Hyperlipidemia and male infertility

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ABSTRACT

Hyperlipidemia is a common disease affecting 25% of adults in developed nations. Approximately 50% of the middle-aged adult population have been reported to have total cholesterol level above the normal range. Worldwide, the incidence of dyslipidaemia is increasing in both low and high income countries. It is a major risk factor for the prevalence and severity of ischemic heart disease. Less recognized but growing in importance are the effects of dyslipidaemia on reproductive functions. A growing evidence has linked dyslipidaemia and abnormal lipid metabolism with alteration of male fertility. The purpose of this review is to summarize the data gathered from both experimental animal models and human studies on the effects of hyperlipidemia on semen parameters, spermatogenesis, male reproductive organs, hormones and fertility.

Introduction

Hyperlipidemia is an elevation of serum total cholesterol, low-density lipoprotein (LDL-c), very low density lipoprotein (VLDL), or triglycerides (TGs), or a low serum high-density lipoprotein (HDL-c) [1,2]. It is a common disease affecting 25% of adults in developed nations. In the United States, half of people of more than 65 years of age were treated with antihyperlipidemic agents between 2007 and 2010 [3]. Worldwide, the incidence of dyslipidaemia is increasing in both low and high income countries [4]. Diet is an important factor that may induce hyperlipidemia. Modern diet which is highly constituted by fat, sugar and refined grains products is an important extrinsic factor for the development of this disease [5]. Hyperlipidemia is a major risk factor for the prevalence and severity of ischemic heart disease which together with stork are the primary causes of death [1]. Less recognized but growing in importance are the effects of hyperlipidemia on reproductive functions [6]. A growing evidence has linked dyslipidaemia and abnormal lipid metabolism with alterations in semen quality and fertility [7]. Hypercholesterolemia is a subclass of hyperlipidemia [9]. It is characterized by high serum LDL-c and blood cholesterol. High-cholesterol diet is the main factor in the development of hypercholesterolemia, which is a well-established risk factor for atherosclerosis and coronary heart disease [10,11]. Approximately 50% of the middle-aged adult population have been reported to have total cholesterol level above the normal range [12]. Cholesterol is an essential component for cell membrane composition, permeability, fluidity, endocytosis and signal transduction. It is the precursor of steroid hormones biosynthesis and its homeostasis is critical for male

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reproductive system. Thus, cholesterol must be strictly regulated for optimal cell functions as any disturbance in its homeostasis can affect male reproductive fitness and fertility [13].

**Normal physiology and histology of male reproductive system**

Male reproductive system is responsible for production, storage and transport of sperm under hormonal control. The sperm and testosterone hormone are produced in two testes protected in the scrotal sac. The sperm pass from the testis to the epididymis where the storage of sperm occurs. Just before ejaculation, the sperm pass from the epididymis to the vas deferens. The vas deferens joins the ejaculatory duct from the seminal vesicle. At time of ejaculation, the sperm mix with the seminal fluid produced by seminal vesicle and prostate to produce semen which passes out of the body through urethral meatus [14].

Testicular tissue consists of seminiferous tubules that constitute approximately 80% of the testicular mass. It is the site of spermatogenesis. Between the seminiferous tubules located Leydig or interstitial cells, which is the site of testosterone production [15]. Behind each testis there is an epididymis which is a convoluted tubule with three parts; head (caput), body (corpus) and tail (cauda). It is lined by epithelial cells that have secretory and absorptive functions maintaining sperm in a viable and immotile status and enhance their maturation [16]. Sperm consists of a head, neck and tail (midpiece and principal piece) [17]. The sperm head composed of three parts; the nucleus, the acrosome and the perinuclear theca [18]. Movement of sperm is provided by the tail. Sperm mitochondria are concentrated within the midpiece [19].

Gonadotropin releasing hormone (GnRH) from the hypothalamus, gonadotropins; follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland and testosterone and inhibin from the testes are the group of hormones that regulate the spermatogenesis process [20]. The main target of FSH is Sertoli cells. Through production of several mediators, FSH is essential for development of germ cells, movement of sperm from testis to epididymis, and for control of pH of seminal fluid. Leydig cells are the main target of LH which stimulate testosterone production [21]. (Figure 1) illustrates the histology of testis with the site and stages of spermatogenesis.

**Effects of hyperlipidemia on semen quality, testes and epididymides**

Bataineh and Nusier (2005) [22], studied the effects of a cholesterol-enriched diet on male reproductive functions. They found that hyperlipidemia (hypercholesterolemia and hypertriglyceridermia) induced in rats by a high-cholesterol diet administration associated with the following pathological changes: 1) reduction in sperm motility and density; 2) reduction in epithelial cell height of caput and cauda of the epididymis; 3) reduction in seminiferous tubules diameter and Leydig cell nuclear diameter, primary and secondary spermatocytes and spermatids; 4) reduction in the number of females impregnated by the males that ingested cholesterol and 5) reduction in the number of implantations and the number of viable fetuses in female rats impregnated by hyperlipidaemic males [22]. Hypercholesterolemia coupled with hypertriglyceridermia associated also with a reduction in sperm count, and an increase in the sperm abnormalities combined with a reduction in testosterone level, testicular and seminal vesicles’ weights [23]. In the next few years, Rato et al., (2013) [24], demonstrated that high energy diet (HED) produced no changes in the sperm count or viability but increased the number of sperm with abnormal morphology and sperm motility. Intra-testicular lactate/alanine ratio increased in HED-fed rats suggesting the oxidative stress damage as one of the underlying mechanisms. In that year another observation by Soltani et al., (2013)[25]; however, demonstrated that induction of hypercholesterolemia, accompanied by
hypertriglyceridemia and obesity through HED supplementation, resulted histologically in more abundant inter-tubular space, reduction in seminiferous tubules and tubular lumen diameters and an increase in the height of the seminiferous epithelium. In 2013 another aspect, which is the correlation of serum lipids with sperm parameters and testicular histology, has been studied. Serum levels of triglycerides and VLDL showed a negative correlation with total sperm count, percentage of live sperm, number of live and normal sperm, and serum testosterone concentration [26]. The negative correlation of serum triglycerides was also observed with seminiferous tubule area and diameter of Leydig cell nuclei. On the other hand, serum HDL-c level showed a positive correlation with the number of live and normal sperm, testosterone level, seminiferous tubule area, diameter of Leydig cell nuclei and testicular weight [26]. To further support the negative impact of hyperlipidemia on male reproductive system, Mortazavi et al., (2014)[27], reported that in addition to the induction of pathological changes in the seminiferous tubules and the negative impact on sperm motility and spermatogenesis, hypercholesterolemia coupled with hypertriglyceridemia associated with a reduction in sperm viability and normal morphology. Further investigations demonstrated loss of germ cells, interstitial tissue inflammation and fibrosis, a decrease in testicular weight and function as well as testosterone

Figure 1. Histology of testis with the site and stages of spermatogenesis. Adapted from [19].
production in rat induced model [28]. Sperm energetic metabolism has been investigated as a possible underlying mechanism in the impairment of sperm quality in HED-fed rats. The administration of HED has resulted in hypertriglyceridemia associated with a defective sperm energy metabolism. This was indicated through the reduction of the activity of pyruvate and lactate dehydrogenase, citrate synthase and enzymatic activities of respiratory complexes. Moreover, there was a reduction in the sperm content of adenosine triphosphate (ATP) and an increase in the sperm oxidative stress damage [7]. Clinically, hypertriglyceridemia and high serum VLDL associated with low sperm motility [29]. High intake of saturated fat in human resulted in a reduction of sperm concentration and total sperm count. This reduction was in a dose response association [30]. In addition to reduced sperm concentration, HED consumption caused a reduction in normal sperm morphology [31].

**Hyperlipidemia and erectile dysfunction**

Erectile dysfunction (ED) is the failure to attain or maintain sufficient erection for satisfactory sexual intercourse [32]. There are accumulative evidences suggest the association between dyslipidaemia and ED. Amongst them is the significant correlation between total cholesterol and LDL-c with ED which justifies the importance of hyperlipidemia management in the prevention and treatment of ED [33]. In a study conducted to determine the correlation between abnormal lipid profile and ED, Rao et al., (2005) [34] reported that in 200 male patients abnormal in at least one of the lipid profile parameters, HDL-c and TC/HDL ratio are good predictors for ED. Erectile dysfunction can be attributed to the increase in levels of inflammatory cytokines, which related directly to endothelial dysfunction through nitric oxide pathway [32]. Presence of elevated levels of inflammatory cytokines leads to endothelial dysfunction. Cytokines induce impairment of endothelium-dependent relaxation of vascular beds and reduces nitric oxide release [35]. The endothelial dysfunction and vascular obstruction due to atherosclerosis caused by increased LDL-c and total cholesterol is suggested to be the final pathway leading to the clinical manifestation of ED [36].

**Effects of hypercholesterolemia on semen quality, testes and epididymides**

Hypercholesterolemia induced by a high-cholesterol diet in rabbit model showed a negative impact on Leydig and Sertoli cells secretory function, spermatogenesis, sperm cytoskeleton, epididymal sperm maturation process and sperm fertilizing capacity [37]. It has also resulted in a reduction of fertility index, sperm count, motility, viability, testicular weight as well as induced testicular degenerative changes, atrophy of seminiferous tubules with arrest of spermatogenesis [38,39]. Additionally, hypercholesterolemia resulted in a reduction of ejaculate volume, sperm count and motility with an increase in the sperm morphological abnormalities mainly in the forms of abnormal sperm heads and presence of cytoplasmic droplets [40,41]. In 2011, Ouvrier and his collaborators tried to answer the question of how male reproductive system affected by extra dietary lipids. They demonstrated that a high-cholesterol diet administration to LXRo; β knockout mice aged 4 months resulted in hypercholesterolemia associated with a considerable reduction in the sperm motility and viability coupled with an increase in the number of broken cells and premature loss of acrosome. These findings are further accompanied by a reduction in the testicular testosterone. Moreover, a significant increase in neutral lipid accumulation in the smooth muscle cells lining of caput epididymal tubules and reduction of caveolin-1 [functional marker for smooth muscle cells (SMC)] and sma-actin [structural marker for SMC] in peritubular smooth muscle cells of proximal caput epididymis, together with absence of luminal cilia and reduced epithelial height were
observed in the high-cholesterol diet-fed LXRα; β knockout mice. In this caput epididymis phenotype, peritubular cells involved in an infiltration-like process through the epididymal epithelium, which were found to be SMC. Peritubular foam cells in the caput epididymis were identified by testing the expression of foam cells marker CD68. These foam cells were found to be originated from SMC transdifferentiation not from macrophage infiltration. Due to the similarity of this epididymal phenotype with atherosclerosis, it was proposed to be named as epididymosclerosis. These changes rendered the 4 months LXRα; β knockout mice completely infertile, and raise up the suggestion that epididymis is an early target for dietary cholesterol overload [6]. In the recently published researches, a high cholesterol diet induced-hypercholesterolemia in rabbit model reduced sperm concentration and motility percentage, and increased the percentage of sperm with morphological abnormalities, which were mostly in forms of coiled or bent tail, bent neck and double tails. It reduced testicular and epididymal weights, induced testicular tubular degenerative changes, reduced seminiferous tubules diameter with irregularity and thickening of their basement membrane, thickening of tunica albuginea, Leydig cells hyperplasia, reduction of Johnsen’s score and impaired spermatogenesis, epididymal atrophy, increased epithelial height of caput and cauda, and reduced diameter of ductal lumens of caput and cauda of the epididymis [15,16,42]. Clinically, serum total cholesterol, serum free cholesterol and phospholipids, independent of obesity, are negatively associated with sperm head morphology (lower percentage of sperm with intact acrosome, smaller sperm head area and perimeter), semen volume, and live/total sperm count [43].

Hypercholesterolemia and capacitation

Mammalian sperm cell membrane has a lipid bilayer consists of phospholipids and cholesterol. During passage of sperm from the testis to the female genital tract, sperm membrane undergoes several modifications. Membrane lipids particularly cholesterol are responsible for the physiological alterations in the membrane fluidity and cell responsiveness to the environment [40]. Cholesterol of sperm plasma membrane regulates membrane permeability, lateral mobility of integral proteins and functional receptors within the membrane. Loss of cholesterol from the membrane is responsible for destabilization of the membrane during capacitation [44]. Capacitation is the functional maturation of the sperm which takes place within the female genital tract. It is essential for the sperm ability to fertilize an egg. It involves changes in the sperm head and flagellum including the ability of sperm to undergo acrosomal reaction and acquisition of motility hyperactivation [45]. The initial step toward the capacitation is the removal of sperm external coating-proteins that protect the sperm on its path to oocyte and prevent early occurrence of acrosomal reaction [44]. Cholesterol efflux from the sperm membrane causes a decrease in the cholesterol/phospholipid ratio which leads to changes in the membrane fluidity and causes membrane protein redistribution that required for capacitation [46]. It is also important for signaling mechanisms that regulate capacitation process. Signaling mechanisms can be initiated through the cholesterol loss via two mechanisms: 1) an interaction between membrane proteins which occurs as a subsequent to the increase in the membrane fluidity and 2) freeing of certain signaling molecules from their interaction with cavolin giving them the ability to form specific signaling complexes [47]. Cholesterol efflux is an early event in the capacitation followed by a reduction in the cholesterol/phospholipid ratio which changes the membrane dynamics and increases its permeability to bicarbonate and calcium ions. This is followed by the activation of adenylyl cyclase and increase production of cyclic adenosine monophosphate (cAMP). A signal cascade initiated through activation of protein kinase A (PKA) which phosphorylates sperm protein tyrosine residue. Finally, the sperm acquire hyperactive motility and the ability to bind to zona pellucida to undergo the
acrosomal reaction [48]. Hypercholesterolemia alters the concentration and distribution of cholesterol of sperm plasma membrane and subsequently reduces the acrosomal reaction and capacitation [40,41]. High cholesterol level inhibits capacitation either through its direct effect on certain surface proteins that have roles in signaling transduction, or indirectly via restricting the conformational changes of sperm surface proteins and consequently decreases their activity [47].

**Effects of hyperlipidemia and/or hypercholesterolemia on male reproductive hormones**

Sexual hormones are mainly steroid hormones synthesized from cholesterol. Hence, cholesterol is crucial for the reproductive physiology of both male and female starting from sex differentiation to production of gametes [49]. Numerous studies have been conducted to determine the influence of HED and hypercholesterolemia on male reproductive hormones. The results of those studies were consistent for some but not all of the hormones tested. Soltani and his teamwork [25] reported that induction of hypercholesterolemia, accompanied by hypertriglyceridemia and obesity, in rabbits by HED supplementation caused a significant increase in FSH with slight increase in LH, increase in plasma testosterone with a reduction in testicular testosterone and an increase in the plasma estradiol level; however, in the same year Rato and his colleagues (2013) [24] observed that HED supplementation to rats reduced serum and testicular testosterone with no change in serum estradiol level. In the next year other studies demonstrated that induction of hypercholesterolemia through administration of cholesterol-enriched diet to rats resulted in a reduction of FSH with no significant changes detected in testosterone, LH, prolactin or cortisol levels [50,51]. Couple of years later, Mu and his collaborators studied the effects of HED administration to mice and rats. They revealed that obesity and hypercholesterolemia were associated with hormonal disturbances in the form of a decrease in FSH, LH and testosterone and an increase in leptin and estradiol [52,53]. In the latest investigation, induction of hypercholesterolemia through feeding of rabbits with a high cholesterol diet reduced serum and testicular testosterone, increased serum FSH with no significant change in serum LH (Hamad Mohamed et al., 2020) [54].

**High-energy diet/ hypercholesterolemia-induced oxidative stress and male infertility**

Oxidative stress is defined as the loss of normal balance between production of reactive oxygen species and the antioxidant carrying capacity, which leads to potential cellular damage [55]. Low level of reactive oxygen species (ROS) is necessary for normal sperm functions particularly capacitation, acrosomal reaction, hyperactivation, motility, sperm-oocyte adhesion and fertilization [56]. On the other hand, sperm are very vulnerable to oxidative stress, which can initiate apoptotic cascade with a subsequent loss of motility, DNA integrity and vitality [57]. This vulnerability is owing to the high concentrations of polyunsaturated fatty acids in the sperm membrane and low concentrations of the cytoplasmic antioxidant enzymes. In addition, the intracellular scavenging enzymes cannot protect the plasma membrane surrounding the tail and acrosome [58]. The main factors protecting sperm DNA from the oxidative stress are packaging of DNA by histone protamines and antioxidant compounds [59]. In infertile men, sperm mitochondria are the major source of ROS production in the sperm. Dysfunction of the mitochondria induces more ROS production that can produce further damage to the mitochondrial membrane proceeded by more production of ROS [60]. Oxidative stress and ROS can cause infertility through different mechanisms including: 1) initiation of lipid peroxidation process through free radical attack of lipids of sperm membrane with a subsequent loss of membrane and morphological integrity, loss of function, impairment of motility and viability and induction of
apoptosis [61]; 2) sperm DNA damage [62] and 3) reduction of motility [63]. Direct damage of mitochondria via ROS reduces the required energy for sperm motility. Motility impairment, either through damage of sperm membrane or through reduction of energy availability, results in less sperm reaching oocyte for fertilization [64]. Damaging of sperm DNA by oxidative stress compromises paternal genomic contribution to the embryo [65]. Furthermore, sperm oxidative stress damage in infertile men positively associated with higher levels of cytochrome C and caspases 9 and 3 indicating higher percentage of apoptosis in sperm exposed to higher levels of ROS [66]. Oxidative stress induced sperm damage is a significant contributory factor in 30–80% of male factor infertility [28]. High levels of ROS in the semen, irrespective of the normality or abnormality of semen parameters, could be used as an independent marker for infertility diagnosis particularly in infertility of unknown cause [67]. The chance of inducing pregnancy is five folds less in infertile men who produce high levels of ROS than those producing lower levels of ROS [68]. High levels of free radicals with low levels of antioxidant enzymes, induced by HED administration, reduced testicular and epididymal weights and reduced sperm concentration, motility and viability. Additio-nally, it provoked sperm DNA fragmentation [69]. Moreover, high levels of sperm oxidative stress damage caused by HED induced defects in sperm energy metabolism with a subsequent impairment of sperm quality [7]. Oxidative stress is also implicated in the pathogenesis of testicular dysfunction induced by a high-fat diet, which indicated by elevation of testicular malondialdehyde (MDA) and reduction of testicular glutathione (GSH) and superoxide dismutase (SOD) [70]. Hypercholesterolemia-induced oxidative stress were proposed to induce reproductive and testicular dysfunctions which are cytotoxic to the sperm and induce apoptosis causing a reduction in the sperm count [4,72]. Production of high levels of ROS is associated with a decrease in the sperm count and percentage of motile sperm. The reduction in the sperm production is suspected to be due to testicular atrophy that results from damage of seminiferous epithelium due to prolonged exposure to high levels of ROS [68]. Different combinations of antioxidants have been used in cases of male infertility associated with high level of ROS and oxidative stress. Vitamins like E, C and A, L-carnitine (LC) and L-acetyl-carnitine (LAC), selenium and N-acetyl-cysteine are among the antioxidants that have been studied. They enhanced spermatogenesis, improved sperm parameters, improved testicular histology and male reproductive hormones and fertility (Hamad Mohamed et al., 2020) [71]. (Figure 2) demonstrates the impacts of hyperlipidemia on male reproductive system

**Role of Liver X receptors in lipid metabolism and male infertility**

Liver X receptors (LXRs) are nuclear receptors with transcription factor characteristics [73]. They are stimulated by oxysterols, metabolic derivatives or oxidized forms of cholesterol. They have important roles in controlling of lipid, cholesterol and metabolic homeostasis and regulation of proliferation, differentiation, inflammation and reproduction [74]. There are two isoforms of LXRs; LXRα (NR1H3) which are expressed mainly in the tissues that have important activities in lipid metabolism such as liver and brown adipose tissue. The second isoform is LXRβ (NR1H2) which is ubiquitously represented [75]. Several studies have emphasized on the importance of LXRs in male fertility. Liver X receptors Knockout (LXRα−/−) male mice demonstrated a dramatic reduction in the fertility capacity with aging, where there is abrupt fertility reduction around the age of 6 months followed by a complete loss of mature germ cells at the age of 10 months [Frenoux et al., 8; 76]. Liver X receptors alpha (LXRα) are abundantly expressed in Leydig and germ cells; whereas, LXRβ are mainly expressed in Sertoli cells and to a less extent in the germ cells
Loss of LXRβ disrupts cholesterol homeostasis resulting in an accumulation of cholesterol esters in the Sertoli cells, which leads ultimately to testicular destruction that is more severe in the absence of the two isoforms of LXRs [76].

Fatty acids metabolism has an important function in sperm structure and male reproduction. Impairment of this metabolism affects spermatogenesis. The testes have an active lipid metabolism that maintain the rearrangement of fatty acids during spermatogenesis. In double LXR knockout mice, the level of mRNA of sterol response element binding protein-1 c (srebp1c) and fatty acid synthase (fas) were found to be decreased [77]. Expression of LXRβ receptors is universal throughout the epididymis; whereas, LXRα receptors are expressed slightly less in the cauda than in the caput of the epididymis in wild type mice (Frenoux et al., 2004)[8]. Neutral lipid accumulation in the smooth muscle cells and apical epithelial cells of the epididymis observed in LXRα; β−/−. Cholesterol ester accumulation is most probably a subsequent to the loss of ATP-binding transporters A1 (ABCA1) involved in cholesterol efflux [78]. Loss of LXRβ modifies the genes involved in fatty acid metabolism in the caput of the epididymis. Stearoyl Co-A desaturases 1 and 2 (scd1 and scd2) and srebp1c are reduced in LXRα; β−/− and LXRβ−/− mice. These genes encode enzymes responsible for the desaturation of fatty acids mainly palmitic and stearic acid to produce palmitoleic and oleic acids involved in the production of triglycerides, or incorporated in the cholesteryl esters [73]. Sperm analysis of LXR knockout mice demonstrated that a significant reduction in the sperm count was observed in LXRβ−/− mice; whereas, sperm viability was reduced in both LXRβ−/− and

Figure 2. Impacts of hyperlipidemia on male reproductive system.
LXRα−/− [74]. Liver X receptors knockout (LXRα; β−/−) mice showed a severe reduction in sperm count associated with structural abnormalities. In addition they exhibited structural fragility and abnormal flagella with various degrees of angulation (Frenoux et al., 2004)[8].

Conclusion

Overconsumption of a high-cholesterol or a high-fat diet induces hypercholesterolemia and/or hyperlipidemia which adversely affect normal male reproductive functions and fertility. Hyperlipidemia induces alterations in testicular and epididymal structures and functions, affects sperm energy metabolism and spermatogenesis. It induces oxidative stress with its detrimental effects on male reproductive system. It induces apoptosis, reduces sperm concentration, motility and viability, increases sperm morphological abnormalities and provokes sperm DNA fragmentation. Moreover, hyperlipidemia reduces acrosomal reaction and capacitation, promotes disturbances in male reproductive hormones and causes erectile dysfunction.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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