

# Hyper-Lipidemia and Male Fertility: A Critical Review of Literature

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## Abstract

Hyper-Lipidemia/hypercholesterolemia is a major health problem all over the world and it is emerging as an important cause of adverse health outcomes including cardiovascular complications, metabolic disorders and infertility. Over the years, many population based studies have highlighted a trend towards deterioration of semen quality and decline of male fertility. The rise in worldwide dyslipidaemia combined with the trend of decreasing semen quality and male fertility, has called an attention of scientific community. A large number of research papers have been published to explore the links between hyperlipidaemia and male infertility. The aim of this review is to critically examine and summarize the data gathered during the past few years from both experimental animal models and human studies on the relation between hypercholesterolemia and semen parameters, endocrine status, spermatogenesis and male fertility. For this purpose, the PubMed, Scopus and Google Scholar databases were comprehensively searched with the help of various search terms. Experimental studies based on hypercholesterolemic/high fat diet fed animal models and studies conducted on normal infertile/obese infertile men clearly demonstrate a negative impact of hypercholesterolemia on testicular functions, reproductive hormone synthesis and secretion, sperm maturation, sperm quality parameters and ejaculatory functions leading to male infertility. Various mechanisms have been suggested for such actions.

**Keywords:** Fertility; Hypercholesterolemia; Hyperlipidaemia; Semen parameters; Spermatogenesis; Sperm maturation; Testicular function

## Introduction

Dyslipidaemia is on the rise in young people in both developed and developing countries. It is believed that with increasing prevalence of sedentary life styles and dietary changes, hyperlipidaemia is emerging as an important cause of adverse health outcomes including cardiovascular complications, obesity, metabolic disorders, infertility and so on [1].

According to an estimate global infertility ranges between 10-15% of couple, affecting 50-80 million people all over the world. Male infertility has a substantial share of the total infertility burden [2,3]. Over the years, a number of population based studies have highlighted a trend towards deterioration of semen quality [4,5]. Due to environment contamination and change of life style, the infertility rate is going to increase in future.

Lipids have an important role in the functional activity of sperm cells, sperm viability, maturity, capacitation and fertilization [6,7]. Excessive intake of high cholesterol or high fat diet may induce hypercholesterolemia/hyperlipidemia and disturb cholesterol homeostasis in the body which may adversely affect normal male reproductive functions. Several animal and clinical studies have been conducted to focus on the association of hyperlipidaemia/hypercholesterolemia with male infertility. However, these studies show some variation in the results and also the exact molecular mechanism(s) of action are still poorly known. Therefore, the purpose of this review is to critically explore the links between hypercholesterolemia/hyperlipidaemia and male infertility, to address how it disrupts the male reproductive function and fertility.

## Significance of Lipids in Sperm Maturation

Lipids play multiple roles that either individually or collectively influence many cell processes. Cholesterol is one of the most important bio-molecule in animals and has significant role in cellular function

and integrity. It is essential for membrane composition, permeability, fluidity, endocytosis and intracellular signalling. It is also a precursor of all sexual hormones [8,9]. Cholesterol has crucial functions in the area of male and female reproductive physiology, from sex differentiation to gamete formation.

The sperm membrane is composed from heterogeneous mixture of phospholipids, glycolipids and sterol [10] and plays an important role in sperm capacitation and fertilization. It is known that the acrosome reaction and sperm-oocyte fusion both are membrane associated events [11]. Besides this, the lipids of the spermatozoa have been suggested to be important for viability, maturation and function of spermatozoa [12]. Cholesterol's ability to order saturated phospholipids contributes to the formation of rafts that have distinctive protein composition and are supposed to play an important role in signal transduction pathway [13].

Spermatozoa leaving testes are neither mobile nor fertile. As spermatozoa transverse through the epididymis and female genital tract, they undergo multiple biochemical and physiological modifications, such as the removal of seminal plasma proteins/glycoproteins absorbed to the surface of ejaculated spermatozoa, as well as modification and reorganization of sperm plasma membrane molecules [14]. As spermatozoa travel through the epididymis, modification in the content of cholesterol and different phospholipids takes place to promote membrane fluidity [15-19]. The modification of the sperm

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cholesterol during epididymal maturation has been investigated in several mammalian species. A significant (50%) decrease in the level of sperm cholesterol has been reported in hamster [20], mouse [21], and rat [22] and ram [23] whereas no significant change in sperm cholesterol content was observed in boar [24] and a significant increase was observed in goat [25]. During epididymis transit, the relative proportion of Polyunsaturated Fatty Acids (PUFAs) in sperms has been reported to increase [26]. These biochemical modifications of sterols and fatty acids occurring in the epididymis have a direct influence on the sperm plasma membrane architecture and dynamics [27]. The loss of cholesterol results in the decrease of cholesterol/phospholipid ratio and consequently increases of the fluidity of sperm membrane. Cholesterol depletion is important in the remodeling of lipid rafts on the sperm surface [28]. Cholesterol diffusion was higher in the sperm head region than in the tail and shows heterogeneous distribution when detected with filipin [29]. Cholesterol efflux from the sperm plasma membrane triggers signal transduction pathway, facilitates  $Ca^{+2}$  influx into sperm and is associated with changes in sperm membrane dynamics and structure, triggering the acrosomal reaction and sperm-oocyte fusion [17,30-32].

### Hyperlipidaemia and Male Fertility

In recent years much attention has been focused on the association of serum lipid profile with seminal plasma or sperm lipid content, semen quality and male infertility. A number of human studies have indicated an association between hypercholesterolemia and subsequently male infertility [33-36]. Contrary to these findings, others have found no correlation between serum cholesterol and the amount of cholesterol in the semen and in sperm or seminal plasma suggesting that sperm cholesterol content is regulated locally within the male reproductive tract [7,18,37-39]. It has been suggested that in male reproductive tract, lipid homeostasis is performed by testicular and post-testicular mechanism [7,40]. Khalili et al., [41] also showed that concentration of serum lipid was not generally related with the quality of sperm parameters.

There is a very little information regarding the direct association of serum Triglycerides (TG) with sperm parameters, independent of hypercholesterolemia. Zmuda et al., [42] reported a decrease in endogenous testosterone associated with an increase in triglycerides level. Alquabaty [43] also reported significant negative correlation between serum total testosterone level and triglycerides and insignificant correlation between serum testosterone and total cholesterol level in infertile men. Vignon et al., [44] also found that an increase in triglycerides have deleterious effect on spermatogenesis in men. Ergun et al., [45] have observed that increased triglycerides may have deleterious effect on spermatogenesis correlated with decrease sperm motility and testosterone in a group of infertile men. Contrary to these findings, Kulka et al., [46] showed no correlation between triglycerides concentration and sperm parameters (sperm concentration, motility and morphology). However, alteration in phospholipid concentration was associated with abnormal semen analysis. Change in fatty acid and phospholipid composition of human sperm membrane has also been reported in human asthenozoospermic samples. The cholesterol/phospholipid ratio was found to be higher in spermatozoa obtained from patients with idiopathic infertility [47].

In the past few years, a large number of studies have also been carried out on high cholesterol/high fat diet fed animal models

(mouse, rat and rabbit) to determine the association between serum lipid profile, seminal plasma or sperm lipid content and infertility (Table 1). The result of these studies have shown detrimental effect of hypercholesterolemia on testicular histology and functions including spermatogenesis and steroidogenesis, epididymal sperm maturation process, sperm quality parameters, sperm fertilizing capacity and fertility index [48-57].

It has been demonstrated that modifying the dietary intake of fatty acids, modified the fatty acid composition of sperm plasma membrane in rabbit [58] and in boar [59,60]. In normal goats, level of HDL cholesterol is positively correlated with testicular histology, seminal parameters and serum testosterone level while high serum triglycerides level exert adverse effect on testicular and seminal parameters and serum testosterone level [61]. Diaz-fondevila et al., [62] and Diaz-fondevila and Bustos-Obregan, [63] have reported that rabbits fed high cholesterol diet did not show increased cholesterol content of testis and seminal plasma. They suggested an adverse effect of cholesterol enriched diet on Leydig and Sertoli cells secretory function. Similar to this, Yammamoto et al., [51] also reported a significant reduction in sperm concentration, sperm motility and morphology in hypercholesterolemic rabbit. However, there was no significant difference in cholesterol concentration of seminal plasma or testicular tissue when compared with control. They suggested that hypercholesterolemia has a detrimental effect on Leydig and Sertoli cell secretory function, sperm maturation process and the overall sperm fertilizing capacity. Hypercholesterolemia in animals may cause a significant difference in filipin-sterol complex in plasma membrane of acrosome region of sperm which could modify the sperm membrane fusion capacity and functionality and decrease in kinetics of acrosome reaction [63].

Tanaka et al., [52] have suggested that hypercholesterolemia is an independent risk factor for testicular dysfunction in rats and the reduction in serum and testicular testosterone level is due, at least in part, to a reduction in testicular LH/HCG binding. Martinez-mortos et al., [64] have found that dietary cholesterol modulates bioactive peptides of the rennin-angiotensin system localized in the testis which result in inhibition of steroidogenesis and consequently decrease in testosterone production in Balb C mice.

Ouvrier et al., [56] have reported that an overload of dietary cholesterol in Lxr- deficient male mice (liver X receptor deficient mouse model) causes complete infertility. Spermatozoa of cholesterol fed Lxr deficient male mice were found to be dramatically less viable, less motile and highly susceptible to a premature acrosome reaction, although spermatogenesis was not affected, as shown by normal sperm count, testicular weight and histology. It was suggested that infertility resulted from post-testicular defect. High cholesterol diet alter the caput epididymal epithelium in a segment and cell specific manner, characterized by peritubular accumulation of cholesterol ester lipid droplets in smooth muscle lining of the epididymal duct which impair peristaltic contraction and consequently sperm progression in the lumen of the tubule, perturbing the finely orchestrated process of sperm maturation.

It has also been proposed that hypercholesterolemia induces reproductive and testicular damage by excessive generation of free radicals and increased oxidative stress, which are cytotoxic to spermatozoa [53,65-67]. Administration of antioxidants and lipid lowering agents has been shown to protect the testis and reproductive functions during hypercholesterolemia [53,65,66]. Furthermore,

S.N.	Animals	Diet/ induction of hyperlipidemia (Dose and duration)	Lipid profile	Effect on hormones	Sperm parameters	Effect on genital organs	Reference
1.	Male Wistar rat	2% cholesterol added in diet for 21 days	Serum cholesterol was significantly higher	No significant changes were seen in testosterone, LH and prolectin levels but the level of FSH was decreased significantly.	-	-	[3]
2.	Male rat and rabbit	Cholesterol feeding for 120 days	The TC and LDL cholesterol values were increased while the HDL cholesterol/TC ratio was significantly decreased		-	TC, TG and phospholipids concentration in the testes were increased, whereas, glycogen was significantly reduced. Significant reduction in secondary spermatocytes and spermatid cell population, seminiferous tubules, and Leydig's cell nuclear dimensions were observed in both cholesterol fed rats and rabbits.	[48]
3.	New Zealand white male rabbit	Chow containing 3% cholesterol for 12 weeks	Total lipid and TC levels in serum were significantly higher. However, testicular cholesterol content showed no significant change.	Basal peripheral serum testosterone profiles were not significantly different. However, testosterone responses to HCG stimulation were significantly lower	Epididymal sperm content, percentage of motile spermatozoa, and motility grade were significantly lower in hypercholesterolemic rabbits.	Showed no significant effect on testicular weight. The proportion of cleaved oocytes to fertilize oocytes was significantly lower in hypercholesterolemic rabbits.	[49]
4.	Male albino rat	Cholesterol (400 mg/kg) with 5% fats for 2 months, orally	Serum TC and TG levels were significantly increased	-	Sperm motility and density were reduced significantly,	The seminiferous tubules from testes of HFD fed animals were wavy in outline and shrunken and showed inhibition of spermatogenesis. The testicular population of germ cells was reduced. The number of degenerative Leydig cells increased significantly.	[50]
5.	New Zealand white male rabbit	Chow containing 3% cholesterol for 12 weeks	Mean values of total lipids in peripheral serum, testicular tissue and seminal plasma samples were significantly greater. Cholesterol level in serum increased significantly; however, there was no effect on testicular or seminal plasma cholesterol concentration.	Basal peripheral serum testosterone profiles were not significantly different from control. In contrast, testosterone responses to HCG stimulation were significantly lower in hypercholesterolemic rabbits.	Sperm concentration, sperm motility, length of sperm mid-piece was significantly lower in hypercholesterolemic rabbits.	The difference in the mean values of left testicular weight between control and hypercholesterolemic rabbits was not significant. Mean androgen-binding protein activity in testicular cytosol was significantly lower, the hypercholesterolemic rabbits showed detrimental effect on Leydig and Sertoli cell secretory function, spermatogenesis, sperm maturation and overall sperm fertilizing capacity.	[51]
6.	Male SD rat	Standard chow containing 2% cholesterol for 4 weeks	Serum TC was significantly higher	Serum testosterone, testicular testosterone and LH/HCG binding were significantly lower	-	-	[52]

7.	Adult male and female SD rat	Cholesterol diet (400 mg/kg body weight) for 60 days, orally	Significant increase (p<0.001) in cholesterol and TG levels.	-	Significant reduction (p<0.001) in sperm motility and density in cauda epididymides and testes	A significant reduction (p<0.001) in epithelial cell height of caput, cauda epididymis and SV was observed. Significant reduction (p<0.001) in seminiferous tubules and Leydig cell nuclear diameters was also observed. Spermatoocytes and spermatid numbers in seminiferous tubules were significantly reduced (p<0.001). There was significant reduction in the numbers of female impregnated, implantation sites and vital fetuses.	[54]
8.	Male White New Zealand rabbit	Diet supplement with cholesterol (0.05%) for 12 months	Significant increase in serum cholesterol.	-	Semen pH, sperm concentration and vitality were not affected by dietary cholesterol. However, ejaculate semen volume and sperm motility were significantly decreased. Moreover, sperm showed increased morphological alterations.	Spermatozoa from cholesterol fed rabbits showed a reduced sperm membrane response to the hypo-osmotic swelling test and to the induction of protein tyrosine phosphorylation under capacitation condition. Hypercholesterolemia adversely affects semen quality, sperm motility, capacitation and acrosome reaction.	[55]
9.	Lxr-knockout mice	Lipid-enriched diet containing 1.25% cholesterol for 4 weeks	Significant increases in plasma TC, LDL, HDL and TG levels.	-	Sperm morphology showed a significant increase in the percentage of broken cells and impaired motility but testicular sperm production was not affected	The delivery rate (percentage of mated females giving birth to live offspring) indicated that high cholesterol diet fed Lxr $\alpha$ ; $\beta$ -/- male mice were totally infertile.	[56]
10.	New Zealand white male rabbit	Cholesterol enriched diet (2% weight/weight ratio) for 12 weeks	serum TC level was elevated in rabbits	-	-	Increase in inter-tubular connective tissue and diameter of vessels, abundant spermatogonia and primary spermatocytes along with reduced and disorganized germinal epithelium was noted in hypercholesterolemic rabbits.	[57]
11.	New Zealand white rabbit	Cholesterol alone or fish oil or PUFA enriched diet for 2 months	Increased serum TC and LDL-cholesterol levels. Nevertheless, the high cholesterol and total lipids levels in serum did not affect the cholesterol levels in seminal plasma but affect the seminal plasma total lipids.	-	Decreased capacity of sperm acrosome reaction as compared to control. The cholesterol/ phospholipid ratio in sperm of hypercholesterolemic rabbits remains unchanged.	-	[63]
12.	Male Balb/C mice	Cholesterol 1% and cholic acid 0.5% with standard diet for 15 days	Significant increase in serum TC level	Significant decrease in serum circulating level of testosterone due to modulation of RAS cascade at the testes level.	-	-	[64]
13.	Male Swiss albino rat	Normal diet containing 1% cholesterol, 0.5% cholic acid and 2% sheep fat for 2 months	Significant (p<0.01) increase in TC, TG and LDL levels but HDL level decreased significantly (p<0.01).	Plasma testosterone level significantly (p<0.01) declined	The value of sperm motility, sperm count decreased significantly (p<0.01), however sperm abnormality was increased significantly	Weight of the testes and SV decreased significantly (p<0.01) in cholesterol fed rats	[65]

14.	ApoE-knockout C57BL/6J male mice	HFD	-	-	-	Ultra structural observations showed dramatically histopathological alterations in testicular tissues. The basement membranes of seminiferous tubules were partially thickened and wavy-like, vacuolar degeneration of mitochondria and dilation of endoplasmic reticulum were identified as well as the number of mitochondria and lipid droplets decreased significantly in Leydig cells and Sertoli cells.	[67]
15.	21 day old male SD rat	HFD for 9 weeks	Plasma TG and TC levels increased remarkably.	The testosterone level decreased, estradiol concentraon also lowered at the end of the 3rd, 4th and 5th week but dramatically increased at the 9 <sup>th</sup> week.	-	The testicular coefficient declined; however the Lees's index showed an increase. Spermatogenic epithelial cells showed disordered arrangement; the spermatogenic cell layers and the number of mature sperms were reduced.	[70]
16.	21 day old rat	Fat-enriched diet for 6 weeks	-	The testosterone to estradiol ratio (T/E2) in model group was significantly lower than control.	-	Impairment of seminiferous tubules development with only 4 germ cell layers showing disordered arrangement.	[71]
17.	Male New Zealand rabbit (juvenile)	HFD	Concentrations of TC, TG and LDL-cholesterol increased	The levels of testosterone, LH and FSH decreased	-	Penial length was short (P < 0.05) and testicular coefficient declined (P<0.01), alteration in testicular development with sabotage of spermatogenic epithelium was detected.	[72]
18.	Male C57BL/6J mice	HFD for 25 weeks	Body fat percentage was significantly higher in high-fat-fed mice	Measurement of testosterone produced inconclusive results	There were no disparities in morphology or total sperm count collected from the cauda epididymis but a 20% decrease in sperm motility was evident.	Significantly reduced numbers of plugs and pregnancies in female impregnated by obese male mice was observed. However, these obese mice exhibited no significant differences in the average weight of either testes or epididymis.	[93]
19.	C57BL6 male mice	HFD (21% fat) for 10 weeks	Increased serum TC, TG levels and adiposity	Decreased serum testosterone level	Decreased sperm motility, sperm capacitation and increased abnormal sperm tail morphology.	Showed increase in sperm DNA damage, reactive oxygen species and mitochondrial membrane potential without any effect on sperm count	[95]
20.	Male Wistar rat	HFD with a content of 20% fat for 15, 30 or 45 weeks	-	Serum testosterone, FSH and LH levels were similar, but estradiol and leptin levels were increased in HFD rats.	There was no statistically significant difference related to the number of mature spermatids in the testis and daily sperm production. However, an alteration in sperm motility parameters was recorded.	Reproductive organs weights did not show any differences except the relative weight of empty SV which was lower. There was no effect on sexual behavior but fertility potential was declined in HFD rats.	[97]
21.	21 days old SD male rat (Weaning)	HFD for 90 days	Showed an increase in BMI and body weight, serum glucose and cholesterol levels were non-significantly increased.	Reduction was observed in the testosterone levels while circulating leptin and estradiol levels showed a significant increase	Reduced sperm viability (-28.88%), motility (-26.49%) and concentration (-23.86%)	An increase in the lipid peroxidation rate in epididymis along with degenerative morphological changes was observed.	[98]



22.	Male Wistar rat	Fed standard chow enriched with 4% cholesterol and 1% cholic acid, for 5 months	Caused a significant elevation in serum TC and LDL levels, whereas HDL and TG levels were comparable to control	Plasma total testosterone and estradiol levels did not differ between groups, but their free fraction, along with SHBG levels, were significantly affected	-	High cholesterol diet affected the structure of the ventral prostate and both absolute and relative weights of ventral prostate were significantly lower.	[124]
23.	C57BL/6 mice	Atherogenic diet containing 15% fat, 1.25% cholesterol, and 0.5% sodium cholate for 8 weeks	Atherogenic diet induced significant increase in serum TC and hepatic TC and TG levels, however, serum TG level showed a significant decrease. No significant change in testicular cholesterol was observed.	There was no statistically significant difference in the basal peripheral serum and testicular testosterone values between test and control group. In the meantime, testosterone responses to HCG stimulation in serum, testis, and liver were lower in hypercholesterolemic mice.	-	The expression of three testosterone regulated proteins (MUPs, CAIII and GST P2) in liver was statistically lower in hypercholesterolemic mice. The study suggests an adverse effect of atherogenic diet on testosterone biosynthesis.	[178]
24.	Male Wistar rat	Fed normal diet containing 1.5% cholesterol for 4 weeks	Induced a significant increase in serum TC level	Levels of FSH, LH and testosterone in serum of male rats were severely declined	The hypercholesterolemic rats have no live sperm in their semen, therefore, their sperm viability reached zero.	The ratio of testes and epididymis weight to BW in hypercholesterolemic rats were significantly low as compared to control group.	[179]
25.	Male SD rat	HFD comprising the standard diet supplemented with 20% (w/w) pure sunflower seed oil for 6 weeks	-	-	Sperm concentration, viability and motility were significantly decreased with an increase of damage in sperm DNA.	The testis and epididymis weight coefficient (expressed as relative to BW) of rats fed with high-fat diet was significantly lowered. There was significant increase in lipid peroxidation and decrease of antioxidant parameters in serum and sperms.	[180]
26.	Male Wistar rat	High-fat and high caloric index cafeteria foods for 10 weeks	TG levels were significantly higher ( $P < 0.05$ )	The testosterone level was significantly lower; however, the levels of LH, FSH and estradiol were not statistically different from control rats.	-	-	[181]
27.	Male Wistar rat	HFD (composed of milk fat and approximately 60% fat) for 12 weeks	The levels of serum TC, TG and HDL-cholesterol / LDL-cholesterol in HFD group were significantly higher	-	Viability, motility and normal morphology of sperm significantly decreased	Induced pathological changes in seminiferous tubules and affected spermatogenesis.	[182]

BW: Body Weight; CAIII: Carbonic Anhydrase; FSH: Follicle Stimulating Hormone; GST P2: Glutathione S-transferase; HCG: Human Chorionic Gonadotropin; HDL: High Density Lipoprotein; HFD: High Fat Diet; LDL: Low Density Lipoprotein; LH: Luteinizing Hormone; MUPs: Major Urinary Proteins; RAS: Renin Angiotensinogen System; SD: Sprague Dawley; SHBG: Sex Hormone-Binding Globulin; SV: Seminal Vesicle; TC: Total Cholesterol; TG: Triglycerides.

**Table 1:** Effect of Diet Induced Hyperlipidaemia/Hypercholesterolemia on Male Reproductive Function in Various Experimental Animals

treatment of hypercholesterolemia patients with statins at the dose effective in improving lipid profile has shown modulating effect on semen parameters and gonadal endocrine dysfunction [68,69].

### Hyperlipidaemia and Testicular Development

High fat diet induces nutritional obesity, hyperlipemia, adverse effect on testicular development and hormonal profile in pubertal rat [70,71] and rabbit [72]. There was a significant decline in the testosterone and testosterone to estradiol ratio (T/Es). High lipid diet can induce obesity and increases the apoptosis of testicular spermatogenic cell population [71].

### Hyperlipidaemia and Erectile function

Accumulative evidences also suggest that hyperlipidaemia is associated with erectile dysfunction. A high level of total cholesterol and low level of High Density Lipoprotein (HDL) cholesterol are important risk factors for erectile dysfunction [73-75]. Nikoobakht et al., [76] reported that plasma cholesterol and LDL level in individual suffering from erectile dysfunction were significantly higher than control. However, no difference in the mean plasma TG and HDL level was seen. Impairment of endothelium dependent relaxation of numerous vascular beds in men with hypercholesterolemia has been established by many workers [77-81]. These impairments have also been found to be reversible using lipid lowering therapies [82]. Oxidized low density

lipoprotein is the major causative cholesterol responsible for impaired relaxation response [83].

Studies based on animal models of hypercholesterolemia also found a correlation between high concentration of LDL cholesterol and ejaculatory dysfunctions [84-86]. These hypercholesterolemic animals show both deficient endothelium and neurogenic dependant cavernously relaxation [84,85]. Manning et al., [87] also observed a correlation between high LDL and organic erectile dysfunction and a clear positive correlation between LDL and caverno-venus insufficiency. In contrast to above findings, other workers did not find any relationship between high blood cholesterol and TG levels and ejaculatory dysfunction [88-91]. There are also reports where high HDL-cholesterol [88] and low LDL-cholesterol [92] was inversely correlated with erectile dysfunction.

### Hyperlipidaemia Induced Obesity and Male Fertility

Consumption of high fat diet for long term may cause blood hyperlipidaemia and may induce obesity. In diet induced obese male mice, decrease in sperm motility [93,94], fertilization rate [92], as well as increase in sperm DNA damage and Reactive Oxygen Species (ROS) without showing any significant change in sperm concentration in cauda epididymis have been reported [94]. It has also been reported that in obese mice, proteins regulating acetylation and DNA damage repair systems are altered [95]. In contrast to these reports, no impairment of fertility in male DBA/2J mice fed with high fat diet was observed by Tortoriello et al., [96]. Fernandez et al., [97] observed a significant increase in obesity index and serum leptin levels without any significant effect on serum testosterone level and sperm counts in testes and epididymis of rats fed high fat diet. However, there was an alteration in sperm motility parameters, reduction in fertility and an increase in estradiol level in these rats.

Viguera-villasenor et al., [98] also reported a significant increase in circulating leptin and estradiol levels; however, the testosterone level was reduced in rats fed high fat diet. Although, they observed no structural alteration in seminiferous tubules but there was significant reduction in sperm viability, motility and concentration with an increase in lipid peroxidation.

Wang et al., [70] and Yang et al., [71] reported that in pubertal rats, the high fat diet induced an increase in total cholesterol and triglycerides levels, and poor development of testicles. There was a significant decrease in blood testosterone level, testosterone to estradiol ratio and increase in estradiol level. Chen et al., [99] reported significant increase in apoptotic index of spermatogenic cells in testes of pre-pubertal rats fed high fat diet.

The available evidences on the role of obesity and Body Mass Index (BMI) on male infertility are controversial [100-104]. Some studies related to man have shown association of BMI with reproductive parameters like poor semen quality [105], decreased sperm concentration [106], decreased number of normal motile sperm cells [107,108] increased Reactive Oxygen Species (ROS) and increased DNA fragmentation index [109,110]. Contrary to this, some workers showed little or no relation between obesity and sperm concentration [109,111,112], sperm motility or morphology [108,113] even when the serum concentration of sex hormones were altered [111,113]. Shukla et al., [114] concluded that obesity negatively affects male reproductive potential not only by reducing sperm quality but in particular, it alters physical and molecular structure of germ cells in the testes and

ultimately affects the maturity and functions of sperm cells.

Hajshafiha et al., [115] reported that BMI was not found to be associated with mean values of semen parameters including sperm count, sperm morphology and sperm motility. However, a significant correlation was found between BMI and estradiol, Sex Hormone Binding Globulin (SHBG) levels and also the testosterone to estradiol ratio. Similarly, Strain et al., [116] and Pauli et al., [117] found no significant difference in the spermatoc parameters between obese and normal humans.

Several studies have documented a negative effect of obesity on semen quality both in normal fertile [118,119] and sub fertile-infertile males [100,120]. Obese and overweight men exhibit a high incidence of infertility in association with metabolic disturbances and altered hormonal profiles (decreased serum testosterone, FSH, inhibin B levels and increased levels of estrogen) [100,120-122]. Evidences suggest that increased estrogen as a result of aromatization in the adipose tissue may be an important mechanism for hypoandrogenemia and altered sperm parameters [102].

### Hyperlipidaemia and Prostate Growth and Function

Increased cell proliferation and enlargement of ventral prostate in rats kept on the diet rich in cholesterol or saturated fat has been reported by many workers [123-129]. Inclusion of saturated fat in the diet changed the expression of androgen receptor and peroxisome proliferation activated receptor  $\gamma$  (PPAR $\gamma$ ) [130]. Rahman et al., [126] reported increased expression of alpha-adrenergic receptors in the hyper-lipidemic rats. Increased oxidative stress and incidence of prostate adeno-carcinoma and hyperplasia were also observed in the rats kept on high cholesterol diet for long period [131]. Increased expression of NADPH oxidase subunits, activation of NF-KB signalling and decreased expression of glutathione peroxidase clearly indicated the increased oxidative stress and activation of inflammatory response in ventral prostate of rats fed high fat diet [132,133].

Presence of dyslipidaemia is a frequently observed condition in Benign Prostate Hyperplasia (BPH) patients. High levels of total cholesterol, LDL-cholesterol, triglycerides, low level of HDL-cholesterol increases the risk of BPH and cholesterol lowering treatment may reduce the risk [134,135]. Physical activity, which is known to decrease serum lipid level, is also associated with decreased risk for BPH [136]. Hyperlipidemia is closely associated with the obesity, higher Body Mass Index (BMI) and these parameters show a positive correlation with BPH [137-142].

Excessive fat intake is associated with adiposity, development of insulin-resistance and obesity, and these conditions are known to increase the expression of Autotoxin gene (ATX) and therefore, Lysophosphatic Acid (LPA) levels [143]. Kulkarni and Getzenberg, [144] proposed ATX-LPA axis as a possible link between excessive dietary fat intake and prostatic hyperplasia.

Epidemiological and preclinical studies suggest that high level of serum cholesterol plays a role in incidence and progression of prostate cancer, even hypercholesterolemia does not raise circulating androgen levels [145-154]. Circulating cholesterol level is directly correlated in tumoral expression of the key steroidogenic enzyme CYP17A, testosterone levels and tumor size with castration sensitive LNCaP xenograft mouse model, suggesting that hypercholesterolemia increases intra-tumoral *de novo* steroidogenesis resulting in acceleration of the growth of prostate tumor [155]. Some *in vitro* studies have suggested

that elevated levels of cholesterol in prostate tumor cells could be due to dysregulation of the key regulators of cholesterol homeostasis [99,156] which could have significant role in progression of prostate cancer into androgen independent state [157,158] while reduction in cholesterol level retards prostate cancer growth, possibly by inhibition of tumor angiogenesis [159,160]. A number of studies have also shown that use of cholesterol lowering drugs may reduce the risk of prostate cancer when used prior to cancer development [161-169]. However, some studies do not support these findings [170-172]. Godwin [173] suggested that serum cholesterol is not associated with the overall incidence of prostate cancer.

Hypercholesterolemic diet stimulates growth of LNCaP human PCa xenograft [160,174]. In Hypercholesterolemic environment, tumour accumulated more cholesterol in their membranes, exhibited enhanced activation of Akt (a kinase linked to aggressive Pca) and lower level of apoptosis [175-177].

## Conclusion

Lipids, especially cholesterol play significant role in the structural and functional activity of spermatozoa. Excessive intake of high cholesterol/high fat diet may induce hypercholesterolemia and disturbs cholesterol homeostasis in the body. Experimental studies carried out in various Hypercholesterolemic animal models during the last few decades clearly demonstrate a negative impact of hypercholesterolemia on the structure and functions of testes and accessory sex organs, sperm maturation, sperm quality parameters and ejaculatory functions leading to male infertility. Numerous mechanisms have been proposed to explain such effects, like deregulation of hypothalamic- pituitary-gonadal axis, impairment of steroid genesis and secretory function of Sertoli and Leydig cells, enhanced oxidative stress and excessive generation of free radicals and altered expression of some testicular genes. A large number of human studies have also indicated an association between hypercholesterolemia and poor semen quality and subsequent male infertility. However, most of these studies have been conducted on normal infertile or obese men. Whether the hypercholesterolemia has any impact on sperm/seminal plasma cholesterol/lipid content is still poorly known. Thus, on the basis of above reports it can be proposed that dyslipidaemia is an important factor contributing to male infertility. Therefore, regulation of serum lipid profile may be useful to some extent, for proper male reproductive functions and management of male infertility.

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