

Review Article

Relevance of lipid homeostasis to male infertility

Shrabani Saugandhika¹ , Surabhi Yadav¹, Vineet Choudhary¹ 

¹Department of Biotechnology, All India Institute of Medical Sciences, New Delhi, India.



***Corresponding author:**

Shrabani Saugandhika,
Scientist, Department of
Biotechnology, All India
Institute of Medical Sciences,
New Delhi, India.

shravani_2017@aiims.edu

Co-corresponding author:

Vineet Choudhary,
Associate Professor,
Department of Biotechnology,
All India Institute of Medical
Sciences, New Delhi, India.

vchoudhary@aiims.edu

Received: 11 July 2025

Accepted: 16 October 2025

Published: 19 December 2025

DOI

10.25259/JRHM_30_2025

Quick Response Code:



ABSTRACT

Lipid homeostasis is vital for maintaining membrane dynamics, energy storage, and overall cellular function, influencing a myriad of physiological processes, including reproductive health. Although often overlooked, disruptions in lipid metabolism are increasingly linked to impaired male fertility. A significant number of male infertility cases considered to be idiopathic are now increasingly associated with elevated levels of seminal reactive oxygen species and subsequent sperm deoxyribonucleic acid damage. Through assisted reproductive technology, such cases are fertilized by intracytoplasmic sperm injection or a sperm donor, without pursuing further targeted treatment. A better understanding of idiopathic male infertility is pivotal for successful conception and embryo health, which underscores the need for innovative strategies to address male infertility. This review emphasizes the significance of lipid homeostasis in male reproductive health and elaborates on how dyslipidemia manifests in testicular dysfunction. We discuss how lipidomics can serve as a powerful tool to identify lipid-based biomarkers for more effective diagnosis and management of male infertility.

Keywords: Assisted reproductive technology, Dyslipidemia, Lipid homeostasis, Male infertility, Reactive oxygen species, Sperm

INTRODUCTION

Lipids play essential roles in numerous cellular processes, including providing structural integrity through membrane formation, acting as signaling molecules, and serving as essential energy reserves, especially during glucose unavailability through β -oxidation of fatty acids.^[1] Because of these pivotal roles, cells possess the ability to synthesize and catabolize lipids in the form of fatty acids or cholesterol. Lipid homeostasis involves regulated synthesis, uptake, transport, storage, and breakdown of lipids. Imbalance in this tightly controlled regulation leads to dyslipidemia, a condition associated with numerous pathological conditions such as obesity, atherosclerosis, cardiomyopathy, and immunological impairments.^[2] Disrupted lipid homeostasis results in lipid accumulation that often triggers oxidative cell death through ferroptosis and lipid peroxidation.^[3] Therefore, maintaining proper lipid homeostasis is crucial as lipid peroxidation results in the formation of toxic lipid species that adversely impact several organ systems, including the reproductive system. While an imbalance in lipid metabolism mostly manifests in hyperlipidemia, the present study elaborates its adverse impact on male fertility. Previously, it has been shown that both hyper- and hypolipidemia in rats are associated with vitamin D deficiency that negatively impacts male fertility and low cholesterol levels that disrupt steroidogenesis.^[4,5]

Recent evidence has reported alterations in semen quality and male fertility due to abnormal lipid metabolism.^[6] However, the molecular basis for the adverse impact of lipid dysregulation on male fertility is not well understood. Usually, infertility research focuses on female fertility factors rather

than emphasizing male contributions to conception and embryo health.^[7] Assisted reproductive technology (ART) studies report that 30% of infertility is due to male factors, but most of these are deemed idiopathic, limiting further options for diagnostic research.^[8] However, most idiopathic infertility cases show a rise in pathological levels of reactive oxygen species (ROS) along with sperm DNA fragmentation. Importantly, excess lipids within the testis drive oxidative stress, generating ROS that sets off a cascade of deleterious effects, starting from membrane lipid peroxidation to sperm DNA fragmentation and cellular dysfunction.^[9] Therefore, it is crucial to understand the importance of lipid homeostasis in testicular physiology and sperm biology to develop novel therapeutic interventions tailored for treating male infertility.

Lipids have physiological significance in testicular functioning, such as remodeling of germ cell membrane-lipids during spermatogenesis and lipid droplets (LDs) of Leydig cells (LCs) serving as the source for testosterone synthesis. However, abnormal accumulation of lipids needs to be guarded against as it contributes to sperm cell dysfunction.^[9] Clinical studies have revealed a reduction in sperm motility and count in men consuming high-fat diets. Furthermore, the risk of infertility in obese men as compared to normal-weight men is found to increase threefold.^[6] Studies in animal models have shown that a high-fat diet impairs spermatogenesis through oxidative stress, and ROS-induced mitochondrial lipid peroxidation in sperms decreases sperm motility and concentration.^[10]

At present, apart from antioxidant supplementation, no effective therapeutic strategies have been developed to target lipid stress in male infertility.^[11,12] This underscores the need for comprehensive studies into the mechanisms regulating lipid homeostasis in male reproductive health. This review explores the significance of lipid homeostasis in male fertility, outlines the deleterious impact of hyperlipidemia on testicular functions, and highlights the emerging lipidomic technologies to identify biomarkers for diagnosing infertility in hyperlipidemic males.

PHYSIOLOGICAL ROLE OF LIPIDS IN TESTICULAR FUNCTION

Lipids are integral to the male reproductive system, playing key roles in both spermatogenesis and steroidogenesis. Disruption in lipid homeostasis due to comorbidities such as obesity, hyperlipidemia, and diabetes causes alterations in lipid profile, adversely impacting fertility in men.^[13] In this section, we explore the role of lipids in extensive membrane remodeling during germ cell development, in sperm structure and physiology, and in testosterone synthesis. Finally, the contribution of the lipid-metabolizing proteins to spermatogenesis and their polymorphic variants' impact on fertility is discussed.

Spermatogenesis marks dynamic changes in germ cell lipidome

The developing male germ cells undergo drastic changes in their lipid content during spermatogenesis.^[14] As sperm lack membrane-bound organelles and relies heavily on the lipid content in their plasma, acrosomal, and nuclear membranes for proper function, amidst spermatogenesis, extensive membrane-lipid changes occur during meiotic division, spermiogenesis, epididymal maturation, and finally before fertilization.^[15] Moreover, studies have reported that failure of these modulations adversely impacts male fertility.^[16-18]

During meiosis, the germ cells encounter a shift in polyunsaturated fatty acids (PUFAs) content to facilitate membrane fluidity and stability during the cell division process. While along spermiogenesis, there is a significant enrichment in docosapentaenoic acid, which confers proper membrane characteristics to mature sperms, essential for their motility, membrane fluidity, and ability to fuse with the oocyte.^[16] These changes occur under controlled lipid homeostasis, as an increase in saturated fatty acids (SFAs) inhibits PUFA synthesis.^[19]

Although sperms lack active protein synthesis, post-testicular sperm maturation occurs in the epididymis through lipid-rich exosomes, known as epididymosomes.^[20] A study reports that in rams, during epididymal maturation, enrichment in omega-3 fatty acids, particularly docosahexaenoic acid (DHA), occurs in sperms, reducing arachidonic acid, which ensures further increase in membrane fluidity and flexibility, needed for capacitation and fertilization process [Table 1].^[17] Studies report that the epididymosomes carry a diverse set of proteins, non-coding ribonucleic acids (RNAs) (ncRNAs), and distinct lipids, which they transfer to the sperm during epididymal storage. The proteins (enzymes and chaperones) help in post translational modification (PTM) of sperm proteins while ncRNAs transmit information, and importantly, the lipids help information of membrane lipid rafts, which play a vital role in sperm capacitation and acrosome reaction (AR).^[21] Interestingly, specific epididymosomes vary in lipid composition based on their location in the epididymal segment, which indicates they probably modulate sperm membrane fluidity by donating the cargo they carry.

As sperms ascend the female reproductive tract, further membrane lipid remodeling occurs, such as efflux of cholesterol and loss of phospholipids containing SFA tail, leading to extra increase in membrane fluidity, which signals the onset of capacitation.^[22] Essentially, physiological ROS promotes cholesterol oxidation at the sperm membrane surface, forming oxysterols that bind to extracellular albumin (hydrophilicity) and release cholesterol.^[23] This leads to hydrolysis of some phospholipids to lysophospholipids and

fatty acids, which act as signaling factors promoting sperm motility, viability, and AR.^[24] Cholesterol depletion also redistributes lipid rafts on the sperm membrane, facilitating sperm receptor organization for sperm-oocyte interaction.^[25] Taken together, the above findings demonstrate the pivotal role of dynamic lipid profile in the development and maturation of sperm.

Lipid composition of the sperm cells and their function

Sperm membranes have distinct features crucial for their physiological functions. Primarily, the membrane lipid content varies between the head and tail, with the tail having more lipid than the sperm head. Particularly, DHA and ceramides are present in the tail membrane that promotes sperm motility, while head lipid contains sphingomyelin (SM) and phosphatidylcholines (PCs) vital for the fertilization process. Besides sperm head membrane also exhibits lateral heterogeneity, meaning there are distinct regions with different lipid and protein compositions, which support raft formation and reorganization during AR and binding to the zona pellucida.^[24] Thus, the lipid content of sperm membrane is highly specialized, though considerable diversity exists among species. In general, the sperm membrane contains about 70% phospholipids, 25% neutral lipids, and 5% glycolipids.^[24]

Phospholipids are the major lipid component in sperm plasma membrane that includes glycerophospholipids (GPLs) and SMs. The GPLs are diacyl lipids on a glycerol backbone with a polar molecule. They include PC, phosphatidylethanolamine (PE), phosphatidylinositol (PI), and phosphatidylserine (PS), which contribute to sperm motility, lipid raft reorganization, membrane integrity, and cell signaling, respectively.^[26,27] In GPLs, SFAs are esterified at the sn-1 position while PUFAs are esterified at sn-2.^[27] PUFAs promote sperm membrane fluidity as unsaturated acyl chains weaken interaction with cholesterol, while SFAs increase membrane rigidity, that is also needed for membrane stability and integrity. However, both render sperm susceptible to ROS-driven oxidative damage [Table 1].^[28] Ether phospholipids or plasmalogens (another subclass of GPLs) are present abundantly on the anterior head region of sperm cell membrane, which enhances membrane fluidity and stability, as ether linkages do not get readily cleaved by lipase action.^[29] Cardiolipin, present abundantly in the sperm tail, maintains mitochondrial health needed for energy production and sperm motility.^[30] Lysophospholipids act as a signaling molecule for AR.^[24] SMs have a sphingosine backbone. In mammalian sperm, the head SMs predominantly contain very long-chain PUFAs that promote microdomain formation and fusion, influencing membrane structure. The tail SMs contain SFAs, which regulate flagellar movement in sperm cells.^[31]

Table 1: Seminal Lipids associated with male fertility in humans.

| SI no. | Lipid class and ratio | Studies | Reference |
|--------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1 | Docosa- hexanoic acid (22:6) | Patients with asthenozoospermia and oligo-zoospermia show significantly lower levels of DHA compared to normozoospermic controls. Infertile human semen samples have shown significantly lower levels of DHA compared to healthy controls. Sperm DNA damage and DHA levels show negative correlation while DHA content and semen parameters (sperm count, vitality and motility) exhibit positively correlation. | [32-34] |
| 2 | Eicosapentanoic acid (20:5) | Human semen samples from infertile individuals show significantly lower levels of EPA compared to healthy controls. | [33] |
| 3 | Arachidonic acid (20:4) | High levels of AA were observed in seminal plasma of patients with asthenozoospermia compared to healthy controls. | [35] |
| 4 | Dihomo-linolenic acid (20:3) | Significantly higher levels of DGLA were found in infertile human semen samples compared to healthy controls. | [33] |
| 5 | Linolenic acid (18:3) | Sperm of asthenozoospermic and oligozoospermic patients showed high levels of LA compared to normozoospermic controls. | [32] |
| 6 | PC content | Decreased PC level was found in obstructive azoospermia patients. Low PC levels were marked in idiopathic infertility human samples. | [36,37] |
| 7 | PE: PC ratio | Compared to control significant differences in PE: PC ratio was found in patients with spermatogenic failure and obstructive azoospermia | [36] |
| 8 | LPC: PC | LPC: PC ratio increased in human sperm with damaged membrane structure | [38] |
| 9 | Omega-3 FAs | Lower level found in infertile patients than control | [39] |

Abbreviations: DHA: Docosahexanoic acid, EPA: Eicosapentanoic acid, AA: Arachidonic acid, LA: Linolenic acid, DGLA: Dihomo-linolenic acid, PC: Phosphatidylcholine, PE: Phosphatidylethanolamine, LPC: Lysophosphatidylcholine, FA: Fatty acid

Table 2: List of different lipid-metabolic protein knockout mice and its effect on male fertility.

| Sl no. | Knock out mouse | Gene function | Lipid alteration | Effect on reproductive functions | Reference |
|--------|-----------------|------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-----------|
| 1. | DAPAT -/- | Enzyme involved in ether lipid synthesis | Absence of ether lipid | Spermatogenesis is arrested during the late. Pachytene and of spermatid stage; male infertility | [40] |
| 2. | Pe × 7 -/- | Enzyme for ether lipid synthesis | Depleted plasmalogen levels | Testicular atrophy; male infertility | [41] |
| 3. | Sms1 -/- | De novo synthesis of SM and DAG | Reduction in long-chain unsaturated PCs, LPCs and sphingolipids | Shedding of spermatocytes and spermatids during spermatogenesis and progressive male sterility | [42] |
| 4. | Tysnd1 -/- | Enzyme for ether lipid synthesis | Altered components of choline, ethanolamine and plasmalogens | Incomplete acrosomes of epididymal sperm; males sterile | [43] |
| 5. | FADS2 -/- | Involved in FAs synthesis | Deficiency of highly unsaturated fatty acids | Failure of acrosome formation during spermiogenesis of round sperm into elongated sperm; male infertility | [44] |
| 6. | ASM -/- | Catabolizes SM | Increased levels of sphingomyelin and cholesterol | Abnormalities of sperm morphology, motility and capacitation | [45] |
| 7. | LPAATs -/- | Involved in GPLs synthesis | Reduction in DHA-containing GPLs | Abnormal spermatogenesis due to defects in eliminating cytoplasmic components; male sterility | [46] |
| 8. | Elovl2 -/- | Involved in FAs synthesis | Reduction in PUFAs with 24–30 carbons of w-6 family | Arrested spermatogenesis; male infertility | [47] |

DAPAT: Di-alkyl-2-phosphatidyl-glycerol synthase, Pe × 7: Peroxisomal biogenesis factor 7, Sms1: Sphingomyelin M Synthase 1, SM: Sphingomyelin, DAG: Di-acyl glycerol, PCs: Phosphatidylcholine, LPCs: Lyso-phosphatidylcholine, Tysnd1: Trypsin domain containing 1, FADS2: Fatty acid desaturase 2, ASM: Acid sphingomyelinase, LPAATs: Lysophosphatidic Acid Acyltransferase, Elovl2: Elongation Of Very Long Chain Fatty Acids-Like 2, FAs: Fatty Acids, DHA: Docosahexanoic acid, GPLs: Glycerophospholipids, PUFAs: Polyunsaturated fatty acid

Neutral lipids, the second major lipid component of the sperm plasma membrane, include cholesterol, diacylglycerol (DAG), and small amounts of cholesterol sulfate and cholesteryl esters. Cholesterol plays a key role in stabilizing the membrane by interacting with phospholipid, thereby regulating membrane stability.^[26] Importantly, cholesterol also contributes to the formation of membrane lipid rafts, maintaining their solidity, and also facilitates signal transduction.^[22] DAGs, minimally present in other cell membranes, are abundantly found in sperm plasma membrane, which enhances membrane fusion during AR through intra-acrosomal Ca²⁺influx, which triggers acrosomal exocytosis.^[48,49]

Glycolipids, the third component of sperm plasma membrane, include sulfo-galactosyl-glycerolipid (SGG) or seminolipid, which primarily localizes in the sperm head, mediating binding of the sperm to the zona pellucida, and serves as an important biomarker for sperm fertilization potential.^[50] Importantly, cholesterol efflux alters glycosphingolipid conformation, exposing sugar residues that are recognized by lectins present in egg zona pellucida, aiding in sperm-egg interaction.^[22] Other glycolipids present in the outer leaflets of sperm plasma membranes promote membrane stability and intercellular communication.^[28]

Lipid metabolizing proteins related to sperm function and fertility

To investigate the effect of lipid-metabolizing proteins on male fertility, various knockout mice models have been developed. Male mice lacking key enzymes involved in phosphoinositide kinase (PIK3) signaling, ether lipid synthesis, sphingolipid biogenesis, or fatty acid desaturation exhibit impaired spermatogenesis with varying degrees of infertility.^[51-54] Phosphatidyl-inositol phosphates (*e.g.*, PI4P, PIP2, PIP3) are membrane lipids involved in germ cell development and sperm motility. Deletion of p110 isoform of PIK3 led to embryonic lethality in most mice, and those that survived were infertile males.^[51] Similarly, knockout of Inositol polyphosphate 4-phosphatase II (INPP4B), a key enzyme in the PI signaling pathway, resulted in male mice with smaller testes and reduced sperm production.^[54] Other lipid metabolic gene knockouts also led to defective spermatogenesis and progressive sterility mentioned in Table 2. Besides, polymorphism in some lipid-metabolizing enzymes like cytochrome P450 (CYP), glutathione-S-transferase (GSTs), paraoxonase 1 (PON1), involved in detoxification and antioxidation, are reported to be associated with hyperlipidemia and male infertility. The single nucleotide polymorphism (SNP) variants – CYP1A1

(rs4646903), PON1 (rs662), and null alleles – GSTM1 and GSTT1 cause impaired detoxification that increases oxidative stress, resulting in a drastic decrease in sperm functions.^[55]

LDs: The main source for steroidogenesis

Unlike peptide hormones, steroid hormones are not stored in secretory vesicles but are synthesized and secreted into circulation immediately upon hormonal stimulation. This process requires readily available cholesterol, the precursor for steroid hormone synthesis. To meet this demand, steroidogenic cells such as LCs store cholesterol in the form of cholesterol esters (CE) together with triglycerides (TAG) into LDs, a fat storage organelle enclosed by a phospholipid monolayer embedded with proteins such as perilipins (PLIN) and cell death-inducing DFF45-like effector (CIDE).^[56-58] It has been shown that LD biogenesis occurs in a step-wise manner at specialized endoplasmic reticulum (ER) sites defined by functionally conserved ER membrane protein seipin (Sei1 in yeast).^[59] At these ER sites, seipin interacts with several factors, ensuring the fidelity of LD formation and preventing the detrimental effect of ectopic LD deposition in the ER.^[59] Strikingly, lack of seipin in steroidogenic tissues of mice, particularly in, testis, ovary, and adrenal glands, resulted in markedly reduced accumulation of CE-rich LDs, thus impairing production of steroid hormones.^[60] Primarily mobilization of lipid content from LDs is mediated by lipases that catalyze the breakdown of CE and TAG.^[56] However, recent studies have identified “lipophagy,” a form of selective autophagy, as a key mechanism in LD breakdown in steroidogenic cells, which promotes testosterone biosynthesis.^[61] In murine Leydig tumor cell line (MLTC) LC line and primary rat LCs, luteinizing hormone stimulation leads to dispersion of perinuclear LDs into smaller LDs, which associate with ER and mitochondria.^[62] Proteomic analysis has confirmed that these smaller LDs contain not only PLINs and CIDEs but also autophagosomal proteins, ER marker calnexin, and steroidogenic enzymes.^[62,63]

Several studies have demonstrated that lipophagy facilitates the hydrolysis of CE to release free cholesterol, which is then transported to mitochondria by steroidogenic acute regulatory (StAR) proteins, forming pregnenolone, which is further processed in the ER to produce testosterone.^[64,65] Another study in mice granulosa cells showed the presence of steroidogenic enzymes on the LD surface upon proteomic analysis. Thus, collectively these findings highlight the potent role of LDs as dynamic organelles critical for cholesterol storage and regulation of steroid hormone biosynthesis.^[66]

PATHOPHYSIOLOGICAL ROLE OF LIPIDS IN TESTICULAR IMPAIRMENT

Sperms are “silent cells” devoid of transcription and translation ability; they lack adaptive response to counteract

cellular stress, making them highly susceptible to environmental and pathological stressors. As a result, any disturbance in their biochemical environment can impair their structure and function, ultimately resulting in sperm dysfunction and male infertility [Table 1]. Lipids are crucial for their structural and physiological development; however, high PUFA content renders them susceptible to oxidative damage.^[14] Therefore, maintaining lipid homeostasis plays a central role in governing male fertility.

Dyslipidemia, characterized by blood lipid imbalances such as hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, or a decrease in HDL-cholesterol, not only leads to high-risk diseases like atherosclerosis and ischemia-related strokes but has also been linked to reproductive dysfunction.^[6] The western diet, rich in fats, sugars, salt, and processed grains, contributes significantly to the development of this disorder.^[10,67] Dyslipidemia induces systemic oxidative stress, increasing ROS that damages developing spermatozoa. Since spermatogonial cells undergo lipid remodeling during spermatogenesis, the sperm plasma membrane becomes an easy target of oxidative damage.^[10]

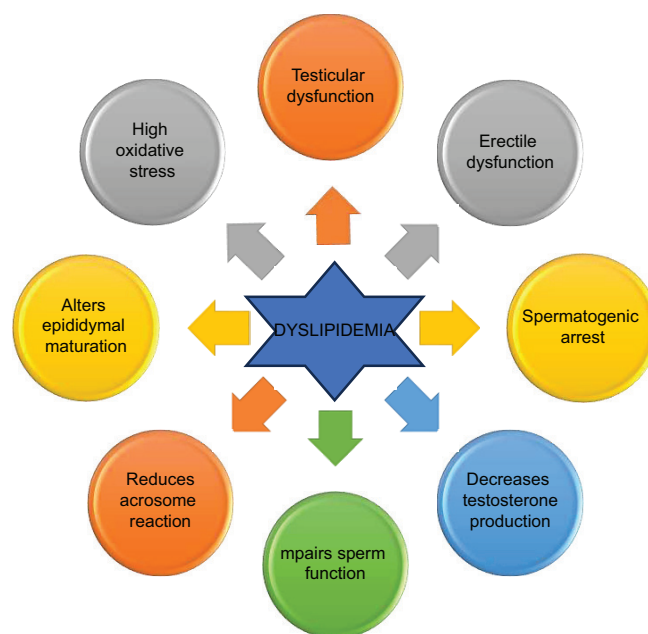


Figure 1: Dyslipidemia negatively affects male fertility. Dyslipidemia impairs male fertility through multiple pathways. It induces testicular dysfunction by damaging Leydig and Sertoli cells, thereby disrupting testosterone biosynthesis and altering the hypothalamic-pituitary-gonadal axis. Elevated lipids promote oxidative stress and inflammatory response, compromising spermatogenesis, epididymal sperm maturation, and acrosome reaction. Consequently, sperm function is negatively affected, with reduced motility, abnormal morphology, and increased DNA fragmentation. These combined effects collectively impair fertilization potential. DNA: Deoxyribonucleic acid

Therefore, excess dietary fat can trigger lipid peroxidation, compromising sperm function and causing a decline in male fertility [Figure 1].

Dyslipidemia promotes ferroptosis: the main culprit for spermatogenic dysfunction

Dyslipidemia-induced oxidative stress triggers membrane lipid peroxidation, resulting in the accumulation of lipid hydroperoxides and other high reactive metabolites, which ultimately overwhelm the cellular antioxidant defenses.^[14] Oxidized PUFAs are cleaved from membrane phospholipids and catabolized through lipoxygenase enzymes (ALOX15, ACSL4, LPCAT3), generating a large amount of ROS, which attenuates antioxidantizing factors (GPX, FSP1, and CoQ10), ultimately inducing ferroptosis - a form of cell death driven by iron-dependent lipid peroxidation.^[52] The resulting reactive radicals damage intracellular macromolecules, promote DNA fragmentation, and increase membrane permeability, leading to germ cell apoptosis, particularly arresting the round spermatids during spermatogenesis [Figure 2].^[14,52] Thus, in spermatogenic cells, derailed lipid homeostasis causes oxidative damage, and when this damage exceeds the cell's threshold of peroxide tolerance, ferroptosis is initiated, leading to germ cell death. Notably, ferroptosis has been implicated as a characteristic feature of many male reproductive disorders, including heavy metal-induced testicular damage, testicular torsion, orchitis, hypogonadism, and even testicular cancers.^[68]

Deregulated lipid homeostasis impairs the testicular microenvironment

In dyslipidemia, disrupted lipid metabolism significantly alters the testicular microenvironment and impairs cellular functions, compromising male fertility.^[68,69] Excess lipids alter the tight junction proteins, disrupting the blood-testis barrier and triggering testicular immune dysfunction.^[70] Conversely, Sertoli cells, which nourish developing sperms, suffer mitochondrial damage from abnormal lipid byproducts.^[69] Finally, increased reactive radicals exacerbate inflammation, damage cells and the intracellular components, activating testicular macrophages to clear apoptotic cells, inadvertently harming neighboring LCs.^[71-73] Overall, lipid imbalance in dyslipidemia severely impacts testicular somatic cells, leading to deterioration in steroidogenic and spermatogenic functions.

Dyslipidemia disrupts steroidogenesis

Dysregulated lipid metabolism hampers steroidogenesis through multiple mechanisms. Testosterone synthesis in LCs relies on cholesterol transport into mitochondria. However, elevated ROS in dyslipidemia oxidizes cholesterol to cholesterol hydroperoxide, and its co-trafficking into LC damages mitochondria, disrupting the redox balance, resulting in decreased testosterone production.^[56] Further, increased fatty acid and TAG levels suppress steroidogenic activity in LCs.^[57] A recent study has shown that culturing rat granulosa cells in high fatty acid media transformed the LD content from CE-rich core to TAG-rich core, reducing

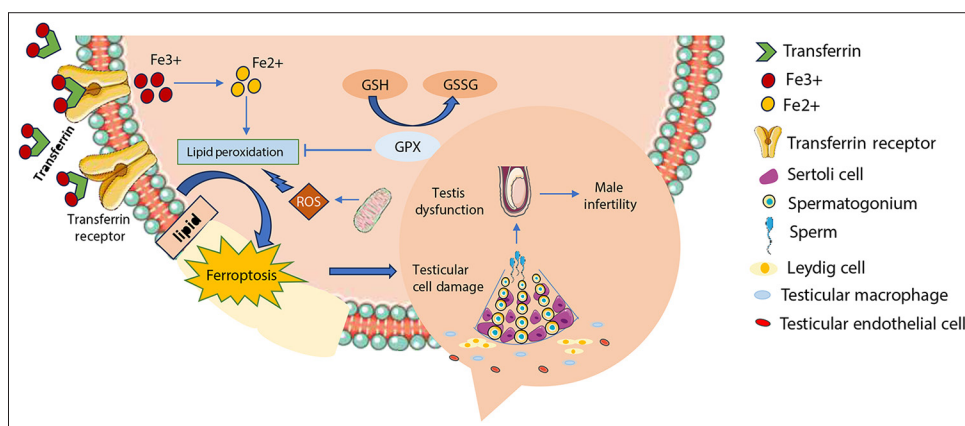


Figure 2: Ferroptosis causes testicular damage. Ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation, has emerged as a contributing factor in testicular damage. In testicular tissue, excessive iron accumulation paired with impaired antioxidant defenses – particularly reduced glutathione peroxidase 4 activity – leads to oxidative lipid damage. This oxidative stress disrupts the functional integrity of both Sertoli and Leydig cells, ultimately impairing spermatogenesis, suppressing testosterone synthesis, and triggering germ cell apoptosis. These cellular disturbances highlight ferroptosis as a potential link between oxidative stress and male infertility. GSH- Reduced glutathione, GSSG: Oxidised glutathione, GPx: Glutathione peroxidase, Fe²⁺: Ferrous ion, Fe³⁺: Ferric ion.

the release of free cholesterol needed for testosterone synthesis.^[74] Normally, lipophagy-mediated hydrolysis of CE-containing LDs into free cholesterol facilitates testosterone production, but, in hyperlipidemia, excess fatty acids inhibit lipophagy of LDs, further limiting cholesterol availability.^[64,73] In addition, another mechanism involves ROS-induced activation of adipocytes to generate leptin, which disrupts the hypothalamic-pituitary-gonadal (HPG) axis, resulting in low testosterone synthesis.^[75] Elevated leptin levels also inhibit the hedgehog signaling pathway required for the proliferation and maturation of Leydig stem cells.^[76]

Studies in animal models and humans

Studies indicate that individuals who are hyperlipidemic but not obese also experience compromised ovarian functions and increased risk of cardiovascular disease. This is primarily due to the lipotoxic effects of circulating LDLs imposed, which can cause cellular distortions.^[77] Several animal and human studies have explored the adverse impacts of dyslipidemia on male fertility [Table 3].

Rabbits, due to their sensitivity to dietary cholesterol and similarities with human lipid metabolism, serve as a valuable model to study hyperlipidemia-induced male infertility. In classical models, rabbits fed a diet with 2% cholesterol exhibited elevated plasma cholesterol levels and β -very low-density lipoprotein.^[110] This hyperlipidemia was associated with increased sperm cholesterol content, reduced acrosomal reaction, and impaired motility despite normal sperm morphology.^[78] The acrosomal membrane revealed a significant increase in filipin-cholesterol complexes, and disruption of the blood-testis barrier was observed.^[79] Interestingly, supplementing the diet with 7% olive oil reversed these effects, likely due to the antioxidant properties of olive oil that prevented lipotoxicity.^[80]

In rodent models, transgenic mice were employed to study the effect of hyperlipidemia on male fertility. Liver X receptors (LXRs) are nuclear receptors with transcription factor function that play an important role in lipid homeostasis and male fertility. The LXR- α isoform is expressed in Leydig and germ cells, while the LXR- β isoform is found in Sertoli cells, both of which are stimulated by oxysterols during oxidative stress to regulate lipid homeostasis.^[81] Transgenic mice lacking both isoforms of LXR developed fertility issues as they aged, as defective cholesterol metabolism resulted in CE accumulation in Sertoli cells, leading to testicular dysfunction in later life. Using this transgenic mouse, a diet-induced post-testicular infertility model was developed. When fed a cholesterol-rich diet, these knockout mice developed severe sperm abnormalities, similar to hypercholesterolemic rabbits, including abnormal morphology, decreased motility, and capacitation failure.^[81] Similarly, rats on a high cholesterol diet for 120 days showed a significant increase in plasma

LDL, reduced sperm function, smaller LCs, lower germ cell numbers, and decreased testosterone.^[10]

High intake of saturated fat in humans correlates with reduced sperm quality, directly proportional to the quantity consumed.^[4] In addition, increased LDL and total cholesterol cause endothelial dysfunction and vascular obstruction, which can lead to erectile dysfunction as elevated levels of inflammatory cytokines cause testicular endothelial dysfunction, impairing endothelium-dependent relaxation of vascular beds.^[82,83] Sperm oxidative stress damage showed a positive association with increased levels of cytochrome C and caspases 9 and 3, which points to heightened sperm apoptosis in infertile men.^[84]

ART studies reveal that oxidative stress-induced sperm damage contributes to 30–80% of male infertility cases. Therefore, sperm DNA fragmentation from high ROS is used as an infertility diagnostic marker.^[6] Additional indicators of testicular dysfunction include elevated testicular malondialdehyde (MDA), a byproduct of lipid peroxidation, and reduced levels of key testicular antioxidants – glutathione (GSH) and superoxide dismutase (SOD).^[6] ART studies reveal that infertile men with high levels of ROS have a fivefold lower likelihood of achieving pregnancy than those with lower ROS levels.^[85] Obesity, frequently resulting from lipid imbalance and oxidative stress, contributes to systemic inflammation that worsens sperm DNA fragmentation due to altered redox homeostasis, further impairing male fertility.^[6]

MAINTENANCE OF TESTICULAR LIPID HOMEOSTASIS

Lipid homeostasis is vital for maintaining testicular functional efficacy, ensuring proper progression of spermatogenesis and steroidogenesis. This balance relies on coordinated lipid uptake, synthesis, and catabolism within the germ and somatic cells. The AR receptors and peroxisomes in testicular cells facilitate in mediating of cholesterol and lipid homeostasis.^[86,87] Binding of testosterone to AR receptors in Sertoli and LCs promotes transcription of genes involved in lipid metabolism.^[86] In addition, in LCs, testosterone controls self-synthesis through feedback regulation of the HPG axis and maintains cholesterol homeostasis.^[88] Long-chain fatty acids are catabolized through peroxisomal β -oxidation, producing DHA needed for spermatid development.^[89] Thus, peroxisome and peroxisomal proteins have an essential function in male fertility, maintaining fatty acid homeostasis and spermiogenesis.

Knockout studies of peroxisomal biogenesis factor (PEX) proteins showed lipid accumulation in Sertoli cells, leading to spermatid arrest and defective peroxisome biogenesis in Sertoli cells adversely impacted lipid homeostasis.^[89] Recently, a study in *Drosophila* suggested the role of mitochondrial fusion in maintaining lipid homeostasis and stem cell growth. Aberrant mitochondrial development in germ stem cells revealed

Table 3: HFD Animal models used to know effect of excess lipid on male reproductive function.

| Sl. No | Animal Model | Diet and duration | Lipid profile | Effect on steroidogenesis | Effect on Sperm Parameters | Effect on Reproductive Organ | Reference |
|--------|-------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1 | New Zealand White male rabbit | Chow with 3% cholesterol was fed for 12 weeks | Serum lipid and TC levels significantly increased. | Testosterone response to HCG stimulation was significantly lower | Epididymal sperm content, sperm motility, and motility grade significantly lowered. | No significant effect on testicular weight but proportion of fertilize oocytes to cleaved oocytes decreased significantly. | [90] |
| 2 | Male albino rat | cholesterol powder fed orally 400mg/kg body wt., along with 5% fat, for 2 months | Serum TC and TG levels significantly increased | - | Sperm motility and density reduced significantly | Reduced no of Germ cells with shrunken seminiferous tubules, increase in no of degenerative Leydig cells, showed decline in spermatogenesis | [91] |
| 3 | New Zealand White male rabbit | Chow containing 3% cholesterol was fed for 12 weeks | Total serum lipids and testicular tissue lipids raised significantly. | Testosterone response to HCG stimulation reduced significantly | Sperm count, motility and length of sperm mid-piece was significantly lower | ABP protein activity lowered, showed decline in Leydig and Sertoli cell secretory function, reduced spermatogenesis and sperm fertilizing capacity | [92] |
| 4 | Male Swiss albino rat | 1%cholesterol with 0.5% cholic acid and 2% sheep fat was fed for 2 months | Serum TC, TG and LDL levels increased significantly | Testosterone level decreased significantly | Sperm motility and count decreased significantly with increase in sperm abnormal morphology | Weight of the testes and seminal vesicle decreased significantly. | [93] |
| 5 | Male White New Zealand rabbit | Cholesterol (0.05%) fed for 12 months | Significant increase in serum cholesterol. | - | Semen volume, motility, and vitality significantly decreased; morphological alterations increased. | Showed decline in capacitation and acrosome reaction. Sperm exhibited reduced membrane response to hypo-osmotic swelling test | [94] |
| 6 | Lxr-knockout Mice | Cholesterol 1.25% was fed for 4 weeks | Significant increase in plasma TC, LDL, HDL and TG levels. | - | Increased sperm abnormal morphology and impaired motility | No live birth from females mated with HFD fed Lxr-knockout male mice, showing HFD fed Lxr α ; β -/- male mice to be infertile. | [95] |

TC: Total Cholesterol, TG: Triglyceride, HCG: Human chorionic gonadotropin, ABP: Androgen binding protein, LDL: Low density lipid, HDL: High density lipid

failure of mitochondrial β -oxidation, leading to lipid buildup and stem cell loss.^[96] Finally, as Sertoli cells have phagocytic activity, they phagocytose lipid-rich residual bodies, absorb cholesterol, esterify it, and store it as LDs, thus maintaining cholesterol homeostasis during spermatogenesis.^[97]

THERAPEUTIC INTERVENTIONS TARGETING TESTICULAR LIPID HOMEOSTASIS

Enzymatic antioxidants (SOD and catalase (CAT)) and non-enzymatic antioxidants (vitC, vitE, ubiquinol, and GSH) are present in testicular tissues to fight ROS, but under certain pathological or metabolic conditions, the concentration of ROS surpasses the defense system, causing testicular damage. To ameliorate such damage, some studies have conducted antioxidant administration in animals to check its efficacy. A recent study investigated the effect of micronutrient supplement mix (vitB6, choline, folate, and zinc) on testicular function in high fat diet (HFD) male rats, which showed that it not only reduced testicular damage but also improved sperm functions.^[98] Further, ROS-scavenging nanoparticles (NPs) have been designed and delivered to maximize antioxidant properties, such as melatonin Au³⁺ NPs, nanoform Se, and SOD-loaded NPs. These NP supplements enhanced antioxidant capacity compared to the solitary use of antioxidants.^[99] Interestingly, certain flavonoid bioactive molecules, such as lycopene (LYC) and quercetin, have demonstrated their potential in reducing ROS and alleviating testicular injury.^[100,101] lipo-polysaccharides (LPS) Li *et al.* showed that when oral LYC was administered to fed rats, it ameliorated testicular lipid dysregulation and inflammatory response (due to LPS) by activating the peroxisome proliferator-activated receptor (PPAR) signaling pathways.^[100] Similarly, mitochondria-targeted quercetin NPs was developed to maintain mitochondrial membrane integrity, and their administration to the TM4 cell line rescued Sertoli cells from ROS.^[101]

During ROS, both autophagy and apoptosis work in concert to control tissue homeostasis, but in some cases, they also work independently, with autophagy contributing to cell survivability and apoptosis, ensuring cell death to control DNA mutation. This suggests intricate mechanisms that link both pathways to function either in an integrated manner or in a mutually exclusive way.^[102] However, in the testis, autophagy plays a cytoprotective role in spermatogonial stem cell (SSC) maintenance, differentiation, and spermiogenesis. It also regulates steroid hormone synthesis in LCs.^[102] Recently, a study has shown that autophagy is activated in human sperms under ROS, and blocking it impairs sperm functions.^[103] Thus, considering the vital role of autophagy in testicular functioning and its interconnection with apoptosis during ROS, a deeper insight into mechanisms that cause autophagy activation and apoptosis inhibition may be a therapeutic approach for treating male infertility.

LIPIDOMICS AS POTENTIAL ANALYTICAL TECHNIQUE IN ART

Despite decades of infertility research, idiopathic male infertility remains unexplored, with limited therapeutic options beyond intracytoplasmic sperm injection in ART. This highlights the pressing need for innovative diagnostic and therapeutic strategies. A promising approach involves assessing testicular lipid stress, especially since elevated ROS levels are frequently observed in sperm samples of idiopathic infertility cases. Identifying and managing lipid-induced oxidative damage could offer new avenues for treatment.^[14]

Emerging Omics technology – such as proteomics, metabolomics, and lipidomics can significantly advance our understanding of male infertility by identifying critical proteins, metabolites, and lipid pathways involved in reproductive function. The sperm plasma membrane PUFA content renders sperm highly vulnerable to lipid peroxidation involving three stages: initiation, propagation, and termination. It begins with the abstraction of hydrogen atoms from PUFA double bonds, generating free radicals that propagate a chain reaction, producing lipid radicals, peroxy radicals, and ultimately cytotoxic aldehydes. End products such as MDA and 4-hydroxynonenal serve as biomarkers of oxidative stress.^[68] Lipidomic profiling of semen samples in idiopathic infertility cases can help detect these peroxidation products, offering potential diagnostic markers. By comparing lipid profiles between fertile and infertile men, researchers can distinguish oxidized lipids linked to pathological conditions.^[104]

Lipidomics approaches include untargeted and targeted lipidomics. Untargeted lipidomics offers a broad view of the lipid landscape, while targeted lipidomics focuses on specific molecules, such as oxidized lipids, using techniques like Selected Reaction Monitoring for precise quantification and biomarker validation.^[104,105]

A recent study performing untargeted analysis of sperm membrane lipids identified a lipid cluster comprising cholesterol sulfate, SGG, and PUFAs in fertile male samples, suggesting that these molecules play key roles in semen quality and function. Another comparative study on the lipid profile of fertile and sub-fertile sperm revealed lipids exclusive to either group, offering a potential source of diagnostic biomarkers.^[106,107]

Advances in mass spectrometry (MS) and high-performance liquid chromatography have improved LC-MS-based lipidomic analysis, providing higher sensitivity, high throughput, and specificity. Ionization methods, including electron ionization, matrix-assisted laser desorption ionization (MALDI), electrospray ionization, and fast atom bombardment (FAB), enable detailed profiling of lipid classes. FAB is especially effective in analyzing fatty acids, monoacylglycerols, and

GPLs.^[108] Bioinformatic tools such as Lipid-Match and Lipid-Pioneer assist in interpreting lipid oxidation data and building comprehensive oxidized lipid databases.^[16]

Another emerging technique, MS imaging (MSI), adds a spatial dimension by mapping lipids within tissues. MALDI-MSI, in development, aims to visualize lipid distribution at single-cell resolution.^[109] This approach has been applied in zebrafish embryos to reveal 3D distributions of phospholipids (PC, PE, PI).^[110] In testicular research, MSI could be used to monitor lipid damage post-torsion or understand germ cell pathologies by mapping oxidized lipids. MSI has recently been used for spatial localization and quantification of androgens in the mouse testis and could help evaluate the permeability of the blood-testis barrier and drug delivery efficiency.^[14,111] Finally, MSI may provide an early indication of reproductive tissue damage following administration of therapies to cancer patients.^[112]

CONCLUSION

In summary, this review highlights the crucial role of lipids in sperm cell biology, including their involvement in dynamic remodeling of germ cell architecture, maintaining membrane integrity, regulating lipid metabolism, and facilitating testosterone synthesis. Conversely, the study also underscores the detrimental effect of lipid overload, particularly in hyperlipidemia, which promotes ROS production, thereby impairing testicular function and contributing to infertility. Notably, the study provides insights into the critical importance of lipid homeostasis in male reproductive health.

Several regulatory mechanisms modulate testicular lipid balance, such as peroxisomal β -oxidation, AR-mediated lipid metabolism, and LXR-driven cholesterol efflux in Sertoli and LCs. However, overaccumulation of lipids disrupts the blood-testis barrier, impairs spermatogenesis, and inhibits testosterone synthesis due to constant oxidative stress from lipid peroxidation. This highlights the likely reason why most idiopathic male infertility cases in ART labs report high ROS levels in sperm samples.

To develop targeted treatments for male infertility, early detection of testicular lipid stress is crucial. This can be achieved through advanced approaches such as lipidomic profiling, integration with other omics technologies, and MS-based molecular imaging (MS-MI) for a more comprehensive diagnostic framework.

Acknowledgment: This work was supported by an Early Career Intramural Project of the All India Institute of Medical Sciences (AIIMS) awarded to Shrabani Saugandhika (project A-619), an Indo-Swiss Joint Research Program of Department of Biotechnology (IC-12044 (11)/6/2021-ICD-DBT awarded to Vineet Choudhary), and DBT/Wellcome Trust India Alliance Fellowship (Grant IA/I/20/2/505191 awarded to Vineet Choudhary).

Ethics approval: Institutional review board approval is not required.

Declaration of patient consent: Patient's consent is not required as there are no patients in this study.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

REFERENCES

1. Wymann MP, Schneider R. Lipid signalling in disease. *Nat Rev Mol Cell Biol* 2008;9:162-76.
2. Pappan N, Awosika AO, Rehman A. Dyslipidemia. 2024 Mar 4. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan.
3. Tang D, Kang R. Lipid metabolism and homeostasis in ferroptosis. In: Tang D, editor. *Ferroptosis in health, and disease*. Cham: Springer; 2023. p. 1-22.
4. Chen C, Zhai H, Huang G, Cheng J, Xia F, Zhao L, *et al.* Is lower low-density lipoprotein cholesterol associated with lower androgen and erectile dysfunction in men? *Nutr Metab Cardiovasc Dis* 2018;28:1304-10.
5. Mohammed Hikal S, El Bayoumi M, Ibrahim S, EL Shawwa M. The effect of lipid disturbance and vitamin D on the fertility in male albino rats. *J Recent Adv Med* 2021;2:10-9.
6. Hamad Zubi ZB, Hamad Alfarisi HA. Hyperlipidemia and male infertility. *Egypt J Basic Appl Sci* 2021;8:385-96.
7. Turner KA, Rambhatla A, Schon S, Agarwal A, Krawetz SA, Dupree JM, *et al.* Male infertility is a women's health issue-research and clinical evaluation of male infertility is needed. *Cells* 2020;9:990.
8. Punab M, Poolamets O, Paju P, Vihljajev V, Pomm K, Ladva R, *et al.* Causes of male infertility: A 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. *Hum Reprod* 2017;32:18-31.
9. Alahmar AT. Role of oxidative stress in male infertility: An updated review. *J Hum Reprod Sci* 2019;12:4-18.
10. Saez F, Drevet JR. Dietary cholesterol and lipid overload: Impact on male fertility. *Oxid Med Cell Longev* 2019;2019:4521786.
11. Moazamian A, Hug E, Villeneuve P, Bravard S, Geurtsen R, Hallak J, *et al.* The dual nature of micronutrients on fertility: Too much of a good thing? *FS Sci* 2025;6:293-302.
12. Martin-Hidalgo D, Bragado MJ, Batista AR, Oliveira PF, Alves MG. Antioxidants and male fertility: From molecular studies to clinical evidence. *Antioxidants (Basel)* 2019;8:89.
13. Service CA, Puri D, Al Azzawi S, Hsieh TC, Patel DP. The impact of obesity and metabolic health on male fertility: A systematic review. *Fertil Steril* 2023;120:1098-111.
14. Walters JL, Gadella BM, Sutherland JM, Nixon B, Bromfield EG. Male infertility: Shining a light on lipids and lipid-modulating enzymes in the male germline. *J Clin Med* 2020;9:327.
15. Roqueta-Rivera M, Stroud CK, Haschek WM, Akare SJ, Segre M, Brush RS, *et al.* Docosahexaenoic acid supplementation fully restores fertility and spermatogenesis in male delta-6 desaturase-null mice. *J Lipid Res* 2010;51:360-7.

16. Oresti GM, Reyes JG, Luquez JM, Osses N, Furland NE, Aveldaño MI. Differentiation-related changes in lipid classes with long-chain and very long-chain polyenoic fatty acids in rat spermatogenic cells. *J Lipid Res* 2010;51:2909-21.
17. Parks JE, Hammerstedt RH. Development changes occurring in the lipids of ram epididymal spermatozoa plasma membrane. *Biol Reprod* 1985;32:653-68.
18. Feki NC, Théron P, Couturier M, Liméa G, Legrand A, Jouannet P, *et al.* Human sperm lipid content is modified after migration into human cervical mucus. *Mol Hum Reprod* 2004;10:137-42.
19. Worthmann A, Ridder J, Piel SY, Evangelakos I, Musfeldt M, Voß H, *et al.* Fatty acid synthesis suppresses dietary polyunsaturated fatty acid use. *Nat Commun* 2024;15:45.
20. Rejraji H, Sion B, Prensier G, Carreras M, Motta C, Frenoux JM, *et al.* Lipid remodeling of murine epididymosomes and spermatozoa during epididymal maturation. *Biol Reprod* 2006;74:1104-13.
21. Sullivan R, Saez F. Epididymosomes, prostasomes, and liposomes: Their roles in mammalian male reproductive physiology. *Reproduction* 2013;146:R21-35.
22. Leahy T, Gadella BM. New insights into the regulation of cholesterol efflux from the sperm membrane. *Asian J Androl* 2015;17:561-7.
23. Boerke A, Brouwers JF, Olkkonen VM, van de Lest CH, Sostaric E, Schoevers EJ, *et al.* Involvement of bicarbonate-induced radical signaling in oxysterol formation and sterol depletion of capacitating mammalian sperm during *in vitro* fertilization. *Biol Reprod* 2013;88:21.
24. Shan S, Xu F, Hirschfeld M, Brenig B. Sperm lipid markers of male fertility in mammals. *Int J Mol Sci* 2021;22:8767.
25. Cross NL. Reorganization of lipid rafts during capacitation of human sperm. *Biol Reprod* 2004;71:1367-73.
26. Lucio CF, Brito MM, Angrimani D, Belaz K, Morais D, Zampieri D, *et al.* Lipid composition of the canine sperm plasma membrane as markers of sperm motility. *Reprod Domest Anim* 2017;52 Suppl 2:208-13.
27. Vance JE, Tasseva G. Formation and function of phosphatidylserine and phosphatidylethanolamine in mammalian cells. *Biochim Biophys Acta* 2013;1831:543-54.
28. Gautier C, Aurich C. "Fine feathers make fine birds" - The mammalian sperm plasma membrane lipid composition and effects on assisted reproduction. *Anim Reprod Sci* 2022;246:106884.
29. Dean JM, Lodhi IJ. Structural and functional roles of ether lipids. *Protein Cell* 2018;9:196-206.
30. Ren M, Xu Y, Erdjument-Bromage H, Donelian A, Phoon CK, Terada N, *et al.* Extramitochondrial cardiolipin suggests a novel function of mitochondria in spermatogenesis. *J Cell Biol* 2019;218:1491-502.
31. Kaiser F, Huebecker M, Wachten D. Sphingolipids controlling ciliary and microvillar function. *FEBS Lett* 2020;594:3652-67.
32. Zalata AA, Christophe AB, Depuydt C.E, Schoonjans F, Comhaire, F.H. The fatty acid composition of phospholipids of spermatozoa from infertile patients. *Mol Hum Reprod* 1998; 4:111-8.
33. Gulaya N, Margitich V, Govseeva N, Klimashevsky V, Gorpynchenko I, Boyko M. Phospholipid composition of human sperm and seminal plasma in relation to sperm fertility. *Arch Androl* 2001;46:169-75.
34. Andersen JM, Rønning PO, Herning H, Bekken SD, Haugen TB, Witczak O. Fatty acid composition of spermatozoa is associated with BMI and with semen quality. *Andrology* 2016;4:857-65.
35. Yu L, Yang X, Ma B, Ying H, Shang X, He B, Zhang Q. Abnormal arachidonic acid metabolic network may reduce sperm motility via P38 MAPK. *Open Biol* 2019; 9:180091.
36. Hamamah S, Seguin F, Barthelemy C, Akoka S, Lepape A, Lansac J, Royere D. ¹H nuclear magnetic resonance studies of seminal plasma from fertile and infertile men. *J Reprod Fertil* 1993;97:51-55.
37. Roy S, Banerjee A, Pandey HC, Singh G, Kumari GL. Application of seminal germ cell morphology and semen biochemistry in the diagnosis and management of azoospermic subjects. *Asian J Androl* 2001;3:55-62.
38. Sugkraroek P, Kates M, Leader A, Tanphaichitr N. Levels of cholesterol and phospholipids in freshly ejaculated sperm and Percoll-gradient-pelleted sperm from fertile and unexplained infertile men. *Fertil Steril* 1991;55:820-7.
39. Roqueta-Rivera M, Stroud CK, Haschek WM, Akare SJ, Segre M, Brush RS, Agbaga MP, Anderson RE, Hess RA, Nakamura MT. Docosahexaenoic acid supplementation fully restores fertility and spermatogenesis in male delta-6 desaturase-null mice. *J Lipid Res* 2010;51:360-67.
40. Gorgas K, Teigler A, Komljenovic D, Just WW. The ether lipid-deficient mouse: Tracking down plasmalogen functions. *BBA-Mol Cell Res* 2006;1763:1511-26.
41. Brites P, Motley AM, Gressens P, Mooyer PAW, Ploegaert I, Everts V, *et al.* Impaired neuronal migration and endochondral ossification in Pex7 knockout mice: A model for rhizomelic chondrodysplasia punctata. *Hum Mol Genet* 2003;12:2255-67.
42. Wittmann A, Grimm MOW, Scherthan H, Horsch M, Beckers J, Fuchs H, *et al.* Sphingomyelin Synthase 1 Is Essential for Male Fertility in Mice. *PLoS ONE* 2016;11:0164298.
43. Mizuno Y, Ninomiya Y, Nakachi Y, Iseki M, Iwasa H, Akita M, *et al.* Tysnd1 Deficiency in Mice Interferes with the Peroxisomal Localization of PTS2 Enzymes, Causing Lipid Metabolic Abnormalities and Male Infertility. *PLoS Genet* 2013;9:1003286.
44. Stoffel W, Schmidt-Soltau I, Binczek E, Thomas A, Thevis M, Wegner I. Dietary ω3-and ω6-Polyunsaturated fatty acids reconstitute fertility of juvenile and adult Fads2-Deficient mice. *Mol Metab* 2020;36:100974.
45. Butler A, He XX, Gordon RE, Wu HS, Gatt S, Schchman EH. Reproductive pathology and sperm physiology in acid sphingomyelinase-deficient mice. *Am J Pathol* 2002;161:1061-75.
46. Iizuka-Hishikawa Y, Hishikawa D, Sasaki J, Takubo K, Goto M, Nagata K, *et al.* Lysophosphatidic acid acyltransferase 3 tunes the membrane status of germ cells by incorporating docosahexaenoic acid during spermatogenesis. *J Biol Chem* 2017;292:12065-76.
47. Yeboah GK, Lobanova ES, Brush RS, Agbaga MP. Very long chain fatty acid-containing lipids: A decade of novel insights from the study of ELOVL4. *J Lipid Res* 2021;62:100030.
48. Xie S, Naslavsky N, Caplan S. Diacylglycerol kinases in membrane trafficking. *Cell Logist* 2015;5:e1078431.

49. Tanphaichitr N, Kongmanas K, Faull KF, Whitelegge J, Compostella F, Goto-Inoue N, *et al.* Properties, metabolism and roles of sulfolactosylglycerolipid in male reproduction. *Prog Lipid Res* 2018;72:18-41.
50. Guillermet-Guibert J, Smith LB, Halet G, Whitehead MA, Pearce W, Rebourcet D, *et al.* Novel role for p110 β PI 3-kinase in male fertility through regulation of androgen receptor activity in sertoli cells. *PLoS Genet* 2015;11:e1005304.
51. Rodemer C, Thai TP, Brügger B, Gorgas K, Just W. Targeted disruption of ether lipid synthesis in mice. *Adv Exp Med Biol* 2003;544:355-68.
52. Wittmann A, Grimm MO, Scherthan H, Horsch M, Beckers J, Fuchs H, *et al.* Sphingomyelin synthase 1 is essential for male fertility in mice. *PLoS One* 2016;11:e0164298.
53. Stroud CK, Nara TY, Roqueta-Rivera M, Radlowski EC, Lawrence P, Zhang Y, *et al.* Disruption of FADS2 gene in mice impairs male reproduction and causes dermal and intestinal ulceration. *J Lipid Res* 2009;50:1870-80.
54. Ceyhan Y, Zhang M, Guo J, Sandoval CG, Vacher J, Kaftanovskaya EM, *et al.* Deletion of inositol polyphosphate 4-phosphatase type-II B affects spermatogenesis in mice. *PLoS One* 2020;15:e0233163.
55. Mahboubi S, Dupont C, Elfassy Y, Lameignère E, Levy R. Exploring the potential impact of nutritionally actionable genetic polymorphisms on idiopathic male infertility: A review of current evidence. *Asian J Androl* 2021;23:441-9.
56. Shen WJ, Azhar S, Kraemer FB. Lipid droplets and steroidogenic cells. *Exp Cell Res* 2016;340:209-14.
57. Kumari RM, Khatri A, Chaudhary R, Choudhary V. Concept of lipid droplet biogenesis. *Eur J Cell Biol* 2023;102:151362.
58. Choudhary V, Ojha N, Golden A, Prinz WA. A conserved family of proteins facilitates nascent lipid droplet budding from the ER. *J Cell Biol* 2015;211:261-71.
59. Choudhary V, El Atab O, Mizzon G, Prinz WA, Schneider R. Seipin and Nem1 establish discrete ER subdomains to initiate yeast lipid droplet biogenesis. *J Cell Biol* 2020;219:e201910177.
60. Shen WJ, Cortez Y, Singh A, Chen W, Azhar S, Kraemer FB. Mice deficient in ER protein seipin have reduced adrenal cholesteryl ester lipid droplet formation and utilization. *J Lipid Res* 2022;63:100309.
61. Tarique I, Vistro WA, Bai X, Yang P, Hong C, Huang Y, *et al.* LIPOPHAGY: A novel form of steroidogenic activity within the LEYDIG cell during the reproductive cycle of turtle. *Reprod Biol Endocrinol* 2019;17:19.
62. Yamaguchi T, Fujikawa N, Nimura S, Tokuoka Y, Tsuda S, Aiuchi T, *et al.* Characterization of lipid droplets in steroidogenic MLTC-1 Leydig cells: Protein profiles and the morphological change induced by hormone stimulation. *Biochim Biophys Acta* 2015;1851:1285-95.
63. Wang W, Wei S, Li L, Su X, Du C, Li F, *et al.* Proteomic analysis of murine testes lipid droplets. *Sci Rep* 2015;5:12070.
64. Ma Y, Zhou Y, Zhu YC, Wang SQ, Ping P, Chen XF. Lipophagy contributes to testosterone biosynthesis in male rat leydig cells. *Endocrinology* 2018;159:1119-29.
65. Gao F, Li G, Liu C, Gao H, Wang H, Liu W, *et al.* Autophagy regulates testosterone synthesis by facilitating cholesterol uptake in Leydig cells. *J Cell Biol* 2018;217:2103-19.
66. Esmaeilian Y, Hela F, Bildik G, İltumur E, Yusufoglu S, Yildiz CS, *et al.* Autophagy regulates sex steroid hormone synthesis through lysosomal degradation of lipid droplets in human ovary and testis. *Cell Death Dis* 2023;14:342.
67. Saugandhika S, Sapra L, Kumari K, Srivastava RK. High salt diet impairs male fertility in mice via modulating the skeletal homeostasis. *Reprod Sci* 2023;30:3339-52.
68. Liu Y, Cao X, He C, Guo X, Cai H, Aierken A, *et al.* Effects of ferroptosis on male reproduction. *Int J Mol Sci* 2022;23:7139.
69. Sozen E, Demirel-Yalciner T, Koroglu MK, Elmas MA, Ercan F, Ozer NK. High cholesterol diet activates ER stress mediated apoptosis in testes tissue: Role of α -tocopherol. *IUBMB Life* 2022;74:85-92.
70. Feng R, Cheng D, Zhang W, Zhang J, Chen S, Xia Y. Immune microenvironment dysregulation: A contributing factor to obesity-associated male infertility. *Biomedicines* 2025;13:1314.
71. Zhang Z, Chen H, Li Q. High-fat diet led to testicular inflammation and ferroptosis via modulation of gut-testis axis. *Int Immunopharmacol* 2024;142:113235.
72. Jing J, Ding N, Wang D, Ge X, Ma J, Ma R, *et al.* Oxidized-LDL inhibits testosterone biosynthesis by affecting mitochondrial function and the p38 MAPK/COX-2 signaling pathway in Leydig cells. *Cell Death Dis* 2020;11:626.
73. Huang C, Hsu HJ, Wang ME, Hsu MC, Wu LS, Jong DS, *et al.* Fatty acids suppress the steroidogenesis of the MA-10 mouse Leydig cell line by downregulating CYP11A1 and inhibiting late-stage autophagy. *Sci Rep* 2021;11:12561.
74. Zhou X, Mo Z, Li Y, Huang L, Yu S, Ge L, *et al.* Oleic acid reduces steroidogenesis by changing the lipid type stored in lipid droplets of ovarian granulosa cells. *J Anim Sci Biotechnol* 2022;13:27.
75. Obaideen M, Önel T, Yıldırım E, Yaba A. The role of leptin in the male reproductive system. *J Turk Ger Gynecol Assoc* 2024;25:247-58.
76. Arora H, Qureshi R, Khodamoradi K, Seetharam D, Parmar M, Van Booven DJ, *et al.* Leptin secreted from testicular microenvironment modulates hedgehog signaling to augment the endogenous function of Leydig cells. *Cell Death Dis* 2022;13:208.
77. Jahangirian J, Jannatifar R, Hafezi M, Amozegar H, Hosseini R, Nasiri N, *et al.* Is there an association between dyslipidemia and the risk of ovarian hyperstimulation syndrome in a population of non-obese polycystic ovary syndrome patients? A cross-sectional study. *Int J Fertil Steril* 2025;19:193-9.
78. Simón L, Funes AK, Monclús MA, Colombo R, Cabrillana ME, Saez Lancellotti TE, *et al.* Manchette-acrosome disorders and testicular efficiency decline observed in hypercholesterolemic rabbits are recovered with olive oil enriched diet. *PLoS One* 2018;13:e0202748.
79. Diaz-Fontdevila M, Peña W, Bustos-Obregón E. Experimental hypercholesterolaemia in rabbits. Effect on lipid domains in homologous spermatozoa. *Andrologia* 1998;30:15-22.
80. Funes AK, Avena MV, Ibañez J, Simón L, Ituarte L, Colombo R, *et al.* Extra-virgin olive oil ameliorates high-fat diet-induced seminal and testicular disorders by modulating the cholesterol pathway. *Andrology* 2023;11:1203-17.
81. Whitfield M, Guiton R, Rispal J, Acar N, Kocer A, Drevet JR, *et al.* Dyslipidemia alters sperm maturation and capacitation in LXR-null mice. *Reproduction* 2017;154:827-42.

82. Rao K, Du GH, Yang WM. Correlation between abnormal serum lipid and erectile dysfunction. *Zhonghua Nan Ke Xue* 2005;11:112-5.
83. Hammoud AO, Gibson M, Peterson CM, Hamilton BD, Carrell DT. Obesity and male reproductive potential. *J Androl* 2006;27:619-26.
84. Wang X, Sharma RK, Sikka SC, Thomas AJ Jr., Falcone T, Agarwal A. Oxidative stress is associated with increased apoptosis leading to spermatozoa DNA damage in patients with male factor infertility. *Fertil Steril* 2003;80:531-5.
85. Gualtieri R, Kalthur G, Barbato V, Longobardi S, Di Rella F, Adiga SK, *et al.* Sperm oxidative stress during *in vitro* manipulation and its effects on sperm function and embryo development. *Antioxidants (Basel)* 2021;10:1025.
86. Raut S, Kumar AV, Deshpande S, Khambata K, Balasinar 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.
87. Yan W. Gene knockouts that affect Sertoli cell function. In: Griswold MD, editor. *Sertoli cell biology*. 2nd ed. United States: Academic Press, Elsevier; 2015. p. 37-469.
88. Eacker SM, Agrawal N, Qian K, Dichak HL, Gong EY, Lee K, *et al.* Hormonal regulation of testicular steroid and cholesterol homeostasis. *Mol Endocrinol* 2008;22:623-35.
89. Brauns AK, Heine M, Tödter K, Baumgart-Vogt E, Lüers GH, Schumacher U. A defect in the peroxisomal biogenesis in germ cells induces a spermatogenic arrest at the round spermatid stage in mice. *Sci Rep* 2019;9:9553.
90. Shimamoto K, Sofikitis N. Effect of hypercholesterolaemia on testicular function and sperm physiology. *Yonago Acta medica* 1998;41:23-29.
91. Purohit A, Daradka HM. Effect of mild hyperlipidaemia on testicular cell population dynamics in albino rats. *Indian J Exp Biol* 1999;37:396-8.
92. Yamamoto Y, Shimamoto K, Sofikitis N, Miyagawa I. Effects of hypercholesterolaemia on Leydig and Sertoli cell secretory function and the overall sperm fertilizing capacity in the rabbit. *Hum Reprod* 1999;14:1516-21.
93. Bashandy AES. Effect of fixed oil of nigella sativa on male fertility in normal and hyperlipidemic rats. *Int J Pharmacol* 2007;3:27-33.
94. Saez Lancellotti TE, Boarelli PV, Monclus MA, Cabrillana ME, Clementi MA, *et al.* Hypercholesterolemia impaired sperm functionality in rabbits. *PLoS One* 2010;5: e13457.
95. Ouvrier A, Alves G, Damon-Soubeyrand C, Marceau G, Cadet R, *et al.* Dietary cholesterol-induced post-testicular infertility. *PLoS One* 2011;6(11):e26966.
96. Sênos Demarco R, Uyemura BS, D'Alterio C, Jones DL. Mitochondrial fusion regulates lipid homeostasis and stem cell maintenance in the *Drosophila* testis. *Nat Cell Biol* 2019;21:710-20.
97. Shi JF, Li YK, Ren K, Xie YJ, Yin WD, Mo ZC. Characterization of cholesterol metabolism in Sertoli cells and spermatogenesis (Review). *Mol Med Rep* 2018;17:705-13.
98. Billah MM, Khatiwada S, Lecomte V, Morris MJ, Maloney CA. Ameliorating high-fat diet-induced sperm and testicular oxidative damage by micronutrient-based antioxidant intervention in rats. *Eur J Nutr* 2022;61:3741-53.
99. Dai Y, Guo Y, Tang W, Chen D, Xue L, Chen Y, *et al.* Reactive oxygen species-scavenging nanomaterials for the prevention and treatment of age-related diseases. *J Nanobiotechnology* 2024;22:252.
100. Li Y, Zhan M, Li J, Zhang W, Shang X. Lycopene alleviates lipopolysaccharide-induced testicular injury in rats by activating the PPAR signaling pathway to integrate lipid metabolism and the inflammatory response. *Transl Androl Urol* 2023;12:271-85.
101. Satrialdi, Pratiwi C, Khaeranny RN, Mudhakhir D. The development of mitochondria-targeted quercetin for rescuing Sertoli cells from oxidative stress. *Res Pharm Sci* 2025;20:109-20.
102. Sharma P, Kaushal N, Saleth LR, Ghavami S, Dhingra S, Kaur P. Oxidative stress-induced apoptosis and autophagy: Balancing the contrary forces in spermatogenesis. *Biochim Biophys Acta Mol Basis Dis* 2023;1869:166742.
103. Uribe P, Meriño J, Matus CE, Schulz M, Zambrano F, Villegas JV, *et al.* Autophagy is activated in human spermatozoa subjected to oxidative stress and its inhibition impairs sperm quality and promotes cell death. *Hum Reprod* 2022;37:680-95.
104. Correnti S, Preianò M, Fregola A, Gamboni F, Stephenson D, Savino R, *et al.* Seminal plasma untargeted metabolomic and lipidomic profiling for the identification of a novel panel of biomarkers and therapeutic targets related to male infertility. *Front Pharmacol* 2023;14:1275832.
105. Wood PL, Scoggin K, Ball BA, Troedsson MH, Squires EL. Lipidomics of equine sperm and seminal plasma: Identification of amphiphilic (O-acyl)- ω -hydroxy-fatty acids. *Theriogenology* 2016;86:1212-21.
106. Di Nisio A, De Toni L, Sabovic I, Vignoli A, Tenori L, Dall'Acqua S, *et al.* Lipidomic profile of human sperm membrane identifies a clustering of lipids associated with semen quality and function. *Int J Mol Sci* 2023;25:297.
107. Borges ED, Vireque AA, Berteli TS, de Lima CB, Sobreira TJ, Ferreira CR, *et al.* Lipidomics of sperm cells of fertile and subfertile men by MRM-profiling. *Fertil Steril* 2018;10:E303-4.
108. Wang Z, Zhu H, Xiong W. Advances in mass spectrometry-based multi-scale metabolomic methodologies and their applications in biological and clinical investigations. *Sci Bull (Beijing)* 2023;68:2268-84.
109. Buchberger AR, DeLaney K, Johnson J, Li L. Mass spectrometry imaging: A review of emerging advancements and future insights. *Anal Chem* 2018;90:240-65.
110. Dueñas ME, Essner JJ, Lee YJ. 3D MALDI mass spectrometry imaging of a single cell: Spatial mapping of lipids in the embryonic development of zebrafish. *Sci Rep* 2017;7:14946.
111. Cobice DF, Livingstone DE, Mackay CL, Goodwin RJ, Smith LB, Walker BR, *et al.* Spatial localization and quantitation of androgens in mouse testis by mass spectrometry imaging. *Anal Chem* 2016;88:10362-7.
112. Ucal Y, Durer ZA, Atak H, Kadioglu E, Sahin B, Coskun A, *et al.* Clinical applications of MALDI imaging technologies in cancer and neurodegenerative diseases. *Biochim Biophys Acta Proteins Proteom* 2017;1865:795-816.

How to cite this article: Saugandhika S, Yadav S, Choudhary V. Relevance of lipid homeostasis to male infertility. *J Reprod Healthc Med*. 2025;6:24. doi: 10.25259/JRHM_30_2025