrastructure of the sperm flagellum: as primary ciliary dyskinesia; spermatozoa consist of altered peri-axonemal structure but have normal axoneme. Dense individual fibers are extended abnormally along the axoneme, location and number of longitudinal columns of fibrous sheath are modified and change in the order of termination of these structures [15].

Sperm with the following syndromes: abnormal axoneme, partial or complete lacking of dynein (a family of cytoskeletal motor proteins that move along microtubules in cells and convert the chemical energy stored in ATP to mechanical work), lack of central sheath and lack of inner arms might be unable to show motility;

- C.** Necrozoospermia—binding of antisperm antibodies or an increase in white blood cell concentration in the ejaculate, which later results in the

overproduction of reactive oxygen species, might lead to damages in the spermatozoa [16].

- D. Dysplasia of fibrous sheath spermatozoa: spermatozoa with very short, thick, rigid and immotile tail, mainly due to disorganized and hyperplastic fibrous sheath [17, 18].

5. Heritable effect on human sperm structure

The hereditary condition which causes the defects in the flagella of sperm is termed as Kartagener's syndrome, immotile cilia syndrome (ICS), or primary ciliary dyskinesia (PCD). It often leads to chronic respiratory problems, male sterility and situs inversus [19]. These states are linked directly or indirectly with the autosomal recessive traits. The aforementioned conditions make the flagella unable to show normal movement. Sperm with these syndromes have abnormal axoneme lacking dynein arm partially or completely, lack of central sheath, lack of inner arms [20]. Due to variety of defects presented in sperm and cilia, many genes are mutated and contribute to the syndrome [21]. Another flagellar defect characterized by severe asthenozoospermia is familiar as dysplasia of fibrous sheath. In this type of disorder, the sperm have disorganized and hyperplastic fibrous sheath, and very short, thick, rigid and immotile tail [17, 18]. Another flagellar defect which appears in sperm cells of infertile men is known as flagellar dyskinesia [15]. This type of defect was observed in brothers and has been suggested that it arises due to the genetic abbreviation [22]. The sperm consist of altered peri-axonemal structure but have normal axoneme. Densed individual fibers are extended abnormally along the axoneme location and number of longitudinal columns of fibrous sheath are modified and else, there are changes in the order of termination of these structures [15].

6. Regulation of sperm motility

Sperm depicts two kinds of motility:

- a. Progressive motility—typical for newly ejaculated sperm.

Spermatozoa acquire the ability of progressive motility in the epididymis. Relatively symmetrical motion of flagella which leads to forward movement has been shown in this type of motility [23].

- b. Hyperactivated motility—after sometimes either in reproductive tract of female or in culture, sperm achieves the hyperactivated motility that is characterized by whip like beating of flagellum, asymmetrical flagellar bends and circular swimming [24].

6.1 Activation of motility

It is broadly acquired that precious motility of sperm is the chief component of fertility of male. During the beginning of progressive motility and origin of hyper activation of sperm, key factors are involved. These key factors are calcium (Ca^{2+}), cyclic adenosine monophosphate (cAMP) and bicarbonate (HCO_3^-). Olfactory and GABA receptors are the possible candidates which trigger the progressive and hyperactivated motility of sperm.

6.2 Role of calcium in motility

Calcium plays a key role in sperm function by different aspects. Recent studies have been demonstrated that in knockout mice there are at least four components participate in the intracellular regulation of calcium level and initiation of sperm motility. These are CatSper1, CatSper2, $Ca_v2.3$ and PMCA4. CatSper1 are localized in the principle piece of sperm and it is a voltage gated Ca^{2+} channels of the testis. Lacking or any mutation in CatSper1 gene reduces the progressive motility and causes infertility. A sperm cell that lacks the CatSper1 showed progressive motility but failed to develop hyperactivated motility [25]. CatSper2 present in flagellum shows similarity to CatSper1 and it is also a voltage-gated ion channel. Sperm of mice having knockout CatSper2 gene depict decreased flagellar amplitude and also failed to develop hyperactivated motility [26]. Disruption of gene for PMCA4, that have Ca^{2+} /calmodulin dependent ATPase activity involve in efflux of Ca^{2+} , also causes infertility in men. In developing sperm cells and sperm flagellum the cyclic nucleotide gated Ca^{2+} channels are present. The role of these channels is to regulate the influx of calcium in various micro domains of the flagella [26].

6.3 cAMP and motility

During sperm motility regulation, cAMP is the second key messenger. Adenylate cyclase converts the ATP into cAMP. Thus, the level of cAMP increases and in turn activates the cAMP dependent kinase A (PKA) which phosphorylates the serine and threonine residues in the flagellum, which ultimately causes the phosphorylation of tyrosine residues in the proteins [27, 28]. In most cells the adenyl cyclase is activated by G protein in response to external stimuli. In mouse sperm the plasma membrane bounds (mACs) activated by G protein take a part in the acrosome reaction, and in chemotaxis and hyperactivation in human sperm [29]. It was

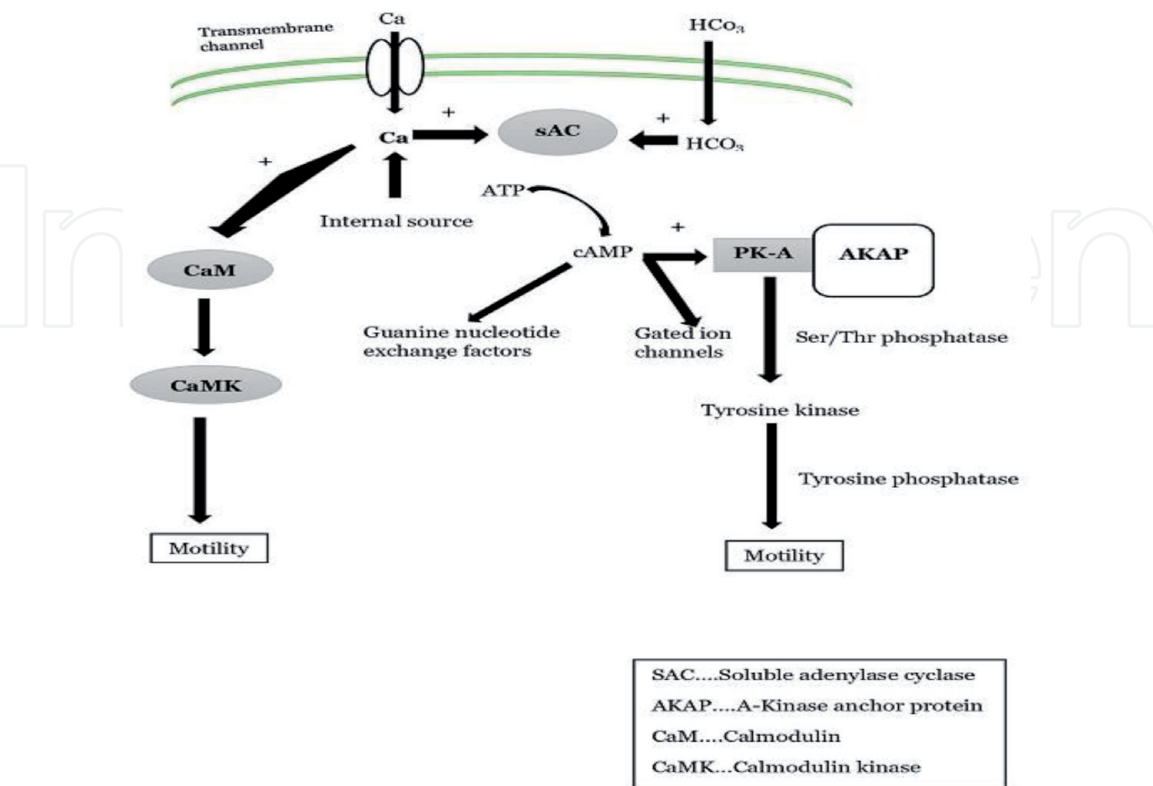


Figure 3.
Signalling pathway showing regulation of motility of sperm in mammals.

demonstrated that HCO_3^- and Ca^{2+} are inculcated in cAMP regulated activation of sperm motility. The activity of soluble adenylyl cyclase is augmented by HCO_3^- with increased activation of enzymes (adenylyl cyclase) and by reducing the substrate inhibition that happens at higher concentration of ATP-Mg^{2+} . Due to low level of HCO_3^- , activity of soluble adenylyl cyclase would be reduced in sperm by substrate inhibition stored in epididymis [30].

6.4 PKA and motility

PKA causes the phosphorylation of tyrosine residue of flagellar proteins. The proteins anchoring with PKA site (AKAP3, AKAP4 and TAKAP-80) in the fibrous sheath, point out that the main role of this structure is to bind PKA in the principle piece of flagellum [31]. Regulatory and catalytic subunits are present in PKA holoenzyme. Four genes ($\text{RI}\alpha$, $\text{RI}\beta$, $\text{RII}\alpha$ and $\text{RII}\beta$) are present in regulatory subunits (R subunit) in human and mouse; three catalytic (C subunit) $\text{C}\alpha$, $\text{C}\beta$ and $\text{C}\gamma$ in human, and two C subunit $\text{C}\alpha$ and $\text{C}\beta$ in mice. The cAMP binding site are present in R and C subunits. C subunits is released when cAMP binds to R subunits and their catalytic site is activated by cAMP. The R and C subunits are involved in the motility of sperm (**Figure 3**).

7. Effect of oxidative stress on male reproductive system

Oxidative stress is a state which causes disproportion between systemic reactive oxygen species and detoxifying capability of biological system to neutralize the reactive intermediates, also called antioxidant defenses. Spermatozoa have antioxidant defense mechanism that quench the ROS and therefore protects the cells of gonads and mature spermatozoa from oxidative damage [32]. Statistics from United States depicted that the major cause of male infertility is ROS. In 30–40% of infertile men's seminal plasma, there is an increase in the level of ROS [33]. In spermatozoa ROS are generated by two methods.

1. At the level of sperm plasma membrane—by nicotinamide adenine dinucleotide phosphate oxidase system.
2. At the level of mitochondria—by nicotinamide adenine dinucleotide-dependent oxidoreductase reaction [34].

The production of ROS at the level of mitochondria is the chief source. Large concentration of mitochondria is present in spermatozoa because of a constant need of energy to spermatozoa for motility. In semen, presence of nonfunctional spermatozoa considerably increases the level of ROS that in turn impair the function of mitochondria and motility of sperm. In human spermatozoa, ROS which is produced in large concentration is O_2^- . It reacts with itself to generate H_2O_2 by dismutation. H_2O_2 and O_2^- generates most destructive and reactive OH^- by Haber-Weiss reaction in the presence of iron and copper. OH^- affects the function of sperm by disrupting the fluidity of membrane [35, 36]. Recent studies depicting that O_2 production in spermatozoa showed the presence of calcium dependent NADPH oxidase also called NOX5 has been residing in acrosomal and midpiece region of spermatozoa [37]. Initially the NOX5 resides in human testis. It is activated upon binding of calcium to its cytosolic domain and causes conformational changes in cells [35]. ROS is generated during the normal metabolism of cells. Under physiological conditions the mitochondrial respiration is the chief source of superoxide anion radicals. Quality of sperm and function is affected by the high concentration of ROS and is potentially toxic.

8. Sources of reactive oxygen species in seminal plasma

The production of ROS in the seminal plasma originated from different endogenous and exogenous pathways. Ejaculate of human contains varieties of mature and immature cells, epithelial cells, leukocytes and round cells. Of these, leukocytes, immature spermatozoa, macrophages and neutrophils are considered to be the main endogenous source. Others life style practices as: excessive alcohol consumption, smoking and environmental factors (e.g., toxins and radiations) may contribute to exogenous ROS production [38–40].

8.1 Endogenous sources of ROS

8.1.1 Leukocytes

Peroxidase-positive leukocytes include polymorphonuclear leukocytes in about 50–60% and macrophages 20–30%. Peroxidase-positive leukocytes originates in large proportion from prostate and seminal vesicles of male. These main sources of ROS are activated by different intracellular and extracellular responses such as inflammation and infection. The latest can produce 100 times reactive oxygen species than normal and also increase the secretion of NADPH through hexose monophosphate shunt [41, 42]. There is a decrease in the level of antioxidant superoxide dismutase and an increase in the concentration of proinflammatory cytokines, which can lead to the increased level of ROS and respiratory burst ultimately leading to formation of oxidative species OS. OS will than cause the damage of sperm if the concentration of seminal leukocytes is abnormally high [43]. Although in phagocytic clearance and immuno surveillance of unhealthy (abnormal) sperm, leukocytes and ROS play a decisive role. Inflammatory changes are depicted in the testes of smokers due to increased concentration of leukocyte activated free radicals. These leukocytes overcome the protective action of antioxidants and lead to oxidative stress. OS causes severe single and double stranded breaks in DNA by changing sperm chromatin integrity, modification of bases, deletions and rearrangement of chromosome [7].

8.1.2 Immature spermatozoa

During the process of spermatogenesis, the developing spermatozoa expel their cytoplasmic content to prepare itself for the process of fertilization. Due to the arrest in spermiogenesis, the abnormal spermatozoa retained excess of cytoplasm around the midpiece. This condition is referred as excess residual cytoplasm (ERC). By virtue of hexose monophosphate shunt the ERC activates the NADPH system, which is used as a source of electron by spermatozoa for production of ROS and OS [30]. Therefore, ERC affects the morphology, motility and fertilization potential of sperm which can lead to infertility [44].

8.1.3 Varicocele

Varicocele is a condition of abnormal enlargement of vein in scrotum, i.e., in the plexus pampiniformis situated throughout the spermatic cord. It is considered to be an etiology of male infertility, because varicocele is found in 19–40% of male partners in infertile couples. Current evidence suggested that oxidative stress is the central element contributing to infertility in men with varicocele [45]. Varicocele arises when damage occurs in valves into the spermatic vein(s) resulting in dysfunction and retrograde blood flow into scrotum from abdomen creating an inappropriate

environment for development of sperm. Several studies reveal that oxidative stress also leads to varicocele in male, which occurs due to decrease in the concentration of antioxidants. It results in the deterioration of structure of cell membrane and in the DNA integrity. Nitric oxide is a lipophilic molecule which is presented in the spermatic vein of varicocele patient. Both NO and superoxide might cause a damage in spermatozoa [46].

8.2 Exogenous sources of ROS

8.2.1 Radiation

Radiation, a natural source of energy, has a considerable effect on humans. Several studies have been depicted that radiation emitted from mobile phone increases the concentration of ROS in human semen resulting in impaired sperm quality [47, 48]. *In vitro* studies showed that in human, spermatozoa electromagnetic radiation urges the production of ROS and damages of DNA. These changes further diminish the vitality and motility of sperm cells [49]. Due to the presence of varieties of charged molecules in the cytosol the flow of electron along the internal membrane of cells can be negatively affected by these radio frequency electromagnetic radiations, and therefore interferes with the functions of the cell and the organelles [50].

8.2.2 Toxins

Toxins which are discharged from industrial products and structural materials accumulates in the body of human and increases the production of ROS in the testes. This might result in the negative impact on the structure and function of sperm [51]. Phthalates which are found in the plastics objects used for industrial and domestic's purpose have been found to impair the spermatogenesis process and causes DNA damages in spermatozoa. Moreover, it has been studied that those laborers who were continuously exposed to metal toxins such as chromium, mercury, manganese and cadmium were more probable to have diminished quality of sperm, sperm count, density and volume [50].

8.2.3 Smoking

Tobacco is familiar to be one of the major causes of worldwide death. It has been reported that more than 4000 toxic chemical compounds have been present in cigarettes which includes nitrosamines, alkaloids and inorganic molecules. In the semen of smokers some of those chemicals were depicted to be the source of imbalance between antioxidant and ROS [41]. This disproportion between the ROS level and antioxidant adversely affects the overall quality of semen. It has been depicted that smoking increases by 48% the concentration of seminal leukocytes and 107% the ROS level in semen [52]. Due to the substantial increase in the level of 8-OHdG which is also a biomarker of oxidative damage, a decrease of the antioxidant level in seminal plasma, like vitamin C and vitamin E occurs, thus causing more risk of oxidative damage [40]. A study performed on smokers found an increased concentration of lead and cadmium in their semen and blood, which led to increase the production of ROS with a decrease in the motility of the sperm [53]. Moreover, the spermatozoa of smoker were substantially more prone to acid mediated denaturation as compare to nonsmoker spermatozoa which led to DNA strand break [54]. Furthermore, it was shown that prolonged smoking damages sperm DNA and apoptosis which results in male infertility.

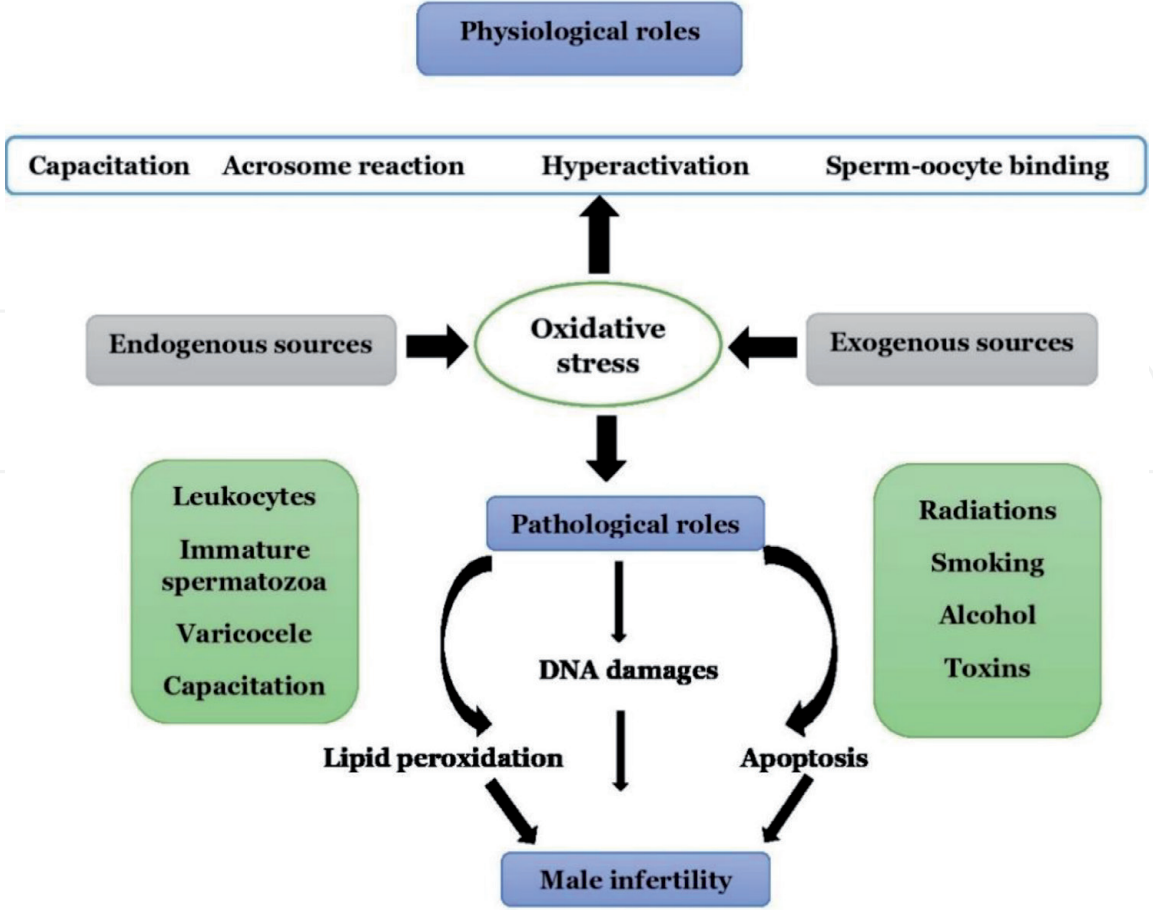


Figure 4.
Demonstration of various factors responsible for male infertility (origin).

8.2.4 Alcohol consumption

Alcohol is widely known as the inducer of ROS and it interferes with the antioxidant defense mechanism of the body, mainly in the liver. Acetaldehyde which is the byproduct of ethanol metabolism, may react with protein and lipids forming the ROS, and may lead to damages in DNA, protein and lipids at the molecular level. The excessive consumption of alcohol is linked with a decrease in the concentration of normal sperm in asthenozoospermia patients [55] (Figure 4).

9. Physiological role of ROS in seminal plasma

Physiological level of ROS plays a significant task in the physiological process such as capacitation, hyperactivation, acrosomal reaction, fusion of sperm and oocyte in order to assure the proper fertilization [56].

9.1 Capacitation

When spermatozoa pass the epididymis, it is supposed to be mature and their activity is checked by different inhibitory factors which are produced by genital duct epithelia. However, at that time sperm is unable to fertilize the ova. Ejaculated mammalian spermatozoa should reside in the female genital tract for several hours before gaining their fertilizability. In humans however, sperm must move out of the seminal plasma immediately after ejaculation and appear

in the fallopian tube within minutes. As soon as sperm cells are moving out of the ejaculate and passing the cervical mucus, they undergo several biochemical changes collectively called capacitation. These changes involve molecules absorbing on, or integrating into, the sperm plasma membrane during epididymal maturation. The removal or alteration of these molecules prepares the sperm toward successful binding, penetration and fertilization with the egg [57]. During the process of capacitation a production of ROS occurs in spermatozoa that initiates various molecular modifications. Firstly, there is an increase in cAMP; in various organisms and varieties of life processes, this cAMP pathway is necessary because it might activate various enzymes and might regulate the expression of genes [58]. cAMP activates the protein kinase A and causes the phosphorylation of PKA substrate like arginine, serine and threonine. This successively leads to the phosphorylation of MEK, threonine-glutamate-tyrosine, and tyrosine phosphorylation of fibrous sheath proteins. This cAMP increase makes the hyperactivation of sperm. Only the hyperactivated spermatozoa undergo acrosomal reaction due to increased motility and acquired all those properties which are necessary for fertilization [59, 60].

9.2 Hyperactivation

Hyperactivation is the peculiar condition of sperm motility. The hyperactivation process is significant for lucrative fertilization and it regarded a subcategory of capacitation. Hyperactivated sperm have characteristics of asymmetric flagellar movement, high amplitude, side to side head displacement and also a nonlinear motility [61].

9.3 Acrosome reaction

Hyperactivated spermatozoon binds to zona pellucida after passing the cumulus oophorus, starting the exocytotic discharge of hyaluronidase and proteolytic enzymes, sperm acrosome reaction (AR) induced by oocyte investment, is a prerequisite event for the spermatozoa. It is obligatory for the sperm cell to enable to penetrate the zona pellucida (ZP) and to fuse with the oocyte. Progesterone (P_4), secreted by cumulus cells, is an important cofactor for the occurrence of this exocytosis event. The AR results from the fusion between outer acrosomal and plasma membranes leading to inner acrosomal membrane exposure. Binding of agonists, P_4 or ZP₃ glycoprotein, to plasma membrane sperm receptors activates intraspermatic signals and enzymatic pathways involved in the AR. Among the proteins or glycoproteins described as potential sperm receptors for ZP, G_i/G_o protein-coupled and tyrosine kinase receptors have been described. ZP- and P_4 -promoted AR is mediated by an obligatory intracellular calcium increase, appearing first at the acrosome equatorial segment and spreading throughout the head. The plasma membrane channels involved in calcium entry are operated by a plasma membrane depolarization and protein phosphorylation mediated by protein kinase C and tyrosine kinase protein. Part of the calcium increase could also be due to intracellular store release through nucleotide (cAMP)-gated channels. Besides adenylate cyclase and phospholipase C activations, intracellular calcium increase also stimulates phospholipase A₂ and actin depolymerization, leading to membrane fusion [62]. The sperm cell crosses the physical barrier of zona pellucida and within few minutes it fuses with the oocytes. ROS is involved in the action of the spermatozoa by phosphorylating three plasma membrane proteins [63].

9.4 Sperm-oocyte fusion

High concentration of docosahexaenoic acid (DHA) plays a considerable part in maintaining the fluidity of the membrane of spermatozoa. ROS enhances the fluidity of membrane and sperm-oocyte fusion rate, during the process of capacitation and acrosomal reaction. Throughout the entire capacitation process, ROS hinder the protein tyrosine phosphate activity and arrest the dephosphorylation and turnoff the phospholipase A₂. PLA₂ increases the fluidity of the membrane by cleaving the secondary fatty acid from the triglycerol backbone of membrane phospholipid [64, 65].

10. Management and prevention of oxidative stress

Sperm DNA of healthy males is protected from osmotic stress by two mechanisms;

- 1. Tightly packed and coiled DNA so that the genetic material is less exposed to ROS [66].
- 2. Production of ROS is minimized by natural antioxidant present in seminal plasma and spermatozoa.

Enzymatic and nonenzymatic antioxidant like superoxide dismutase (SOD), Catalase, Vitamin C, Vitamin E and Carotenoids react with ROS and neutralize it, thus prevent the onset of osmotic stress and also preserves the function of sperm [67] (Table 1).

Antioxidant	Mechanism of action	Effect
Superoxide dismutase	Neutralizes the superoxide anions	Prevents lipid peroxidation.
GSH/GPX	Scavenges the free radicals	Prevents the lipid peroxidation and enhance the sperm membrane characteristics.
Catalase	Splits down the H ₂ O ₂ into H ₂ O and O ₂ .	Also arrests the lipid peroxidation.
Vitamin C	Counteracts free radicals	Protects the viability and motility of sperm.
Vitamin E	Counteracts free radicals	Blocks the lipid peroxidation and enhance the activity of other antioxidant.
Carotenoids	Suppresses the singlet molecular O ₂ .	Blocks the lipid peroxidation.
Carnitine	Acts as energy source and neutralize the free radical.	Prevents the damage of DNA and lipid peroxidation.
Cysteines	Elevates the concentration of GSH synthesized.	Inhibits lipid peroxidation.
Pentoxifylline	Prevents the breakdown of cAMP and quench the formation of proinflammatory factors.	Inhibits lipid peroxidation.

Table 1.
Procedure of action and consequences of different antioxidants.

11. Correlation between biology of male reproduction and sleep

The whole process of spermatogenesis is controlled by hypothalamic pituitary gonadal axis. Hypothalamus secretes GnRH that stimulates the anterior pituitary to secrete LH and FSH. FSH act on the testicular tissue and LH triggers the secretion of testosterone in the testis by Leydig cells. Maximum level of testosterone secretion occurs during sleep. This nocturnal rise in testosterone secretion appears at the same time with the beginning of resting eye movement sleep and it is not concerned with the change in the level of melatonin [68]. In male reproductive system, prolactin hormone secreted by anterior pituitary o has also a key role. Prolactin increases in Leydig cells the utterance of LH receptors at physiological level. The latest leads to increased secretion of testosterone promoting spermatogenesis. The increasing pervasiveness of 24/7 constant distribution of entertainment, disrupts the circadian rhythm and impair the duration and quality of sleep on population level. The schedule of sleep and wake is delayed by the use of electronic devices at night time. More over blue light emitted by LED reduces the secretion of melatonin and thus decreases the prolonged, objective and subjective sleepiness. Sleep restriction disrupts the level of gonadal hormone. The level of testosterone is reduced in 10 volunteer's healthy males in 1 week of restricted sleep. While in another examination of sleep restriction of 4–5 hours in 15 men is also associated with reduction in the level of testosterone. Effect of sleep restriction and resting eye movement deprivation was analyzed by Alvarenga et al. on parameter of sperm and expression of testis specific genes in male rat. Both sleep restriction (SR) and rapid eye movement sleep deprivation (RSD) group has decreased viability of sperm [69].

12. Inflammation and infertility

Inflammation is a complexed process of response to tissue damage and injury. It starts with the aggregation of leukocytes and more plasma molecules to infection site. Several factors may be responsible for inflammation in reproductive tract of male. (i) Blockage of ejaculatory duct (ii) epididymitis that causing pain, swelling in scrotal area, penile leakage and presence of blood in urine (iii) sexual transmitted diseases by several agents like *E. coli* (iv) Urethritis (v) testicular torsion is another pathology affects the fertility in male. It occurs due to abnormality in supportive tissue of testis and causing the testis to pervert inside the scrotum which result in severe swelling and pain [70]. During the process of inflammation, the quality of semen is reduced due to abnormal function of accessory glands, sperm transport hindrance and spermatogenesis dysregulation [71, 72]. Cytokines which are either secreted by activated cells or secreted after receiving stimulus might assist help in normal function of reproductive system [73, 74]. Testicular macrophage is the chief source of cytokine in male but Leydig and Sertoli cells are also depicted to secrete cytokines. Two types of changes are seen due to inflammation in male genitalia; an increase in secretion of seminal fluid leads to redness, local heat and depletion in velocity of seminal flow. Cytokines (TNF- α , IL-6, and IL-1) induce the oxidative damages that impair the quality of semen and have bad impact on fertility of male. Raised level of few cytokines in male semen also disrupts the quality, density and morphology of sperm. The increased level of TNF- α is linked with low sperm count, motility and morphology of sperm. In semen raised level of TNF- α induced apoptosis due to proliferation and differentiation of B-cell, T-cell and NK cells. At the site of inflammation, the blood vessels are dilated permitting the leukocytes in high concentration to migrate out of blood and bind with vascular

endothelium. Accumulation of local fluid due to increased permeability causes pain and swelling. So different types of disorders either due to hormonal imbalance, physical or physiological problems lead to infertility in male [7].

13. Summary

Vast array of knowledge about the structural and functional characteristics of spermatozoa has been obtained in last few decades. This study provides an information about the molecular composition and mechanism of function responsible behind the unique features of spermatozoa. No doubt that the function of spermatozoa is to carry the haploid genome of male and deliver it to the oocyte, so that it can fuse with haploid genome of female to begin the development of future generation. In the last decade the most substantial approaches in knowledge regarding spermatozoa have come by using many tools of molecular biology and proteomics to recognize the gene and protein controlling composition of spermatozoa and using gene targeting method for ascertaining the function of particular gene in sperm. A few of these advances are;

- a. Determination of calcium channels that helps in motility of sperm.
- b. Identification of activated adenylyl cyclase.
- c. Phosphorylation of tyrosine flagellar proteins during capacitation.
- d. Finding the role of heredity on the structure and function of sperm.

About 15% of couples are diagnosed as infertile and in these cases, male contributes 40%. Osmatic stress has been recognized as the inducer of male fertility due to dysfunction of sperm. It has been depicted that antioxidant defense mechanism is disrupted by the production of ROS in large concentration, while only a little concentration of ROS is demanded for normal function of sperm. This augmented production of ROS has negative impact on spermatozoa quality and damage their capacity of fertilizing the egg. ROS itself and their metabolites can cause the death of cells by attacking DNA, proteins and lipids, impair the function of the enzymes, creating irreparable damage and ultimately results to diminish in semen parameter concerned with infertility of male. So, an enhanced knowledge is also needed about the composition, organization and function of spermatozoon so that highly specific approaches are to be developed to regulate the function of sperm and essential for determining the environmental effect on male fertility.

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