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# Obesity and Male Fertility: An In-Depth Review of the Impact of Elevated BMI

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## ABSTRACT

This paper discusses the complex relationship between obesity and male infertility in a detailed manner. According to the introduction, obesity-related infertility is importantly discussed since it affects some 15% of couples in which half cases are attributed for obesity-related infertility is important to discuss since it affects some 15% of couples, and half of cases are attributed to male factors. The body of the analysis discusses various factors related to obesity-associated male reproduction implications, including endocrinopathies insulin sensitivity, sperm DNA fragmentation, erectile dysfunction OSAS asshened semen characteristics chronic epididymitis and epigenetic changes. The above discussion on endocrinopathies shows that excessive white adipose tissues derail the HPG axis, triggering hormonal imbalances which lead to infertility. This paper explains the interaction between insulin resistance and testosterone levels in type 2 diabetes affected men. The paper also focuses on sperm DNA fragmentation, showing the association between obesity and increased levels of sperm DNA damage, mitochondrial dysfunction and abnormality in morphology. Erectile dysfunction is focused on obesity-induced oxidative stress, inflammation and hormonal abnormalities that impair male reproductive function. Additionally, the role of sleep apnea in testosterone secretion and possible association between its severity to lower level of this hormone are presented. There is a further discussion of altered sperm traits, chronic epididymitis and epigenetic changes with regard to the obesity which gives us a broad perspective on male fertility. The paper then concludes its discussion regarding weight loss interventions restoring fertility, focusing on diet and exercise as means for reducing certain parameters associated with modifiable inflammatory markers linked to infertility. In summary, the general assessment highlights that obesity management is crucial in male infertility.

## INTRODUCTION

As defined by ASRM, infertility is any patient with regular, unprotected intercourse and no known aetiology for either partner that suggests impaired reproductive ability. Evaluation should begin at 12 months for female partners under 35 and at six months for female partners 35 or older. This danger accounts for 15% of couples' infertility, 50% of which is male (Leslie *et al.*, 2023). In contemporary countries, obesity is a major health issue that causes infertility (Chaudhuri *et al.*, 2022). Over the last few decades, dramatic changes in semen quality have been found to be a universal trend due to civilised communities' lifestyle modifications around the world, which are mostly sedentary and high in fast food and calories, which are considered the main causes of obesity. This is making obesity more common and rising. Being overweight harms health. Being overweight or obese may cause infertility in men and make it harder for couples to conceive.

Obesity is linked to male infertility in many studies (Amiri & Tehrani, 2020). Obesity may disrupt the hypothalamic-pituitary-gonadal (HPG) axis' synchronised correlation and complicated signal connections with other reproductive hormones (Chaudhuri *et al.*, 2022). Physical factors like supra pubic heavy adipose tissue deposits increase scrotal temperature, oxidative stress (OS), and pro-inflammatory mediators, impairing semen parameters (Chaudhuri *et al.*, 2022). Obesity also substantially disrupts sperm genetic and epigentic conformation, altering DNA methylation patterns and impairing spermatogonia, causing infertility (Cescon *et al.*, 2020). Given new evidence-based ideas concerning obesity-related male infertility, its cause and mechanism must be investigated. This article reviews obesity's relationships with infertility characteristics that may affect male infertility directly or indirectly.

## MATERIALS AND METHODS

This paper is written with an overview of related articles published in Pubmed. A systematic review of the literature was performed to identify the complex relationship between obesity and male reproductive potential. Our review considered studies that investigated the following outcomes: likelihood of obesity on male infertility, sperm concentration and DNA fragmentation, erectile

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dysfunction, epigenetic changes and effecting other male reproductive functions including endocrinopathies & insulin sensitivity. The review was carried out to include all published literature. No date restrictions were applied, but language was restricted to English. Studies were retrieved up to December 2023, with an updated search performed in February 2024. Inclusion criteria followed were for studies carried out on male adults aged >18 years without history of reproductive disorders. Data had to be reported with men categorized by body mass index (BMI), including a normal weight group (BMI $\leq$ 25) and an obese group (BMI $\geq$ 30). All types of quantitative research were eligible for inclusion in the review including case series and reports. The exclusion criteria applied were non-peer-reviewed sources, studies with low methodological quality, or irrelevant topics. For relevance screen search results typically involved multiple stages including screening titles and abstracts followed by full-text assessment. Data extraction from the included studies involved a systematic process to record information, such as study design, sample characteristics, key findings, and quality assessment criteria.

We employed bibliometric and gap analysis to systematically analyse and synthesize the literature to identify patterns, themes, and gaps on the subject of effect of male obesity on male reproductive potential that helped us in the development of this review article. The limitations of this review article methodology included publication & selection biases and constraints due to resources available to us and time constraints.

The literature review discusses complete relationship between obesity and male infertility. It shows that excessive white adipose tissues derail the HPG axis, triggering hormonal imbalances causing hypogonadotropic hypogonadism, causing spermatogenesis disorder that leads to infertility. Obesity can affect levels of testosterone, Inhibin B, SHBG, and increase oestrogen and leptin. Moreover it explains the interaction between insulin resistance and testosterone levels in men with type 2 diabetes. The paper also focuses on the association between obesity and increased levels of sperm DNA damage, mitochondrial dysfunction, and abnormality in morphology.

A broad perspective on male fertility has been provided by reviewing the association between obesity- induced oxidative stress, hormonal impairment leading to male reproductive dysfunction, chronic epididymitis, and epigenetic changes. The paper concludes its discussion on weight loss interventions for restoring fertility focusing on diet and exercise and highlighting that obesity management is crucial in male infertility.

## LITERATURE REVIEW

Adipose tissue can be classified as brown adipose tissue and white adipose tissue. Brown adipose tissue contains multilocular adipocytes vast amounts of mitochondria that express high levels of uncoupling protein 1 (UCP-1), this is leads to the thermogenic activity of the tissue (Omran & Christian, 2020). White adipose tissue stores fat with fibroblasts, preadipocytes, mature adipocytes, and macrophages (Fernández-Sánchez *et al.*, 2011). White fat deposits are greater in obese animals due to adipocyte hyperplasia and hypertrophy, and white adipose tissue may generate endocrine, paracrine, and autocrine chemicals (Fernández-Sánchez *et al.*, 2011).

Secondary hypogonadism in obese people may decrease spermatogenesis and cause erectile dysfunction (Cabler *et al.*, 2010). Obese people have excess white adipose tissue, which increases testosterone to oestrogen conversion and reduces gonadotrophin release due to HPG axis negative feedback loop disruption. Spermatogenesis is disrupted by this. The increased oestrogen from this conversion reduces endogenous gonadotrophin release. Oestrogens inhibit GnRH pulsatility (Colaci *et al.*, 2012). Fat men have increased amounts of aromatization activity, adipose-derived hormones, and adipokines, which convert testosterone to oestrogen (Cabler *et al.*, 2010). Endocrine and secretory white adipose tissue secretes several physiologically active peptides and proteins. These include adipokines, which include immunomodulators, or adipose-derived hormones including leptin, adiponectin, and resistin (Ren *et al.*, 2022).

Adipose-derived hormones regulate food intake, insulin action, energy balance, lipid, and glucose metabolism. Increased white adipose tissue in obese males may enhance adipose-derived hormones (Gómez-Hernández *et al.*, 2016). Additionally, adipose tissue and testicular Leydig cells contain aromatase cytochrome P450 enzyme, which is essential to oestrogen production. Thus, white adipose tissue is thought to cause enhanced oestrogen levels in obese men due to androgen conversion (Katib, 2015; Palmer *et al.*, 2012). White adipose tissue increases hypothalamic-mediated leptin production, which regulates energy intake and expenditure and decreases Leydig cell testosterone production. This may explain why obese men's greater leptin levels may affect the HPG axis and lower testosterone synthesis (Khodamoradi *et al.*, 2022).

Sperm plasma membranes and testicular tissue have leptin receptors, indicating that leptin may operate on these receptors (Sengupta, Bhattacharya, and Dutta, 2019). Leptin may directly affect sperm via the endocrine system independent of HPD axis modifications (Isidori *et al.*, 1999). FSH/LH ratios, inhibin B, and SHBG levels regulate sertoli cell activity and spermatogenesis. Males with high BMIs have lower hormone levels. Low LH and testosterone levels may cause hypogonadotropic hypodonadism and male infertility (Hohl and Ronsoni, 2022). To conclude, obesity may diminish sperm counts due to impaired sertoli cell activity and HPG axis abnormalities caused by testosterone and oestrogen (Davidson *et al.*, 2015).

Type 2 diabetic males should evaluate their testosterone levels. Secondary hypogonadism in males with type 2 diabetes may result from peripheral and central insulin resistance, as well as the impact of proinflammatory cytokines (TNFα and IL-6) on the HPG axis (Bhasin *et* *al*., 2010). Increased insulin levels may lower SHBG levels in obese men's livers, thereby increasing blood levels of active unbound estogrens and testosterone. After SHBG correction, low testosterone levels were linked to insulin resistance and obesity. Insulin resistance affects testosterone and sperm production independently (Tsai *et al*., 2004; Palmer *et al*., 2012).

Sperm chromatin, a compact, organised structure, preserves genetic integrity. Obese males had more sperm with DNA fragmentation, poor mitochondrial membrane potential (MMP), and aberrant morphology and motility. These causes may cause male infertility (Durairajanayagam, 2018). Oxidative stress reduces sperm motility (Nowicka-Bauer and Nixon, 2020; Blumer *et al*., 2008). Continuous ATP generation by mitochondria in the midpiece controls sperm motility. Selective permeability of the mitochondrial membrane maintains an electrolytical gradient between the inner and outside surroundings. This permits oxidative phosphorylation to produce enough ATP. However, excessive reactive oxygen species (ROS) damage phospholipid membranes, limiting oxidative phosphorylation and ATP generation (Fariello *et al*., 2012). Lower sperm mitochondrial activity was detected in obese males.

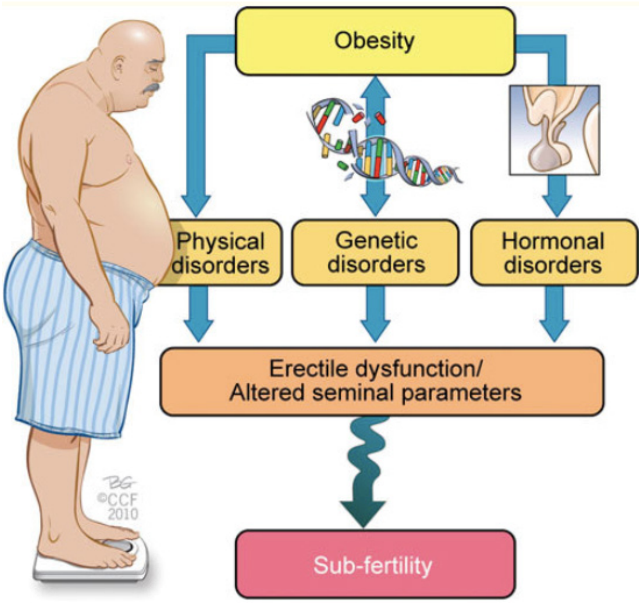


**Figure 1:** Mechanisms involved and the effect on male infertility (Cabler *et al*., 2010)

Erectile dysfunction (ED) in males is the continuous inability to achieve or maintain an erection suitable to perform sexual activity (Geerkens *et al*., 2020). What we know so far shows that ED is more common in overweight men from childless couples than in other guys (Zhang *et al*., 2019). Sultan *et al*. (2023) say that men with a BMI of 28.7 or higher are 30% more likely to have ED than men with a normal BMI (<25). Overweight people and people with ED both have oxidative stress, inflammation, and insulin and leptin resistance, all of which can affect ovulation (Moon, Park, and Kim, 2019). A rise in fat levels in the blood, the release of adipokin from adipocytes that have become too big, and the entry of immune cells into the adipose tissues are some of the most important signs of obesity. These things cause insulin and leptin resistance (Shimobayashi *et al*., 2018). Going against leptin also makes the brain release less gonadotropin-releasing hormone (GnRH). Because of this, testosterone levels drop, which can lead to ED (Moon, Park, and Kim, 2019). Also, sexual dysfunction wasn't linked to infertility caused by ED from a higher BMI. Instead, it was more likely due to other biological changes being harmed by being overweight (Nguyen *et al*., 2007).

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder and is characterised by a decrease or complete cessation in airflow in spite of an ongoing effort to breathe. OSA occurs due to periodic narrowing and obstruction of the pharyngeal airway during sleep., resulting in hypoxia and hypercapnia. (Osman *et al*., 2018; Arnold *et al*, 2017). OSA can have an impact on daily life as it alters the suffers ability to have a calm and continuous nights' sleep, and therefore can lead to increased daytime sleepiness, personality changes or cognitive difficulties related to fatigue (Arnold *et al*, 2017). OSA is more common amongst obese individuals and results in hypoxemia with each pause in breathing. The role of OSA in male infertility is not well understood it is often associated with a decrease in morning testosterone concentration and a decline in pituitary gonadal function which are necessary for normal spermatogenesis. (Cojocaru *et al*., 2023; Cabler *et al*., 2010). It has been suggested that nocturnal testosterone rhythm is disrupted by sleep apnea due to sleep fragmentation (Katib, 2015). Total and free testosterone levels were reduced in obese OSA men in comparison with age- and body weight-matched control men. A negative correlation was established between severity of sleep apnea and testosterone levels, which was still true after adjusting for BMI and waist values. Therefore, it was suggested that the major factor responsible for the decrease in testosterone secretion in OSA is the severity of sleep apnea (Katib, 2015).

## RESULTS AND DISCUSSION

Sperm parameters such as concentration, sperm motility and morphology have shown to be affected by male obesity. There has also been some evidence suggesting that weight loss can efficiently lead to increased levels of serum testosterone levels and hence increased sperm count. (Liu and Ding, 2017). A study reported that spontaneous and progesterone-induced acrosome reactions are potentially impaired in obese men (Liu and Ding, 2017). The correlation between male obesity and its impact on sperm acrosome reaction is sparingly documented in literature. However, it is reasonable to assume that spermatogenesis and sperm maturation is affected by obesity. This results in oxidative stress and membranous lipid alteration, which therefore cause defects in acrosome reaction (Aitken, 2020).

There have been several studies on both humans and animals, to show a correlation between obesity and a decreased in sperm DNA integrity. With obese males it has been shown that they often display an increase in sperm DNA damage, alterations to reproductive hormones and a decrease in sperm motility and sperm concentration (Leisegang *et al.*, 2021). The main pathological mechanism described in literature to explain these changes has been an increase sperm oxidative stress with increases in BMI, mainly because of a rise in seminal macrophage activation. Although the extent of increase was small, this phenomenon led to a decrease in acrosome reaction, lower embryo implantation rates during IVF, decreased sperm motility and an increase in sperm DNA damage (Palmer *et al.*, 2012).

As for the alterations to reproductive hormones, an increased BMI led to a decrease in sperm concentration and serum testosterone but an increase in serum estradiol (Katib, 2015). It was also found that individuals with a higher BMI displayed an increase in chances of developing oligospermia. Obese men were 3.5 times more likely to have oligospermia than men who possess a normal BMI. However, this value was slightly higher than the chances of developing oligospermia in overweight men (Hajshafiha *et al.*, 2013). The chances of developing oligospermia in overweight men was 3 times more likely than men with a normal BMI, therefore showing that a man doesn't necessarily have to be classified as obese in order for his sperm count to be affected.

One of the disadvantages of obesity is the increase in scrotal adiposity and subsequent increase in gonadal heat leading to an alteration in sperm production and parameters. The mechanism of spermatogenesis is sensitive to heat and testicular function is dependent on body temperature and requires a temperature of 2-4°C below body temperature in order to function optimally (Gao *et al.*, 2022) An increase in temperature of 1°C can result in a 14% reduction in spermatogenesis, and therefore a decrease in efficient sperm production (Durairajanayagam, Agarwal, and Ong, 2015). An increase in temperature is related to reduced sperm motility, increased sperm oxidation stress, increased sperm DNA damage, testicular germinal atrophy, spermatogenic arrest and a reduced level of inhibin B, with is a marker for spermatogenesis (Durairajanayagam, Agarwal, and Ong, 2015).

These all lead to lower sperm counts, therefore, it is crucial to maintain testicular temperatures slightly lower than that of the body to avoid abnormal spermatogenesis associated with male infertility (Durairajanayagam *et al.*, 2014). The temperature within the testis is maintained by characteristics of the scrotal sac including minimal subcutaneous fat, thin skin, scant hair distribution and dense sweat glands (Ilacqua, Francomano, and Aversa, 2018). In order to maximize heat loss, the cremaster muscle surrounding the testes and spermatic cords, and the dartos muscle from beneath the scrotal skin all relax. The relaxation of these muscles causes the testes to descend away from the abdomen and the scrotal skin to loosen (Fahmy, 2022). These characteristics increase the total surface area to allow for easy heat dissipation.

Another mechanism by which lower temperatures are maintained within the testis is a counter-current mechanism involving the testicular arteries and veins (Aldahhan and Stanton, 2021). There is a heat exchange of warmer inflowing arterial blood versus the colour outgoing venous blood. This system allows the cooler arterial blood to travel to the testis, and removes warmer venous blood (Rizzoto and Kastelic, 2020).

There are several factors other than increased scrotal tissue that can raise scrotal temperature, either by whole body increase or a local increase. Local elevation of scrotal temperature is often a result of direct heat exposure or effect of body temperature and diminished physiological testicular cooling mechanisms (Sheynkin *et al.*, 2005). Such exposures include the use of laptop computers, plastic lined diapers in children, prolonged car driving, sedentary lifestyles, the use of tight jockey shorts. Testicular heat stress caused by this increase in scrotal adiposity can subsequently causes oxidative stress. The increase in oxidative stress can therefore impair sperm motility, sperm-oocyte interaction and DNA integrity. The combination of increase in temperature and lack of activity also impairs spermatogenesis (Durairajanayagam, 2018).

The membrane of sperm consists of saturated fatty acids, such as myristic acid, palmitic acid and stearic acid, as well as unsaturated fatty acids such as oleic acid, arachidonic acid, palmitoleic acid and docosahexaenoic acid. The composition of such fatty acids within spermatozoa are vital for sperm functions such as motility, viability and fertility (Martínez-Soto, Landeras, and Gadea, 2013). Whereas polyunsaturated fatty acids, such as docoseahecaenoic acid (DHA), related to sperm concentration, motility and morphology (González-

Ravina *et al.*, 2018). These unsaturated fatty acids are also susceptible to reactive oxygen species (ROS) and cause lipid peroxidation. Therefore, excess ROS found in obese males has the potential to result in lipid peroxidation causing poor membranal lipid fluidity, alterations to acrosome reaction and sperm motility (Sinha and Gupta, 2018).

It was found that the regulation of fatty acid metabolism in the testis may be altered by BMI, hence resulting in changes to fatty acid composition of spermatozoa. This suggests that sperm quality in men with high BMI may be vastly affected by changes to fatty acid compositon of spermatozoa (Andersen *et al.*, 2016). Membrane cholesterol is another key constituent of spermatozoa, and this varies during sperm maturation and capacitation. The main role of mammalian spermatozoa is to fertilize their female contrary, the oocyte, and the capacity to achieve this phenomenon is gained during a multi-step process known as "posttesticular maturation" (Ramal Sanchez *et al.*, 2018).

Cholesterol plays a vital role in the modifcations of the composition of sperm plasma membrane which are crucial for fertility (Rajoriya *et al.*, 2020). These epididymal maturation steps prepares sperm cells for capacitation, which is the next maturation step, and also relies on the plasma membrane cholesterol (Visconti *et al.*, 2011). To summarise, levels of cholesterol in sperm is highly variable, but it has been suggested the higher sperm cholesterol levels in obese males have a contribution to infertility. The mechanism of this is due to that fact that development of acrosomal responsiveness and ability to fertilise in vitro is affected by cholesterol content of sperm. These changes are thought to lead to alteration to sperm morphology, decreased motility and premature acrosome reaction (Liu and Ding, 2017).

Although the current mechanism is unknown, it is evident that obese men have redundant areas of fat found at the suprapubic and inner thigh regions which can cause mechanical inflammation to the scrotal contents. This include epididymitis, in which during physical activities the friction from rubbing and sheering forces can result in inflammation (Katib, 2015). Any changes to the epididymis, regardless of the cause, alters the environment within the epidydmis. Such changes can have a knock-on effect on sperm maturation and inflammation can thus lead to scarring and cyst formation which subsequently results in blockage of epididymal ducts (Schagdarsurengin *et al.*, 2016). Although either one or both of the ducts can be blocked, cases that involve bilateral epididmytis have more impact on male fertility.

DNA methylation and acetylation of histones is dyanmic and are vital processes for the function of normal spermatogenesis, and therefore a successful pregnancy. DNA methylation involves the reversible attachment of a methyl group to a nucleotide in a heritable manner (Ge *et al.*, 2017). Epigenetic changes regulate gene expression and transcription intensity without changing the genetic information within DNA. These include DNA methylation, hydroxymethylation, histone modifcations and non-coding RNA expression (Mendelson, 2017).

Genetic modifications can be affected by genetic and environmental factors, one of these being obesity. It has been found that increased BMI can lead to alterations in DNA methylation (Dick *et al.*, 2014; Ozanne, 2015). Furthermore, it has been suggested that children born to obese fathers are more likely to suffer from metabolic disease and develop childhood obesity. Therefore, suggesting that paternal obesity can contribute to the health of offspring (Soubry *et al.*, 2016). Consequently, it has been shown that paternal obesity can influence epigenetic modifications in sperm.

It has been suggested that weight loss can lead to an altered androgen profile and therefore improve semen quality. It is evident that obesity in males has a negative effect on fertility, hence sperm function and subsequent impact on offspring. Therefore, interventions such as alterations to diet and exercise are able to reverse the obesity state and hence the alter the impact on sperm and offspring. By altering BMI, this has a cumulative effect at changes at the molecular level, thereby decreasing oxidative stress and any DNA damage (Savini *et al.*, 2013).

It has been shown in the literature that numerous studies suggested that weight loss naturally by dieting and/or exercise led to an increase in androgen, inhibin B and sex hormone-binding globulin levels and decreased serum concentrations of insulin and leptin (Kasturi, Tannir, and Brannigan, 2008). These changes result in improved semen parameters in obese men (Chavarro *et al.*, 2010). Moreover, weight loss by the reduction of adipose tissue coupled with exercise or a low-fat and low energy diet has been seen to be linked to a decrease in TNFα, IL-6 and other inflammatory cytokine levels related with infertility (Manna and Jain, 2015). Other than the fertility issue many other health issues are also related to obesity including Non-alcoholic fatty liver disease which is the most common liver disease and is closely linked with obesity and metabolic syndrome Onyango, (VC *et al* . 2023). Therefore by adopting weight loosing strategy it will not only imorove the fertility but also will help with general well-being.

## CONCLUSION

Obesity can have physical and psychological impacts along with other serious comorbidities. As discussed above, the literature has proven that obese men are at risk of increased chances of infertility due to mechanisms involving hormonal, physical, adipokine and cytokine changes. These changes can eventually lead to abnormal sperm parameters, changes to sperm function and sperm molecular composition. Offspring from obese fathers also have the potential to develop metabolic disorder, and childhood obesity.

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