

# Obesity, a serious etiologic factor for male subfertility in modern society

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## Abstract

Obesity, defined as excessive accumulation of fat in adipose tissue, is a metabolic disorder resulting from behavioral, environmental and heritable causes. Obesity increases the risks of hypertension, diabetes, cardiovascular disease, sleep apnea, respiratory problems, osteoarthritis and cancer. Meanwhile, the negative impact of obesity on male reproduction is gradually recognized. According to the clinical investigations and animal experiments, obesity is correlated with reductions in sperm concentration and motility, increase in sperm DNA damage and changes in reproductive hormones. Several mechanisms can elucidate the effects of obesity on sperm functions and male subfertility, i.e., the excessive conversion of androgens into estrogens in redundant adipose tissue causes sexual hormone imbalance, subsequently resulting in hypogonadism. Secondly, adipokines produced by adipose tissue induce severe inflammation and oxidative stress in male reproductive tract, directly impairing testicular and epididymal tissues. Moreover, increased scrotal adiposity leads to increase gonadal heat, continuously hurting spermatogenesis. Therefore, obesity alters the systematic and regional environment crucial for spermatogenesis in testis and sperm maturation in epididymis, and finally results in poor sperm quality including decreased sperm motility, abnormal sperm morphology and acrosome reaction, changed membrane lipids and increased DNA damage. Furthermore, recent studies indicate that epigenetic changes may be a consequence of increased adiposity. A major effort to identify epigenetic determinants of obesity revealed that sperm DNA methylation and non-coding RNA modification are associated with BMI changes and proposed to inherit metabolic comorbidities across generations. This review will explain how obesity-related changes in males to influence sperm function and male fertility as well.

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## Introduction

Obesity is a metabolic disease determined by lifestyle such as physical activity, environmental factors (food variety and intake) and genetic factors. In recent decades, it becomes a major health problem and increases worldwide at an alarming rate. Approximately 1.9 billion people are overweight (body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>) or affected by obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) in the world (World Health Organization 2014) and are at risk of developing type 2 diabetes, cardiovascular disease and related metabolic and inflammatory disturbances. Additionally, there is growing interest and progress in understanding the impact of obesity on male reproduction. Recently, both clinical and experimental reveal the negative consequences of obesity on male reproductive function. According to the clinical investigation, men with overweight or obesity can decrease sperm quality including sperm concentration, sperm motility, acrosome reaction decline, increased sperm DNA damage and lower embryo implantation rates as well, comparing to those of normal BMI men (Jensen *et al.* 2004, Dupont *et al.* 2013,

Sermondade *et al.* 2013, Samavat *et al.* 2014, Shukla *et al.* 2014, McPherson *et al.* 2015, Soubry *et al.* 2016). In consequence, obesity was associated with a more than 20% increased cases of subfertility and infertility (Cui *et al.* 2016).

Notably, male fertility depends on certain amounts of spermatozoa with sufficiently high quality. The spermatogenesis and sperm maturation are highly complex and specialized processes under strictly regulatory mechanisms, which are involved in the sex steroids, testicular niche, Sertoli cells, epididymic fluid and so on. However, there is an undisputed fact that obesity affects male reproductive potential. In general, the excessive visceral adiposity in obese individual leads to the changes in hormone levels and promotes chronic inflammation in reproductive tract (MacDonald *et al.* 2010, Dulloo & Montani 2012), and high fat content in scrotum area also causes an increase in scrotal temperature. Thus, all these consequences of obesity subsequently can damage the microenvironments of testes and epididymis, which are crucial for the production and maturation of spermatozoa. In practical terms,

obesity primarily impairs the physical and molecular structure of sperm during both spermatogenesis in testis and sperm maturation in epididymis, finally reducing sperm quality and causing male infertility risk.

### **Obesity leads to hypogonadism**

Male obesity is associated with hypogonadism. Most obese males have altered reproductive hormonal profiles, e.g. elevated estrogen and leptin levels, and decreased testosterone, follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), ghrelin and inhibin B levels (MacDonald *et al.* 2010, McPherson & Lane 2015, Martins *et al.* 2015, 2016, Cui *et al.* 2017). In obese men, the hyperactivity of aromatase (cytochrome P450 enzyme) in redundant white adipose tissue causes excessive conversion of androgens into estrogens. Therefore, gonadotrophin secretion from the pituitary decreases through feedback inhibition on the hypothalamus and pituitary gland, and then further impacts on testosterone production through falls in gonadotrophin-releasing hormone (GnRH)-luteinizing hormone (LH)/FSH pulses (Mah & Wittert 2010, Michalakis *et al.* 2013, Rey *et al.* 2013). The disruption of the negative feedback loop of the hypothalamic-pituitary-gonadal (HPG) axis finally leads to the significant decline in testosterone production.

Undoubtedly, these sexual hormone imbalances may be one of the important causes for male infertility or subfertility induced by obesity. It is known that, both testicular development at puberty and spermatogenesis maintenance at adult depend on a high level of testosterone. Normal intra-testicular testosterone levels are 50–100 times comparing to that in serum. Actually, this high level intra-testicular testosterone is required for maintenance of the blood–testis barrier (BTB), the specific cell junctions between Sertoli cells, as well as maintenance of the cell adhesion between Sertoli cells and germ cells (Lie *et al.* 2013). Meanwhile, testosterone is indispensable in meiotic progression and spermatid maturation. Thus, the high levels of testosterone, associated with Sertoli cells, construct the niche suitable for the developing germ cells throughout the different phases of spermatogenesis. Additionally, FSH is another important regulator of Sertoli cells, stimulating virtually all functions related to spermatogenesis. Therefore, the low testosterone and FSH levels in obese men can be a cause for impaired spermatogenesis and finally lead to reduced sperm counts and subfertility (Cheng *et al.* 2010, Ramaswamy & Weinbauer 2015).

### **Obesity induces inflammation**

Accumulated evidences suggested a positive correlation between chronic inflammation or pro-inflammation state and human obesity, while parallel relationships have been observed in animal models

(Divella *et al.* 2016, Griffin *et al.* 2016, Kolb *et al.* 2016). The white adipocytes produce and secrete a large number of molecules, collectively called adipocytokines or adipokines, and the majority of adipokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukins (IL-1, IL-6 and IL-18) are pro-inflammatory cytokines, which are the mediators of inflammation and will further increase inflammation and attract macrophages. It is thought that pro-inflammatory cytokines contribute to the disruption in glucose homeostasis and insulin resistance that are often linked with obesity. Besides the adipocytes, these pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6, are also increased in the serum, testicular tissue and the seminal plasma of obese males (Zhang *et al.* 2015, Huang *et al.* 2016).

It is now well documented that pro-inflammatory cytokines exert some impacts on the HPG axis and on fertility (Tsatsanis *et al.* 2015). The systematic inflammatory diseases, such as rheumatoid arthritis, consequently display reduced testosterone levels. The pro-inflammatory cytokine TNF- $\alpha$  puts direct inhibition on LH function and subsequently, leading to low testosterone and male subfertility (Iwasa *et al.* 2009). Therefore, the increased systematic inflammatory cytokines in the serum of obesity males can induce a loss of androgen production at various levels of the hypothalamic–pituitary–Leydig cell axis.

In testis, pro-inflammatory cytokines can directly impair the seminiferous epithelium. Sertoli cells are in response to many of these pro-inflammatory cytokines, most notably IL-1, TNF- $\alpha$  and interferon. It has been postulated that these molecules affect the expression and assembly of the junctional proteins, e.g. zonulin/zonula occludens-1 (ZO-1), occludin, claudins and actin–myosin cytoskeletal proteins, thereby induce opening of the cell junctions between the adjacent Sertoli cells and lead to disturbances in the niche of seminiferous epithelium essential for spermatogenesis (Zhang *et al.* 2014, Chojnacka *et al.* 2016, Li *et al.* 2016, Stanton 2016). In fact, impaired BTB and decreased expression of junctional proteins in Sertoli cell have been observed in many obese animal models induced by diet (Liu *et al.* 2014, Fan *et al.* 2015).

Additionally, sperm maturation in epididymis is crucial for sperm to acquire the motile ability and fertile capacity. The epididymal epithelium transports proteins and lipids through epididymosomes to the sperm membrane, for which is necessary for sperm maturation (Sullivan 2015). Pro-inflammatory state induced by obesity can also damage epididymal epithelium function, by altering the environment within the epididymis, modifying the epididymosomes content and increasing the influx of neutrophils and macrophages to the epididymal lumen, resulting in higher cytokine expression and epithelial apoptosis, thus impeding sperm maturation and fertilization ability. Consequently, the presence of pro-inflammatory cytokines produced

within the testis and epididymis or entered from the circulation during systematic inflammation, impinge upon the critical regulations of the spermatogenesis and sperm maturation.

### **Obesity enhances oxidative stress**

One of the main factors relevant to disrupted sperm function in obese males is the oxidative stress caused by excess of reactive oxygen species (ROS), mainly including superoxide anion, nitric oxide, hydroxyl radical and oxidants. ROS can be produced normally in cellular metabolism, whereas in excessive state, it can induce oxidative stress and cause damage to DNA and plasma membrane integrity in sperm and increase stress on the testicular environment as well (Rato *et al.* 2014). Obesity, associated with the chronic inflammatory state, causes a higher metabolic rate and an increased ROS formation in testicular tissue, reproductive tract and semen. The pro-inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , disrupt the seminiferous epithelium and epididymal epithelium by creating high levels of ROS. Additionally, inflammatory that attracts infiltrating phagocytic leukocytes are also capable of inducing oxidative stress in the male reproductive tract (Henkel 2011, Lavranos *et al.* 2012). Several studies have shown that oxidative stress in semen and testis were positive correlations to the increase in BMI and sperm DNA damage, and negative correlation to the decreased sperm motility and acrosome reaction (Bakos *et al.* 2011, Tunc *et al.* 2011). Thus, obviously, excessive oxidative stress is one of the potential mechanisms leading to poor sperm quality in obese males.

Besides, raised gonadal temperature in obese male may also contribute to altered sperm parameters. The process of spermatogenesis is highly sensitive to heat, with optimal temperature ranging between 34°C and 35°C in human. However, in obese male, increased scrotal adiposity directly leads to increases in gonadal heat (Garolla *et al.* 2015). Definitely, increased testicular heat can substantially reduce sperm motility and concentration and increase sperm DNA damage and sperm oxidative stress as well (Du Plessis *et al.* 2010).

Furthermore, a positive correlation exists between increasing BMI and higher sperm/seminal plasma ROS levels (Tunc *et al.* 2011, Taha *et al.* 2016). In particular, spermatozoa are individually susceptible to oxidative stress owing to their specially simplified organelles and limited antioxidant defensive capacity. In spermatozoa, ROS are mainly generated from the sperm mitochondria and in normal condition, they may be facilitated with sperm-egg recognition, fusion and fertilization later (Amaral *et al.* 2013); however, high levels of ROS prone to attack the lipids in sperm plasma membrane as well as the DNA in nucleus and mitochondria (Aitken *et al.* 2016).

### **Obesity impairs sperm parameters**

The effect of male obesity on sperm parameters, such as sperm concentration, sperm motility and morphology, has been well documented in human and animal models. Many clinic investigations show that abnormal semen parameters can attribute to obesity including decreased sperm concentration, decreased sperm motility and increased abnormal morphology (Shukla *et al.* 2014, Guo *et al.* 2017). Actually, obese men are more likely to exhibit a reduction in semen quality than men with a normal weight and responsible to high risk of infertility. Consistently, abnormal sperm parameters including reduced sperm motility, decreased sperm counts and increased sperm deformity are also observed in the animal models with diet-induced obesity, thereby result in male subfertility (Bakos *et al.* 2011, Fernandez *et al.* 2011, Fan *et al.* 2015). On the other hand, it was verified that many factors altered in obese male may impair sperm quality including sexual hormone imbalance, oxidative stress and chronic inflammation. Notably, there is also some evidence indicating that weight loss, by exercise, lifestyle changes or bariatric surgery, can efficiently result in increased serum testosterone levels and sperm count (Hakonsen *et al.* 2011, Palmer *et al.* 2012), suggesting benefits for a possible weight loss on male fertility.

Moreover, a preliminary study reports that acrosome reaction, both spontaneous acrosome reaction and progesterone-induced acrosome reaction, is impaired in obese men (Samavat *et al.* 2014). Similarly, declined sperm acrosome reaction induced by calcium ionophore A23187 is also observed in diet-induced obese mouse model (Fan *et al.* 2015). Although the correlation between male obesity and sperm acrosome reaction is sparsely documented, it is reasonable that the impact of obesity on spermatogenesis and sperm maturation, which results in oxidative stress and membranous lipids alteration, may also cause some defects in acrosome reaction.

Additionally, several comparative proteomic studies have been conducted to illuminate the mechanisms of obesity's influence on sperm quality. Using difference gel electrophoresis or liquid chromatography tandem mass spectrometry (LC-MS), differential expressed proteins in spermatozoa from obese males are identified (Paasch *et al.* 2011, Liu *et al.* 2015). The low abundant proteins in obesity-associated asthenozoospermia are mainly associated with an array of biological functions including actin organization, flagellar assembly, vesicular traffic, protein degradation and stress resistance, and most of these proteins are involved in acrosome biogenesis, nuclear reshaping and flagellum formation during spermiogenesis that may directly causes abnormal sperm function.

### **Obesity increases sperm DNA damage**

In general, the backbone of the DNA helix is frequently cleaved in spermatozoa owing to the uncondensed DNA and results in either single-strand breaks (SSB) or double-strand breaks (DSB). DNA fragmentation index (DFI) is a parameter representing the percent of spermatozoa in a semen sample that have single/DS breaks in nuclear DNA. In clinics, DFI at 3–5% is considered normal, whereas rise to 25–30% may increase the risk of infertility (Bungum *et al.* 2011).

The integrity of DNA in the sperm nucleus is an important determinant of semen quality since it is vital for fertilization rates, embryo quality, pregnancy rates and miscarriage rates as well. There are numerous human and animal studies to show the significant negative associations between obesity and sperm DNA integrity (Kort *et al.* 2006, Chavarro *et al.* 2010, MacDonald *et al.* 2010, Bakos *et al.* 2011, Fariello *et al.* 2012, Duale *et al.* 2014). Although various methods are applied to measure sperm DNA integrity, such as terminal-deoxynucleotidyl transferase-mediated nick end labeling (TUNEL), single-cell gel electrophoresis (Comet) assay and sperm chromatin structure assay (SCSA), the most results consistently confirm the relationship between obesity and increased DNA damage. One of the main contributors in obesity for sperm DNA structure damage is ROS. The oxidative attack particular to sperm DNA can lead to DNA fragmentation directly, as well as to cause the formation of base adducts particularly 8-hydroxy-2'-deoxyguanosine (8OH-dG), which results in base mismatch and DNA mutation (De Iulii *et al.* 2009, Aitken *et al.* 2016). Meanwhile, the replacement of histone by protamines in late round spermatids also plays a critical role in sperm DNA protection. Histone acetylation is necessary for histones replacement by protamines, and alterations in histone acetylation are commonly found in the diet-induced obese mouse models, resulting in increased levels of DNA damage (Gaucher *et al.* 2010, Palmer *et al.* 2011, Davidson *et al.* 2015). On the other hand, because of the limitation in antioxidant defensive capacity and defectiveness in DNA repair system, the DNA damage induced by ROS in spermatozoa is particularly crippling and increases the risk of failure in further fertilization and embryonic development (Gavriliouk & Aitken 2015).

### **Obesity alters sperm lipid composition**

The sperm membrane is composed of various saturated fatty acids (i.e. myristic acid, palmitic acid, stearic acid etc.) and unsaturated fatty acids (i.e. palmitoleic acid, oleic acid, linoleic acid, arachidonic acid, docosahexaenoic acid etc.). The fatty acid composition of spermatozoa is important for the sperm function, including sperm motility, viability and fertility (Aksoy *et al.* 2006, Martinez-Soto *et al.* 2013,

Gangwar & Atreya 2015, Andersen *et al.* 2016). The polyunsaturated fatty acids in spermatozoa, especially docosahexaenoic acid (DHA), are positively associated with sperm concentration, morphology and motility (Aksoy *et al.* 2006, Tavilani *et al.* 2007, Keber *et al.* 2013). The membranal lipids of the spermatozoa are mainly determined during spermatogenesis in testis and sperm maturation in epididymis. Therefore, the fatty acid composition of spermatozoa is also in relation to BMI, which consists with the changes of inflammatory and oxidative stress in testis and epididymis. Indeed, BMI is negatively correlated with sperm DHA and palmitic acid levels (Andersen *et al.* 2016). The fact indicates that changes in the fatty acid composition of spermatozoa could be one of the mechanisms underlying reduced sperm quality in men with high BMI.

Meanwhile, membranal cholesterol is a main constituent in spermatozoa, which is quite various during sperm maturation and capacitation. The membranal cholesterol efflux that removes off cholesterol from sperm membrane during sperm capacitation is essential for modifying the membranal fluidity and further contributes to sperm motility maintenance and normal acrosome reaction (Wertheimer *et al.* 2008, Whitfield *et al.* 2015). Both clinic and animal studies have revealed the significant rise in sperm cholesterol content in obese males. These changes to sperm are proposed to cause sperm morphological abnormalities, decreased motility and premature acrosome reaction (Schisterman *et al.* 2014).

Normally, the membranal constituents of spermatozoa are composed of high contents of unsaturated fatty acids, with especially high levels of DHA that contributes up to 30% of the total fatty acid composition (Aksoy *et al.* 2006, Tavilani *et al.* 2007, Andersen *et al.* 2016). However, the membranal unsaturated fatty acids are susceptible to ROS and result in lipid peroxidation (Henkel 2011, Aitken *et al.* 2016). Hence, induced by excess amount of ROS in obese males may lead to lipid peroxidation that is related to poor membranal lipid fluidity and further affect sperm motility and acrosome reaction.

### **Obesity influences sperm epigenetic modification**

Epigenetic modifications, such as DNA methylation and hydroxymethylation, histone modifications and non-coding RNA expression, modulate the transcription intensity and regulate gene expression in time and space without altering the genetic information in DNA. Both genetic and environmental factors can affect the epigenetic modifications and eventually influence the phenotype. Obesity is considered as a metabolic disorder resulting from the obesogenic environment such as high energy intake and low exercise rate. However, recent studies on epigenetic modifications influenced by obesity demonstrate that alterations in DNA methylation are a consequence of increased BMI (Dick *et al.* 2014,

Ozanne 2015, Wang *et al.* 2016, Mendelson *et al.* 2017, Wahl *et al.* 2017).

Moreover, some clinical and animal studies suggest that paternal obesity may also have an impact on the metabolic health for his and/or her offspring and grand-offspring, which means that children born from obese parents are more likely to develop childhood obesity and suffer from adverse metabolic diseases (Fullston *et al.* 2015, McPherson *et al.* 2015, Slyvka *et al.* 2015, Chowdhury *et al.* 2016, Hur *et al.* 2017, Lecomte *et al.* 2017). Meanwhile, it is equally clear that children from obese fathers are at higher risk of developing metabolic disease in later life, for which is independent of their mother's body weight. Current evidences further indicate that obesity and its related metabolic comorbidities inherited across generations through non-genetic mechanisms are dependent on the epigenetic modification in gametes (Grandjean *et al.* 2015, Terashima *et al.* 2015, Soubry *et al.* 2016, Hur *et al.* 2017). Thus, it is believed that epigenetic modifications in sperm can be influenced by obesity and inherited trans-generation, although the research about obesity-related epigenetic modifications in sperm are few concerned on.

As known, methylation of DNA and acetylation of histones are dynamic phenomena during spermatogenesis, by which is vital for the normal processes of spermatogenesis and fundamental for a successful pregnancy. DNA methylation is the reversible and heritable attachment of a methyl group to a nucleotide. The most common form of DNA methylation occurs at the 5' carbon of cytosine in CpG dinucleotides, creating 5-methylcytosine. DNA methylation in sperm is associated with acetylation of histones, resulting in its replacement by protamines (Delaval *et al.* 2007). In particular, DNA methylation in spermatozoa displays two statuses, in which are either closed to no methylation or very high methylation, and methylated CpGs are almost exclusively found in protamine-associated DNA (Hammoud *et al.* 2009, Donkin *et al.* 2016). However, the extent of histone replacement and DNA methylation in sperm varies widely on a species-specific basis. A genomewide study reports that 9081 unique genes in sperm are differentially methylated between obese men and normal lean men, which are enrichment for the term 'nervous system development' (Donkin *et al.* 2016). Additionally, in high-fat diet-induced obesity rat model, numerous differentially methylated regions corresponding to 92 genes involved in cellular localization, transport and metabolic processes are identified in the spermatozoa and some differentially methylated regions are inherited trans-generation (de Castro Barbosa *et al.* 2015). The methylation of DNA in sperm is susceptible to environmental factors that might result in methylation status changes.

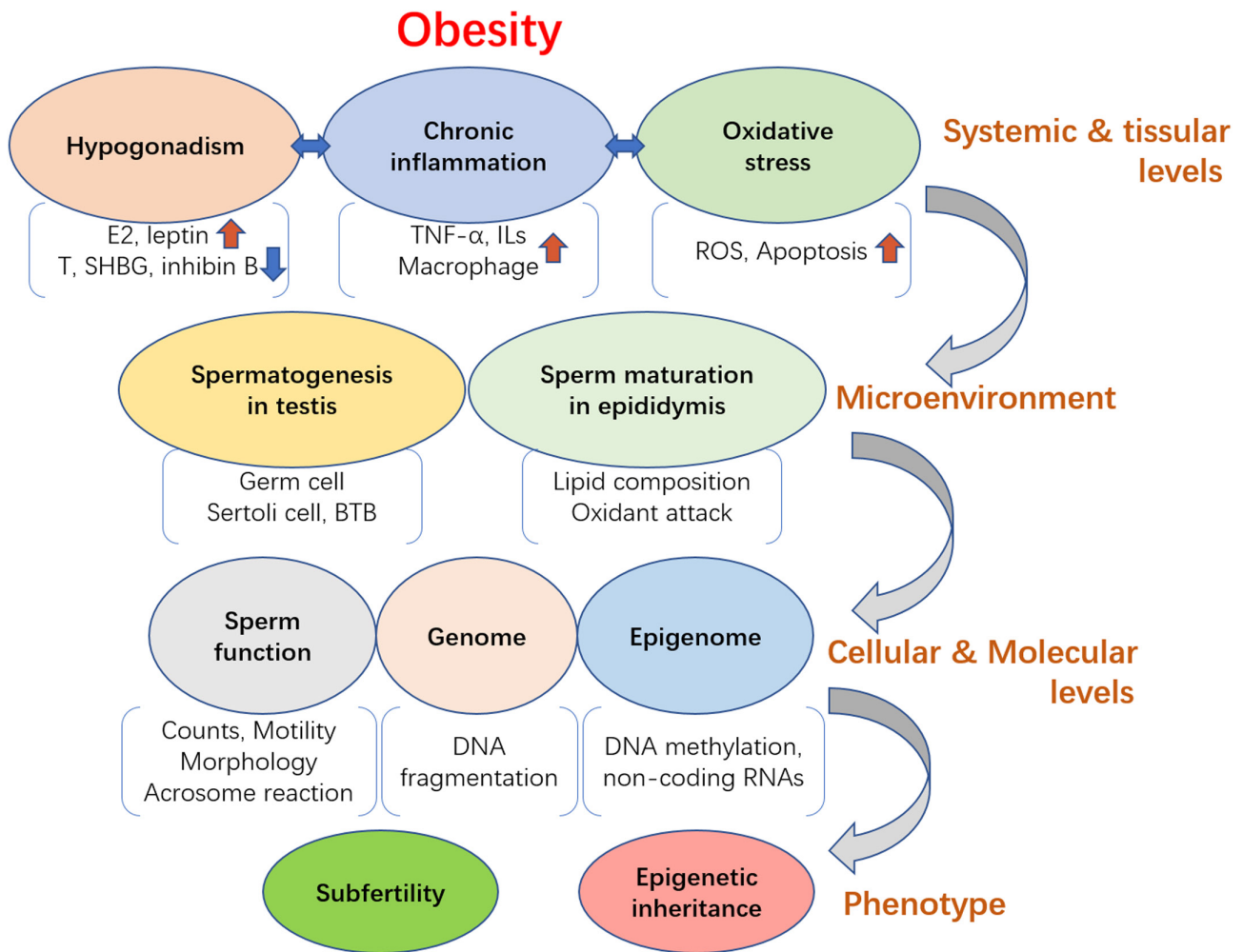
Furthermore, the presence of non-coding RNA in sperm from many species may have post-fertilization

functions including transmission of acquired characteristics (Miller & Ostermeier 2006, Sandler *et al.* 2013, Gapp *et al.* 2014). The non-coding RNA in sperm contains ribosomal RNA (rRNA), microRNAs (miRNA), PIWI-interacting RNAs (piRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA) and tRNA-derived fragments (tRFs). Analysis of the non-coding RNA content in sperm from either human or rat model reveals that the expression levels of several miRNAs, piRNAs, tRFs and snRNA fragments were altered in the spermatozoa from obese males (de Castro Barbosa *et al.* 2015, Donkin *et al.* 2016). Some of the differential expressed piRNA are speculated to modulate the expression of genes involved in behavior and food intake and may participate in their offspring's predisposition to obesity (Donkin *et al.* 2016). On the other hand, the altered miRNA let-7c expression in sperm concurs that in adipose tissue from the offspring, suggesting the transgenerational inheritance of metabolic dysfunction sired by obese fathers (de Castro Barbosa *et al.* 2015, Chen *et al.* 2016b). Therefore, epigenetics may provide a key for elucidation of the intergenerational influences on obesity.

In addition to the adverse effects induced by obesity on male sperm epigenetic modification, there are several evidences suggesting that some other negative impacts may be transmitted to the offspring (de Castro Barbosa *et al.* 2015, Fullston *et al.* 2015, Chen *et al.* 2016a, Chowdhury *et al.* 2016, Hur *et al.* 2017, Lecomte *et al.* 2017). For instance, epidemiologic evidences showed that environmental challenges imposed on the father, such as stress, specific diets, toxins, tobacco smoking and alcohol consumption, have been found to influence the development of the offspring via the non-genetic alterations within sperm including small non-coding RNAs, DNA damage, DNA methylation and histone modifications (Chen *et al.* 2016b, Rando 2016, Schagdarsurengin & Steger 2016, Fullston *et al.* 2017).

## Conclusion

In summary, it gradually unveils a fact that male obesity has negative impacts on fertility, sperm function and on the health of the offspring for a long term. Male obesity alters the environment essential for spermatogenesis and sperm maturation, including HPG axis-related sexual hormone imbalance, increased scrotal temperature, induced chronic inflammation and oxidative stress in testis and epididymis and declined Sertoli cell activity. The impaired spermatogenesis and sperm maturation can further cause poor sperm quality, including declined sperm motility, inappropriate lipid composition, increased ROS and DNA damage and abnormal epigenetic modification that may be transgenerational transmitted, finally leading to male subfertility or infertility indeed (Fig. 1).



**Figure 1** Effects of obesity on male fertility. Male obesity can lead to hypothalamic pituitary gonadal (HPG) axis-related hormone imbalance, induce chronic inflammation and enhance oxidative stress at both systemic and tissue levels. Therefore, the environment that is essential for spermatogenesis in testis and sperm maturation in epididymis such as Sertoli cell activity, BTB integrity and epididymal epithelium activity is gradually impaired by hormone deficiency, inflammation and oxidative attack. Then, the impaired spermatogenesis and sperm maturation can cause poor sperm quality, including declined sperm concentration and motility, inappropriate lipid composition, increased DNA damage and abnormal epigenetic modification, finally leading to male subfertility and health problems that may be transmitted to the offspring via epigenetic inheritance.

Nevertheless, the mechanisms of obesity that influence male reproduction remain somewhat unclear and still need to be further investigated, although the molecular alterations associated with obesity have been generally reported (Craig *et al.* 2017, Oliveira *et al.* 2017). For instance, among the multiple factors relevant to male subfertility associated with obesity, inflammation in reproductive system is one of what have been overlooked in previous studies. Obesity-related chronic inflammation is considered to raise the risk of cardiovascular disease, tumorigenesis, diabetes and etc., which means that the systematic chronic inflammation alters the individual homeostasis. Particularly in reproductive system that is essential for spermatogenesis and sperm maturation, chronic inflammation can affect the sperm fertilizing

capability as well as the sperm epigenome. Thus, the inflammatory indicators in semen could potentially be a useful evaluation standard for sperm quality and are worthy of in-depth exploring. Meanwhile, the sperm epigenetic alterations induced by obesity will pass on to the subsequent generation and may result in the metabolic changes in the offspring even in the grand-offspring. Therefore, it is crucial to understand the changes of key epigenetic signatures in sperm induced by obesity and the transmission of these fingerprints across generations. Besides, based on the mechanism of epigenetic alteration and inheritance occurring in male obesity, it may be easier to explore the phenotypic inheritance in other types of environmental or health challenges, such as smoking, aging, nervousness and toxin.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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