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| RESEARCH ARTICLE

The Impact of Obesity on Male Reproductive Functions

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| ABSTRACT
Obesity is a major factor that can contribute to the risk of infertility in men. This study is aimed at assessing the impact of obesity on the parameters of male fertility. The study utilizes the comparative analysis of different research to determine how weight gain and obesity can interfere with the reproductive functions in men. The findings of this study indicate the strong association of obesity with co-morbidities, including male infertility, that is seriously affecting the male population. It also recognizes the role of management options such as weight reduction and antioxidant support for the prevention of obesity-linked infertility in men.

| KEYWORDS

Obesity; Male Reproductive Functions; infertility; co-morbidities

| ARTICLE INFORMATION

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1. Introduction

1.1 Rising Prevalence of Male Obesity and Related Infertility

Obesity in men could be the major factor contributing to the rising incidence of infertility. Obesity in men is also the reason so many couples are turning to advanced fertility treatments to conceive a child. Infertility refers to a condition in which a couple has failed to conceive after trying for over a year [Craig, 2017; Katib, 2015; McPherson, 2017].

According to the World Health Organization (WHO 2006), about 1.6 billion adults were overweight, and 400 million were obese in 2005. Throughout the world, obesity is becoming increasingly common in adults. It is increasing in a reasonably similar fashion throughout the western world, with some nations having witnessed the rise earlier than others [Phillips, 2010; Campbell, 2015].

Studies have revealed that the average Australian adult has a higher than healthy weight for the respective height. In the latest national survey, it was found that nearly 63% of adults were above a healthy weight (35% overweight, 28% obese) [Shukla et al. 2014].

Obesity is becoming more common. In 2011-12, about 1 in 4 adults were obese compared with 1 in 5 adults in 1995. This increase was found to have occurred across all age groups and genders, although at different rates.

The proportion of the adult population with a BMI of 35 kg/m2 and over has also increased substantially from 1 in 20 adults in 1995 to 1 in 10 adults in 2011 [Katib, 2015; Fui, 2014].

Excess weight has been directly or indirectly related to biological changes that could increase the risk of infertility [Rambhatla, 2016]. There was a significant decrease in semen volume, sperm count, sperm motility, and sperm function tests in overweight and obese men. This suggests that an increased BMI could be correlated negatively with male fertility.

Many global studies, including systematic reviews, meta-analysis, and population-based research, have been conducted to assess the epidemiology and prevalence of male infertility. The studies conducted in North America and Australia are believed to be more accurate than those conducted in other developed countries.

The rate of male infertility was found to be about 8% to 9% in men over the age of 40 in Australia and about 4.5% to 6% in the same age group of men in North America. In Europe, about 7.5% of men were found to have infertility.

In a study done on Wistar rats, rats were administered a high-fat diet to induce obesity for 15, 30, and 45 weeks. The rats were then evaluated for adiposity index, serum leptin, reproductive organ weight, and sperm counts. The final results showed that obesity could lead to reduced sperm motility and a higher risk of male fertility.

2. Obesity and HPG Axis

Obesity is known to trigger chronic low-grade systemic inflammation [Belloc, 2014]. It produces a multifactorial effect on male reproductive functions.

Under normal conditions, gonadotropin-releasing hormone (GnRH) is produced in the hypothalamus. GnRH stimulates the production and release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland [Kahn, 2017]. FSH and LH act on the testicles to stimulate spermatogenesis and steroidogenesis [Katib, 2015; Kahn, 2017, Chambers, 2015].

FSH binds with the receptors on the testicular Sertoli cells and regulates spermatogenesis. LH binds the testicular leydig cells receptors [Phillips, 2010; Shukla, 2014; Palmer, 2012].

Studies in the 1970s and 1980s first described hormonal abnormalities seen in the HPG axis in obese men. Obese men had normal LH levels, decreased testosterone levels, and reduced sex hormone-binding globulin (SHBG) [Kahn, 2017].

Adipose tissue is an active endocrine organ. It produces about 30 biologically active peptides such as adipokines (immunomodulation agents), leptin, resistin, and pro-inflammatory cytokines such as Interleukin-6 (IL6), which can affect spermatogenesis and sperm functions [Cabler, 2010].

3. Interleukin-6, TNF-alpha, and Male Infertility

IL6 and tumor necrosis factor-alpha are both secreted in high concentrations in the presence of high adipose tissue. IL6 and TNF alpha can cause inflammation resulting in the release of reactive oxygen species (ROS).

ROS are highly reactive free radicals that can produce a toxic effect on the sperms [Shukla, 2014; Lampiao et al., 2008].

IL6 can diminish the penetration capability of the ovum. Leptin is responsible for satiety. It is well-known as a regulator of food intake and energy homeostasis. It increases with fat mass and is involved in glucose metabolism and sexual reproduction and maturation [Cabler et al. 2010].

4. Leptin, Kisspeptin, and Male Infertility

A high leptin level can produce a negative influence on the Leydig cell-linked testosterone synthesis by inhibiting the conversion of 17-OH progesterone to testosterone [Phillips, et. 2010].

Leptin receptors are present not only in the testicles but also in the plasma membrane of the sperm, which creates a direct effect on the sperm independent of the HPG axis [Cabler, 2010]. Leptin also regulates gonadotropin secretion by modulating Kisspeptins in the arcuate nucleus.

Kisspeptins are proteins encoded by the kiss1 gene and act on G-protein-coupled receptors (GPR54) to stimulate GnRH secretion [Palmer et al., 2013].

kiss1 gene was found to be suppressed in obese men [Sanchez-Garrido, 2014]. Additionally, insulin resistance and sleep apnea linked to obesity can both downregulate testosterone and the HPG axis. Fragmented sleep can decrease LH production, further reducing the circulating testosterone levels [Phillips, 2010].

5. Spermatogenesis in Men with Obesity

Aromatase overactivity occurs when an abundance of the aromatase cytochrome P450 is expressed in the adipocytes. Reduction in the production of SHBG by the liver and the increased adipocyte aromatase activity can lead to an increase in the conversion of testosterone to estradiol, which can alter the hypothalamic and pituitary negative feedback mechanisms [Chambers et al. 2015].

Higher estrogen and low testosterone levels decrease FSH and SHBG levels, leading to an overall reduction in spermatogenetic function.

Estrogen stimulates the proliferation of preadipocytes and the growth of mature adipocytes. A very high level of estrogen in men can upregulate the phagocytosis of Leydig cells by macrophages. This can destroy the testosterone-producing cells in the testicles [Cabler, 2010].

Increasing body fat suppresses the HPT axis. Some studies have suggested that testosterone can promote the accumulation of total visceral fat mass, thus exacerbating gonadotropin inhibition. A longitudinal study involving community-dwelling Japanese-American men has demonstrated that the lower baseline testosterone could predict the increase in intra-abdominal fat after 7.5 years of follow-up [Palmer, 2020].

The degree of decrease in total testosterone is proportional to the degree of obesity. Free testosterone level remains within the normal range, especially in young obese men. The reduction in the total testosterone level is a consequence of a reduction in the SHBG level. However, the references related to free testosterone are not well established [Guo, 2017].

Inhibin B is a potential marker of Sertoli cell function. The inhibin B level correlates positively with spermatogenesis. It was found that Inhibin B level is decreased significantly in obese men [Globerman et al. 2015].

In obese men, redundant fat in the inner thigh can cause mechanical inflammation to the scrotal tissues, such as epididymis. The inflammation can lead to blockage in the epididymal duct. It can lead to epididymitis, which can further impair male fertility. [Han, 2021]

Obese men with increased scrotal fat and a sedentary lifestyle may develop an increase in the scrotal temperature and genital heat, which can impair spermatogenesis [Diaz-Arjonilla, et al. 2009].

6. Effect of Obesity On Semen, Sperm Morphology, and DNA

It takes nearly 100 days to produce sperm, as they undergo normal maturation and development. Semen analysis is the most important factor for the evaluation of infertility in men. Semen volume and PH level can be used as the markers of seminal vesicle and prostate function, whereas sperm concentration, morphology, and motility can be used to determine testicular function [Cooper, 2010].

Germ cells are highly susceptible to damage from oxidative stress via reactive oxygen species (ROS) and DNA fragmentation.

Traditional WHO sperm parameters include sperm concentration and motility. It was shown that other parameters, such as molecular structure and the content of the sperm, are equally important [Wang, 2017].

Several studies have investigated the impact of obesity on sperm parameters. About 15 out of 23 studies have reported some evidence suggesting that male obesity can reduce sperm concentration. There were some limitations to these studies due to lifestyle factors such as smoking, alcohol consumption, and recreational drugs.

Most of these studies originated in fertility clinics visited by sub-fertile men, which might have affected the confounding findings.

Rodent models have been established to avoid difficulties in interpreting data in human studies after feeding rodents with a high-fat diet to induce obesity and reduce sperm motility [Mu, 2017].

Systematic review and meta-analysis studies conducted in 2016 have demonstrated that total sperm count, sperm concentration, and semen volume are decreased in obese men [Dupont et al. 2013].

The sperm DNA integrity is associated with successful embryonic development. Many studies have determined the relationship between obesity and DNA integrity damage. Sperm oxidative stress has been linked to increased DNA damage and decreased sperm motility. Two studies, one of which is conducted in humans and another in Rodents, have shown that high BMI is directly linked to an increase in sperm oxidative stress [Eisenberg et al. 2015].

Two studies have reported that there is an increase in the percentage of sperms with low mitochondria membrane potential in obese men compared to that in men having a normal BMI [Lotti et al. 2011].

Many studies have investigated the effect of male obesity on seminal plasma factors.

Some studies have determined that there is a significant positive correlation between the increased concentrations of neopterin, interleukin 8, and seminal plasma fructose in men having a higher BMI [Martini, 2010].

7. Psychological Problems in Men with Obesity

Men with obesity are vulnerable to considering themselves unattractive and undesirable. This can affect their sexual performance. Obesity can lower sexual satisfaction and cause a lack of sexual enjoyment. It can lead to difficulty in sexual performance, avoidance of sexual encounters, and erectile dysfunction (ED). It was found that 79% of men complaining of ED are obese [Kolotkin et al. 2012].

7.1 Effects of Paternal Obesity on the Offspring and Pregnancy Outcome

Evidence has shown that there is an increase in the risk of pregnancy loss after assisted reproductive technology through IVF and ICSI in a couple that has an obese male partner [Skinner et al. 2010]. This can be co-related to abnormal sperm function, DNA fragmentation, and increased ROS in the semen of obese men in comparison to these parameters in men with a normal BMI.

However, even after multiple studies were conducted to assess the effect of paternal and maternal obesity on the offspring, the conclusion was difficult to arrive at due to the multiple environmental and genetic confounding factors [Fullston et al. 2012].

McPherson et al. study done in South Australia to investigate the impact of paternal obesity on the offspring has revealed exercise as an effective intervention for obese fathers. The five-week-old male mice were categorized into a high-fat diet group or a control group. The high-fat diet group was then categorized into two sub-groups for nine weeks, one with exercise intervention and the other with sedentary life.

Later, the mice underwent successful mating with normal-weight female mice to induce pregnancy. The end result of this study has shown that the male offspring born to fathers, who underwent exercise intervention, had normal glucose tolerance, insulin sensitivity, cholesterol concentration, and pancreatic morphology, similar to the control group offspring [Fullston et al. 2012].

Another Study done in mice has reported that switching from a high-fat diet to a low-fat diet can improve sperm parameters and metabolic health in the offspring of obese men [Cropley et al. 2016].

8. Obesity, Versus Disorders Associated With Diabetes, Hypoxia, Metabolic Syndrome, Co-Morbidities, and Fertility

Obesity is strongly associated with metabolic syndrome and insulin resistance. Metabolic syndrome includes abdominal obesity, high blood pressure, elevated fasting blood glucose, and elevated level of triglycerides with low HDL. Men with metabolic syndrome and obesity have an increased risk of cardiovascular diseases. Metabolic syndrome has been associated with hypogonadism and ED [Palmer, 2012].

Hyperglycemia and hyperinsulinemia are confounding factors in rodent studies. Both these factors have been found to induce an inhibitory effect on sperm quality and quantity [McPherson, 2017].

It was found that obese men with diabetes have an increased ROS and sperm DNA fragmentation and damage [Davidson et al. 2015].

Obesity causes disruption of the HPG axis resulting in elevated estrogen and low testosterone levels. These changes can decrease sperm count [Palmer et al. 2012].

Obese men with obstructive sleep apnea may develop disruption in the nocturnal rise in testosterone level, thus interrupting with HPG axis [Davidson et al. 2015].

9. Nutrition Specific Effects

A study done in 2017 to assess the effect of a healthy diet on semen quality has shown that dietary and nutritional factors play a major role in spermatogenesis. Folate and vitamin B12 are required for the synthesis of DNA, proteins, and phospholipids. A high intake of fruits, vegetables, and healthy fat like olive oils with a low intake of processed meat, dairy, and sugar could lead to less DNA damage in sperms, a higher concentration of sperms, and improved sperm motility and count.

Hoffmann et al. study investigated the dose-dependent effects of leptin on Leydig cell function and spermatogenesis. Leptin-deficient obese (ob/ob) male mice were treated with subphysiological and physiological doses of leptin. It was found that the mice treated with the physiological doses of leptin had partial improvement in the reproductive markers without changing BW. The administration of subphysiological to physiological doses of leptin improves Leydig cell function and spermatogenesis [Hoffmann, 2016].

Other studies have shown that testosterone level is positively affected by a high intake of fruits, cruciferous vegetables, tomatoes, leafy vegetables, and fish [Oostingh, 2017].

One study comparing the effectiveness of vitamin C and exercise intervention on men with obesity showed that the consumption of vitamin C could improve sperm concentration and motility [Rafiee, 2016].

It is believed that genetic mutation can predispose men to obesity. But, in the general population, obesity is a reversible and preventable condition.

Lifestyle changes, which include a healthy diet and exercise, can induce weight loss. Weight loss has been shown to normalize androgen, SHBG, leptin, and insulin levels.

If lifestyle modifications fail, the other options could be medical or surgical interventions. Pharmacological interventions such as Xenical and Phentermine, which are approved by FDA, are not effective for long-term weight loss.

9.1 Aromatase Inhibitors and Male Infertility:
The use of aromatase inhibitors in the treatment of male infertility has not been widely used or studied. The findings of one study by Schlegel and Raman involving 140 heterogeneous, infertile men suggested the possible role of aromatase inhibitors in the management of infertility.

Not all the men in this study had infertility caused by hypogonadotropic hypogonadism secondary to obesity. But interestingly, all the men responded to the treatment with aromatase inhibitors with improved sperm analysis results, increased serum testosterone levels, and decreased serum estradiol levels [Raman, 2012].

Double-blinded placebo study done in Netherland involved 42 men with BMI>35kg/m2 and testosterone levels less than 10nmol/L. The participants were recruited and commenced on the Letrozole tablet at a dose of 2.5 mg/week. The dose was increased every month until the serum testosterone level reached 20 nmol/L. Letrozole was found to decrease serum estradiol and increase LH, with somatic or psychological effects [Loves, 2013].

Three aromatase inhibitors - anastrozole, letrozole, and testolactone - have been studied for the treatment of hyperestrogenic hypogonadotropic hypogonadism. All three aromatase inhibitors have been shown to be effective for increasing serum testosterone levels and decreasing estradiol levels. However, letrozole has not been evaluated for the treatment of male infertility. Also, the appropriate dose of this drug for the treatment of men with hypogonadism is less well characterized [Raman, 2012].

9.2 Management of Infertility in Men with Obesity:
Many obese men fail to adhere to weight management programs and consider bariatric surgery for obesity management. In bariatric surgery, the stomach size is reduced. It is advisable only in severely obese patients with BMI >40kg/M2 or when all other treatments have failed. Bariatric surgery is extremely effective in weight reduction [Abiad, 2017].

Another surgical option for infertility treatment includes a scrotal lipectomy to reduce increased scrotal temperature and genital heat stress [Roth, 2008]. Assisted reproductive techniques such as IVF and ICSI are viable treatment options for male infertility [Abiad, 2017].

There was a study done in china to assess the effect of Fluvastatin on reproductive function in obese males. The study was conducted on three-week-old Sprague Dawley rats. The rats were divided into three groups: the control group, a high-fat diet group, and a high-fat diet group with Fluvastatin at a dose of 6mg/Kg bodyweight. After eight weeks, the body weight of all rats was measured. The weight of the testes, sperm parameters, and sex hormone levels were also assessed.

The result showed that Fluvastatin had a protective effect that improved the reproductive function in obese male rats [Cui, 2017].

10. Conclusion
The incidence of obesity is increasing globally. The association of obesity with co-morbidities is seriously affecting the male population. Data from several studies showed that obesity is associated with male infertility. The adverse effect and prevalence of obesity on male fertility are increasing.

The causes of infertility in obese men are multifactorial. Various endocrine and hormonal changes are responsible for altered sperm parameters. The dysregulation of the HPG axis may explain most of the changes observed in the semen and sperm parameters.

There are a variety of management options available, and weight reduction is the most effective among them. Healthy reduction in fat mass in obese infertile men can positively impact hormonal function and testosterone production. Antioxidant support may help in improving sperm parameters. Some studies have reported the effect of change in diet on male fertility. However, more studies are needed to provide conclusive evidence.

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