Invited Editorial

Obesity inflicted reproductive complications and infertility in men

Rahnuma Ahmad [1], *Mainul Haque* [2]

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The characteristic of obesity is body fat accumulation in excess,which has a deteriorating effect on human health. Almost 650 million individuals are obese, while 1.9 billion people are overweight. Obesity is determined on the basis of Body mass index (BMI). The BMI values recommended by World Health Organization (WHO) for weight classification are as follows:i) BMI< 18.5- underweight (ii) BMI 18.5 to 24.9 - Optimal weight (iii) BMI 25.0 to 29.9 – overweight (iv) BMI =>30.0 - Obese [1,2]. However, BMI does not consider the proportion of fat and lean body mass; visceral fat and subcutaneous adipose tissue may result in overestimating or underestimating obesity risk [3]. An increase in visceral adiposity raises the risk of obesity-related complications like type 2 diabetes mellitus (T2DM), cardiovascular disease, neurodegeneration, osteoarthritis, endocrine disorder aging acceleration, and certain cancers like prostate cancer [4-6]. Obesity also has a negative influence on the human reproductive system. The different mechanisms leading to such complications include chronic inflammation, resistance to insulin, oxidative stress, high insulin and leptin levels in blood [7].

Obesity and Infertility

Quality and expectancy of life are negatively impacted by obesity-related complications, including deteriorating effects on the reproductive health of individuals [8]. Infertility may result from an obesity-induced imbalance in the male and female reproductive system [9,10]. Obese females suffer from irregular and excessive menstruation [11], polycystic ovary syndrome (PCOS) [12], increase in endometrial thickness [13], uterine fibroids and endometriosis [14,15], pre-eclampsia and eclampsia (complications of pregnancy) [16] infertility [17] and miscarriage [18].

Although obesity-induced reproductive complications and infertility in males is less discussed than in females, evidence suggests that male obesity may contribute equally to the poor reproductive outcome and negatively impactembryo quality [19].

Male Reproductive Complications in Obesity

Spermatogenesis and sperm quality,that include sperm appearance, movement, concentration, viability as well as integrity of DNA of sperm, is negatively influenced in obese male subjects [9,10,13]. In previous studies, a deterioration in the quality of semen was noted in individuals with BMI above normal range. Sub-fecundity was associated with rising BMI [20-22]. Another study has reported that couples with obese male partners had a greater risk of suffering from infertility than normal BMI couples (OR= 1.66, 95% CI 1.53-1.79, $p<0.0001$). Assisted Reproductive Technology success was also found to be less in obese male subjects [21].

1. Rahnuma Ahmad. Department of Physiology, Medical College for Women and Hospital, Dhaka, Bangladesh.
2. Mainul Haque. Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, 57000 Kuala Lumpur, Malaysia.

Correspondence: Mainul Haque. Faculty of Medicine and Defence Health, UniversitiPertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, 57000 Kuala Lumpur, Malaysia. Email: runurono@gmail.com, mainul@upnm.edu.com. Cell Phone: +60109265543

Molecular Mechanisms Relating Obesity to Male Infertility

Obesity influences the male reproductive system by employing several molecular mechanisms. These include inflammation, oxidative stress, and hypogonadism which affects spermatogenesis [Figure1] [23-25]. Functions of the testes may be hampered due to microenvironmental inflammation and dysregulation of adipocytes impacting the signaling of insulin [9,26,27].

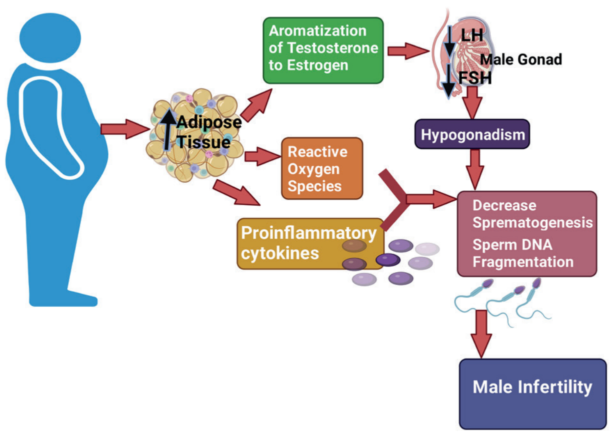

Figure 1: Male obesity and infertility Editorial

Figure 1: Illustrates the different mechanisms by which obesity influences male reproductive system. These include inflammation, oxidative stress, hypogonadism which causes sperm DNA fragmentation and decrease in spermatogenesis resulting in male infertility.↓: Decrease.↑: Increase. This figure has been developed utilizing premium version of Biorender (https://biorender.com/) with license number TH24LTCUL9. Image Credit: Rahnuma Ahmad.

Hormonal Changes in Male Obesity

The hypothalamic-pituitary-gonad axis controls testosterone production. Gonadotropin Releasing hormone causes LH and FSH release fromanterior pituitary gland, that then causesthe release of testosterone from the Testes (under the influence of LH) and FSH produces effects on Sertoli cells. Together the effects of LH and FSH promote spermatogenesis [28,29].

In obese male subjects, however, a reduction in male sex hormones has been observed in comparison to normal BMI subjects [30.] A decrease in sex hormone binding globulin and total testosterone level in serum have been noted, possibly due to increased visceral fat. There has also been noted a rise in testosterone conversion to 17- β-estradiol due to the high activity of aromatase in obese subjects [31,32]. Aromatase activity also increases fat accumulation, negatively impacting the male sex hormones [29].

Estrogen level rises in obesity and suppresses kisspeptin neurons, which lowers GnRH and inhibits the hypothalamic-pituitary-gonad axis, thus decreasing testosterone production [33]. Leydig and Sertoli cell activities are also suppressed by estrogen, which reduces testosterone levels and spermatogenesis [Figure 2] [29]. Testosterone formation is also suppressed due to inflammatory cytokines and adipokines formed from adipose tissue [9,34].

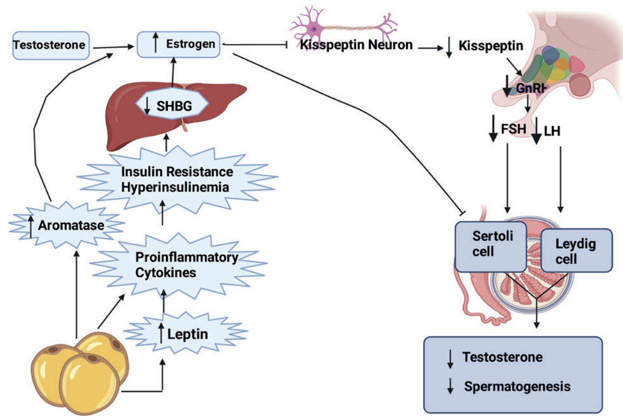

Figure 2: Male obesity and infertility

Figure 2: Illustrates decrease in sex hormone binding globulin (SHBG)due to insulin resistance caused by pro inflammatory cytokines released from adipocytes, the level of which is also augmented leptin from adipocytes. Decrease in SHBG causes increase in estrogen level. Aromatase from adipocyte cause a testosterone conversion to 17- β-estradiol. Estrogen level rises and suppresses kisspeptin neuron and decreases GnRH and inhibits the hypothalamic-pituitary-gonad axis. Thus, there is decrease in testosterone production. Leydig and Sertoli cell activities are also suppressed by estrogen which thus lowers testosterone level and spermatogenesis. Notes: ↓Decrease.: ↑Increase.SHBG: Sex Hormone Binding Globulin, GnRh: Gonadotropin Releasing Hormone, FSH: Follicle Stimulating Hormone, and LH: Luteinizing Hormone. This figure has been developed utilizing premium version of Biorender (https://biorender.com/) with license number RP24M0H4M8. Image Credit: Rahnuma Ahmad

Sperms Parameters in Obesity

In obese men, spermatogenesis may be impaired due to altered hormone levels [5]. Accumulating adipose tissue above the pubis area and around the pampiniform plexus may cause a rise in scrotal temperature. Such changes may eventually cause a fall in motility,concentration and integrity of DNA of sperm with DNA fragmentation [35] .

A lower count of sperm was noted men with BMI above 25 kg/m^2 [31]. In 2013 a meta-analysis noted that oligospermia and azoospermia were more prevalent among obese men [36]. Specific abnormal sperm parameters like asthenozoospermia and teratozoospermia have been reported in men who were obese and overweight [37].

Obesity, Oxidative Stress, and Sperm Parameters

TNF-α and Interleukin 6 are examples of inflammatory cytokines that are releasedin high quantities in obese subjects, leading to chronic inflammation [38]. However, Reactive Oxygen Species (ROS) within physiological limits produce beneficial effect onthe male reproductive system, helping incapacitation and acrosomal reaction. In high concentrations, these lead to DNA, protein, and lipid damage. ROS also may cause double bond oxidation of sperm membrane lipid, consisting of polyunsaturated fatty acids, thus resulting in low membrane fluidity [39-41].

A study on the parameters of sperm has reported some early markers of apoptosis in obese men, like reduced sperm mitochondrial membrane potential, fragmentation of sperm DNA and phosphatidylserine release [37]. Oxidative imbalance occurs when mitochondria are dysfunctional as oxidative agents are produced by mitochondria. Thisnegatively impacting sperm function [42,43]. Another study also observed ROS formation in high concentrations and reduced mitochondrial membrane potential in obese men with infertility [44]. An association was found in a survey between abnormal sperm chromatin compactness and decreased sperm mitochondrial membrane potential indicating that mitochondrial damage may lead to alteration in sperm DNA [45]. Sperm DNA fragmentation was noted in obese subjects in another study [31].

Adipokines in Obesity and Male Infertility

Adipocytes form a kind of adipokine called leptin, which is related positively to body fat percentage and adipocyte size [9]. Leptin causes appetite suppression and decreasesfood intake by neuropeptide Y encoding gene repression, proopiomelanocortin encoding gene, and amphetamine-regulated transcript induction. It also has a significant role in reproduction at the central and peripheral levels [46]. Leptin impacts the hypothalamic-pituitary-ovarian axis by acting on kisspeptin, the receptors of which are found in GnRH neurons, thus stimulating GnRH and promoting FSH and LH secretion [47,48]. Production of leptin in excess in obesity causes development of leptin signal resistance in the hypothalamic-pituitary axis, likely an outcome of regulators of negative feedback mechanism such as suppressor of cytokine signaling, tyrosine phosphatase1B overstimulation. In animal study, animals with obesity such regulators have been found in high concentration in hypothalamus [49,50] . Leptin resistance and reduction in kisspeptin expression in the third ventricular rostral periventricular region and arcuate nucleus have been observed in a study on animals on a high-fat diet [51]. A decrease in kisspeptin leads to GnRH neurons inhibition which eventuallyleads to falls in FSH,LH, and testosterone production [9,52].

Association between the reduction insperm concentration, increased DNA fragmentation of sperm, and increased serum leptin level was reported in subjects with high BMI compared to those having BMI within normal rangeby a case-control study [53]. DNA fragmentation of sperm in an environment of high serum leptin may be due to an increase in ROS and activation of the PI3K pathway in testes when leptin binds to receptors on testes which disruptsthe conversion of histone to protamine and give rise to oxidative stress. DNA of sperm is impacted by free radicals leading to DNA fragmentation as well as apoptosis [46]. High serum leptin alters the function of mitochondria and negatively affects sperm due to a rise in oxidative stress [54]. Testosterone secretion is suppressed in rat Leydig cells exposed to high leptin levels in certain animal studies [55.56]. Leptin negatively impacts Leydig cells cytochrome P450 family 11 subfamilies A member 1 and steroidogenic acute regulatory protein and up-regulation of the AMPK pathway. Downregulation of STAT transcriptional activity and cAMP-dependent steroidogenic gene may occur due to high leptin levels and thus decreases testosterone production [9,57]. Leptin also lowers acetate formation from glucose, inhibitingthe nutrition of Sertoli cells [9]. Such changes impact spermatogenesis negatively [51].

Other adipokines like resistin and chemerin promote inflammation. Insulin resistance is promoted by resistin, and a positive association has been noted between resistin and inflammatory markers [58,59].

Resistin level in seminal fluid was negatively associated withsperm motility and vitality in a study. Seminal fluid inflammatory markers like Interleukin-6 and elastase have been positively associated with a raised level of seminal resistin [60]. Significantly high chemerin levels have been found in subjects with BMI above normal in comparison to those withBMI in normal range [61,62]. Chemerin has been shown to suppress the production of sperm, testosterone synthesis, and sperm motility [48,63].

Obesity and Epigenetic Modification

Studies have found that children fathered by obese male parents are at greater risk of developing obesity [9,64]. Spermatogenesis requires methylation of DNA which is altered in obesity, as studies suggest [65,66.] In obese men, some epigenetic modifications include necdin (NDN), small nuclear ribonucleoprotein polypeptide N (SNRPN) and epsilon sarcoglycan (SGCE)/paternally expressed gene 10 (PEG10) which affect the development of the fetus [67]. DNA methylation changes also cause DNA fragmentation of sperm and decreased pregnancy rate [68,69].

Assisted Reproductive Technology (ART) Outcome in Obese Male

A decrease in the success rate following Intracytoplasmic sperm injection (ICSI) and Invitro Fertilization (IVF) has been linked to obesity in male [70]. A study reported male obesity negatively impacted embryo quality and IVF outcome [71]. Sperm damage due to male obesity was linked in a study to higher miscarriage rates and lower pregnancy rates in ICSI and IVFcycles [72]. The pregnancy rate in 290 IVF and ICSI cycles assessment showed pregnancy rate following IVF was negatively impacted in men with a BMI above 25.0kg/m^2 [73].

Obesity, Infertility and Lifestyle

An unhealthy eating habit and a sedentary lifestyle contributes to obesity significantly and when there is a rise in 10% of sedentary time, the waist circumference increase by 3.1cm [65,74]. Regular exercise helps combat obesity as it promotes general well-beingand improvement of insulin sensitivity [75]. High fat diet has been noted to deteriorate sperm cells' physical and molecular structure [68, 76]. Sperm quality and DNA integrity has been seen to improve when the individual's diet is rich in legumes, fruits, fish and vegetables [77]. Therefore for fertility improvement in individuals with high BMI, evaluating and modifying lifestyle and habits with the help of healthcare professionals is of great importance [78.]

Obesity is a rising epidemic affecting more and more of the global population, who become prone to developing complications related to obesity [75,79.] Obesity results in insulin resistance and complications like T2DM. Such complications create an environment of chronic inflammation and release of inflammatory cytokines [80,81]. Growth factors, hormones, adipokine, and cytokines link obesity to dysfunctions of several body systems includingthe reproductive system [82]. Male infertility resulting from obesity involves various molecular pathways and creates a hormonal imbalance that hampers sperm production. To better manage and prevent obesity-related reproductive complications and obesity itself, it is imperative to learn extensively about the various mechanisms linking fertility and obesity. Each linking pathway can be targeted and used to develop therapeutics which improve reproductive health in obese subjects. Creating awareness regarding the negative effect of obesity on human health among the general population is also necessary.

Conflict of Interest

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