SciDoc Publishers
Infer, Interpret & Inspire Science

International Journal of Diabetology & Vascular Disease Research (IJDVR)
ISSN 2328-353X

Obesity and Male Infertility: An Overview

Editorial

Bárbara Guerra-Carvalho[1,2,3,4], Marco G. Alves[1,2,5,6], Pedro F. Oliveira[3*]

[1] Department of Anatomy and UMIB - Unit for Multidisciplinary Research in Biomedicine, ICBAS - School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal.
[2] Laboratory for Integrative and Translational Research in Population Health (ITR), University of Porto, Porto, Portugal.
[3] LAQV-REQUIMTE and Department of Chemistry, University of Aveiro, Aveiro, Portugal.
[4] Department of Life Sciences, Faculty of Sciences and Technology, University of Coimbra, Coimbra, Portugal.
[5] Biotechnology of Animal and Human Reproduction (TechnoSperm), Institute of Food and Agricultural Technology, University of Girona, ES-17003 Girona, Spain.
[6] Unit of Cell Biology, Department of Biology, Faculty of Sciences, University of Girona, ES-17003 Girona, Spain.

Obesity has reached pandemic proportions in recent decades. In 2016, the World Health Organization estimated that over 1.9 billion adults were overweight (39 percent of the world's adult population) and more than 650 million were obese [1]. These numbers are expected to rise with up to 3.3 billion individuals being overweight or obese by 2030 [2]. Obesity and overweight are both described as an excessive or abnormal accumulation of body fat that is harmful to one's health and are clinically defined based on the body mass index (BMI). BMI≥30 kg/m^2 or ≥25 Kg/m^2 is often used to categorize obesity and overweight in adults, respectively [1]. Nevertheless, this index should only be used as a reference because it does not take into account body fat distribution nor the percentage of lean and fat body mass [3].

Obesity, which was once thought to be an issue only in high-income countries, is now dramatically increasing in low and middle-income countries, impacting adults and children of all ages, regardless of their ethnicity or socioeconomic background. The increased consumption of high-calorie diets, rich in saturated fats and sugars, and sedentary lifestyle habits are two major factors contributing to the increase in the prevalence of obesity. Obesity is a major risk factor for several pathologies, such as cardiovascular diseases, type 2 diabetes mellitus, musculoskeletal disorders, accelerated aging, several cancers, poor mental health, among other disorders [4]. Obesity is also linked to metabolic syndrome, as increased waist circumference, increased triglyceride levels, glucose intolerance, low high-density lipoprotein cholesterol, and hypertension constitute the five factors included in the diagnostic criteria for metabolic syndrome [5].

Infertility has arisen as one important, but often overlooked, comorbidity of obesity. Studies highlight that obesity-related male infertility is induced by immune, hormonal, and metabolic dysfunctions, mostly caused by excessive adipose tissue. These factors have been shown to disrupt the male reproductive potential, particularly through alterations in the hypothalamic-pituitary-gonadal (HPG) axis, impairment of testicular steroidogenesis, and dysregulation of testicular metabolism [6, 7]. In men, obesity has also been linked to erectile dysfunction, abnormal semen parameters, as well as poor pregnancy and ART outcomes [9].

Changes in sperm parameters have been linked to obesity and overweight. Obese and overweight men had a higher risk of oligozoospermia and azoospermia than men of normal weight, according to Sermondade et al [9]. Ma et al. observed similar results, implying that a greater BMI was associated with a decrease in sperm volume, sperm count, and sperm motility [10]. Chavarro et al. also identified a correlation between increased BMI and lower ejaculate volume, but no link between sperm concentration, sperm motility, or sperm morphology and BMI [11]. An increase in BMI was also associated with an increase in the number of sperm with abnormal morphology [12]. In contrast, a study by Pauli et al. found no association between BMI and sperm parameters [13]. Despite some studies have been done to link obesity and overweight to sperm parameters, the mechanisms by which obesity causes poor sperm parameters are still not fully understood. HPG axis dysregulation and hormonal alterations, particularly the decrease in intratubular testosterone concentration, are thought to play a major role in the decrease of sperm quality. Increased inflammation and oxidative stress in the testis, as well as increased testicular temperature, due to adipose tissue accumulation in the suprapubic and scrotal area, may also contribute to poor sperm parameters associated with obesity and overweight [7].

Obesity-induced infertility and subfertility are mediated primarily through dysregulation of the HPG axis, which results partially

***Corresponding Author**:
Pedro F. Oliveira,
LAQV-REQUIMTE and Department of Chemistry, University of Aveiro, Aveiro, Portugal.
E-mail: pfobox@gmail.com

Received: March 26, 2022
Published: March 28, 2022

Citation: Bárbara Guerra-Carvalho, Marco G. Alves, Pedro F. Oliveira. Obesity and Male Infertility: An Overview. *Int J Diabetol Vasc Dis Res.* 2022;8(1e):1-3.
doi: http://dx.doi.org/10.19070/2328-353X-2200016e

from obesity-derived systemic inflammation. The accumulation of visceral adipose tissue is associated with the development of local and systemic chronic metabolic inflammation. Adipocyte hyperplasia results in an augmented production of pro-inflammatory cytokines and chemokines, which attracts immune mediators, such as monocytes, macrophages, and neutrophils within the adipose tissue. In turn, monocytes and macrophages induce adipocytes to produce more inflammatory mediators. This crosstalk between immune cells and adipocytes results in the development of local inflammation (at the visceral adipose tissue) and, ultimately, these effects turn systemic. Adipocyte-derived local inflammation results in the dysregulation of the production of adipokines, such as leptin, adiponectin, and resistin, and consequent alterations in their levels in the plasma [14]. In addition, the increase in circulating levels of inflammatory markers observed in obesity interferes with insulin signaling, causing insulin resistance and consequent hyperglycemia [15]. Besides the chronic inflammatory state, obesity is also associated with high metabolic rates, necessary to sustain the body's metabolic balance. This increase in the metabolic rate is accompanied by increased production of reactive oxygen species (ROS)[6]. Obesity-related oxidative stress is one of the major causes of male infertility due to its harmful effects on spermatogenesis. Moreover, energy metabolism and glucose homeostasis are crucial for successful spermatogenesis [16]. Thus, changes in energy regulation mediators, such as leptin, ghrelin, and glucagon-like peptide-1(GLP-1), associated with obesity, are also suggested as responsible for decreased fertility in obese men [17]. For instance, leptin is a hormone mainly produced by white adipocytes that plays an important role in male fertility. Among other functions, it is responsible for promoting satiety after meals, thus being an important regulator of energy homeostasis. Leptin participates in the regulation of the HPG axis by stimulating the release of kisspeptin, which acts in the hypothalamus to induce the release of gonadotropin-releasing hormone (GnRH). In obese individuals, leptin circulatory levels are usually increased, however, these patients often present leptin resistance. Leptin resistance in obese men causes dysregulation of the HPG axis, with decreased GnRH secretion and consequent decrease in luteinizing hormone (LH), follicle-stimulating hormone (FSH) and testosterone secretion, resulting in hypogonadotropic hypogonadism. Additionally, leptin also acts directly on testes, modulating testosterone production by Leydig cells. Elevated concentrations of leptin act on Leydig cells inhibiting steroidogenesis. Thus, high leptin levels caused by increased adipose tissue, contribute to the decreased testosterone levels in obese men [18].

Adipose tissue is now recognized as a key endocrine organ that secretes a variety of hormones. Aromatase activity rises in lockstep with body fat mass. In obese men, high aromatase activity, resultant from adipocyte hyperplasia and hypertrophy, is advanced to increase the aromatization of testosterone into 17β-estradiol. This increase in estrogen might suppress the activity of kisspeptin neurons, which inhibits the HPG axis and reduces testosterone production by Leydig cells. Additionally, excessive 17β-estradiol levels could also act in testicular somatic cells, inhibiting steroidogenesis in Leydig cells and spermatogenesis in Sertoli cells [19]. Insulin resistance induces hyperinsulinemia in obese patients, which results in lower levels of sex hormone-binging globulin (SHBG), a glycoprotein that binds to sex hormones and inhibits their biological activity. As a result, lower SHBG levels in obese patients may contribute to the increased inhibitory activity of 17β-estradiol in testosterone synthesis and spermatogenesis [20].

Obesity also compromises male reproductive potential through the accumulation of adipose tissue on the suprapubic and scrotal areas, which leads to an increase in the temperature of the testis, and consequent impairment on spermatogenesis. Furthermore, the buildup of lipophilic endocrine disruptors in adipose tissue may enhance their negative impact on spermatogenesis [21].

Obesity and overweight in men have also a negative impact on pregnancy outcomes as well as on the offspring's health. Increased time to pregnancy and lower pregnancy rates have been linked to higher paternal BMI. Obesity results from a variety of environmental factors, including dietary and lifestyle habits, which may impact the epigenetic patterns in sperm cells. Epigenetic modifications in male germ cells, such as altered DNA methylation and RNA content, resultant from an obesogenic environment might be transmitted to the offspring, affecting future generations. Indeed, studies have shown that obese men are more likely to father obese children, probably due to an influence of the paternal metabolic profile at the time of conception in the metabolic profile of the offspring. Although some studies have shown that paternal obesity can have detrimental consequences for the offspring, the mechanisms that mediate the interactions between paternal obesity and offspring outcomes are still unknown and need to be investigated further [22].

Over the past decades, obesity rates have been steadily rising alongside with a significant decline in male fertility. Obesity and overweight are known to have a negative impact on male reproductive potential due to dysregulation of the HPG axis, changes in the hormonal and metabolic homeostasis, impairment of spermatogenesis, and to alterations in sperm parameters. Paternal obesity also has a negative impact on pregnancy outcomes as well as on the health of the offspring. Nevertheless, the mechanisms through which obesity affects sperm parameters and male reproductive potential, as well as the mechanisms involved in the transgenerational effects of paternal obesity on the offspring are still poorly understood and deserve further attention in the upcoming years.

References

[1]. Obesity and overweight Fact Sheet. World Health Organization; 2021.

[2]. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008 Sep;32(9):1431-7. PubMed PMID: 18607383.

[3]. Okorodudu DO, Jumean MF, Montori VM, Romero-Corral A, Somers VK, Erwin PJ, et al. Diagnostic performance of body mass index to identify obesity as defined by body adiposity: a systematic review and meta-analysis. Int J Obes (Lond). 2010 May;34(5):791-9. PubMed PMID: 20125098.

[4]. Chooi YC, Ding C, Magkos F.The epidemiology of obesity.Metabolism. 2019 Mar;92:6-10. PubMed PMID: 30253139.

[5]. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the Metabolic Syndrome. Circulation. 2009 Oct 20;120(16):1640-5. PubMed PMID: 19805654.

[6]. Oliveira PF, Sousa M, Silva BM, Monteiro MP, Alves MG. Obesity, energy balance and spermatogenesis. Reproduction. 2017 Jun;153(6):R173-R185. PubMed PMID: 28283671.

[7]. Leisegang K, Sengupta P, Agarwal A, Henkel R. Obesity and male infertility: Mechanisms and management. Andrologia. 2021 Feb;53(1):e13617. PubMed PMID: 32399992.

[8]. Amiri M, Ramezani Tehrani F. Potential Adverse Effects of Female and Male Obesity on Fertility: A Narrative Review. Int J EndocrinolMetab. 2020 Sep 28;18(3):e101776. PubMed PMID: 33257906.

[9]. Sermondade N, Faure C, Fezeu L, Lévy R, Czernichow S; Obesity-Fertility Collaborative Group. Obesity and increased risk for oligozoospermia and azoospermia. Arch Intern Med. 2012 Mar 12;172(5):440-442. PubMed PMID: 22412113.

[10]. Ma J, Wu L, Zhou Y, Zhang H, Xiong C, Peng Z, et al. Association between BMI and semen quality: an observational study of 3966 sperm donors. Hum Reprod. 2019 Jan 1;34(1):155-162. PubMed PMID: 30407511.

[11]. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic.FertilSteril. 2010 May 1;93(7):2222-31. PubMed PMID: 19261274.

[12]. Shayeb AG, Harrild K, Mathers E, Bhattacharya S. An exploration of the association between male body mass index and semen quality.Reprod Biomed Online. 2011 Dec;23(6):717-23. PubMed PMID: 22019618.

[13]. Pauli EM, Legro RS, Demers LM, Kunselman AR, Dodson WC, Lee PA. Diminished paternity and gonadal function with increasing obesity in men. FertilSteril. 2008 Aug;90(2):346-51. PubMed PMID: 18291378.

[14]. Tsatsanis C, Dermitzaki E, Avgoustinaki P, Malliaraki N, Mytaras V, Margioris AN. The impact of adipose tissue-derived factors on the hypothalamic-pituitary-gonadal (HPG) axis.Hormones (Athens). 2015 Oct-Dec;14(4):549-62. PubMed PMID: 26859602.

[15]. Zeyda M, Stulnig TM. Obesity, inflammation, and insulin resistance--a mini-review.Gerontology. 2009;55(4):379-86. PubMed PMID: 19365105.

[16]. Rato L, Alves MG, Socorro S, Duarte AI, Cavaco JE, Oliveira PF. Metabolic regulation is important for spermatogenesis. Nat Rev Urol. 2012 May 1;9(6):330-8. PubMed PMID: 22549313.

[17]. Alves MG, Jesus TT, Sousa M, Goldberg E, Silva BM, Oliveira PF. Male fertility and obesity: are ghrelin, leptin and glucagon-like peptide-1 pharmacologically relevant? Curr Pharm Des. 2016;22(7):783-91. PubMed PMID: 26648473.

[18]. Carrageta DF, Oliveira PF, Alves MG, Monteiro MP. Obesity and male hypogonadism: Tales of a vicious cycle. Obes Rev. 2019 Aug;20(8):1148-1158. PubMed PMID: 31035310.

[19]. Xu X, Sun M, Ye J, Luo D, Su X, Zheng D, et al. The Effect of Aromatase on the Reproductive Function of Obese Males.HormMetab Res. 2017 Aug;49(8):572-579. PubMed PMID: 28679145.

[20]. Davidson LM, Millar K, Jones C, Fatum M, Coward K. Deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermatogenesis and male fertility. Hum Fertil (Camb). 2015 Sep;18(3):184-93. PubMed PMID: 26205254.

[21]. Rato L, Alves MG, Cavaco JE, Oliveira PF. High-energy diets: a threat for male fertility? Obes Rev. 2014 Dec;15(12):996-1007. PubMed PMID: 25346452.

[22]. Houfflyn S, Matthys C, Soubry A. Male Obesity: Epigenetic Origin and Effects in Sperm and Offspring. CurrMolBiol Rep. 2017;3(4):288-296. PubMed PMID: 29387521.