Endocrine Changes Causing Infertility in Obese Males

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Overweight and obesity are terms used to describe an abnormal and excessive build-up of body fat that may have a detrimental effect on health. Body mass index (BMI) is a measure of body weight per height that is widely used to classify adults as overweight or obese. It is calculated by dividing a person's body weight (in kilograms) by the square of their height (in meters/m^2). The World Health Organization (WHO) defines overweight as a BMI of 25 kg/m^2 or above and obesity as a BMI of 30 kg/m^2 or above. The rising incidence of obesity has coincided with rising levels of poor reproductive outcomes. The molecular basis for the association of infertility in obese males is now being explained through various mechanisms. Insulin resistance, hyperglycemia, and changes in serum and gonadal concentrations of adipokines, like leptin, adiponectin, resistin, and ghrelin have been implicated as causes of male infertility in obese males.

infertility obesity endocrine insulin resistance hyperglycemia adipokines

1. Introduction

Given an obesogenic environment, excessive emphasis on low fat intake, and overindulgence in simple carbohydrates and sugar, obesity has become a global pandemic [1]. Nearly two billion adults (over 18 years of age), comprising 39% of the world's adult population, have been reported to be overweight or obese according to WHO statistics from 2016. Of these, over 650 million fell under the obese category [2].

The rising incidence of obesity has coincided with rising levels of poor reproductive outcomes, including infertility, which are now commonly seen in obese adult males [3][4][5][6]. Men who are obese are 42% more likely than normal-weight men to have oligozoospermia and are 81% more likely to have azoospermia [7].

A wide variety of factors have been shown to influence fertility in obese persons. Some examples are endocrine factors, factors causing increases in inflammatory mediators or oxidative stress, factors that influence the effects of intracellular enzymes, and factors that produce genetic or epigenetic alterations affecting spermatogenesis and sperm function [8][9].

Understanding the molecular basis of poor reproductive outcomes in such individuals may help in better counseling such individuals and advising behavior-modifying strategies to minimize the impact of such factors [10]. Novel interventions may then target the specific responsible molecular factors to create a new frontier in preventive and

therapeutic pharmacological approaches that offset poor reproductive outcomes or infertility in these individuals [11].

Insulin resistance, hyperglycemia, and adipokines have been implicated as causes of male infertility in obese males [12][13][14][15][16][17] (**Figure 1**).

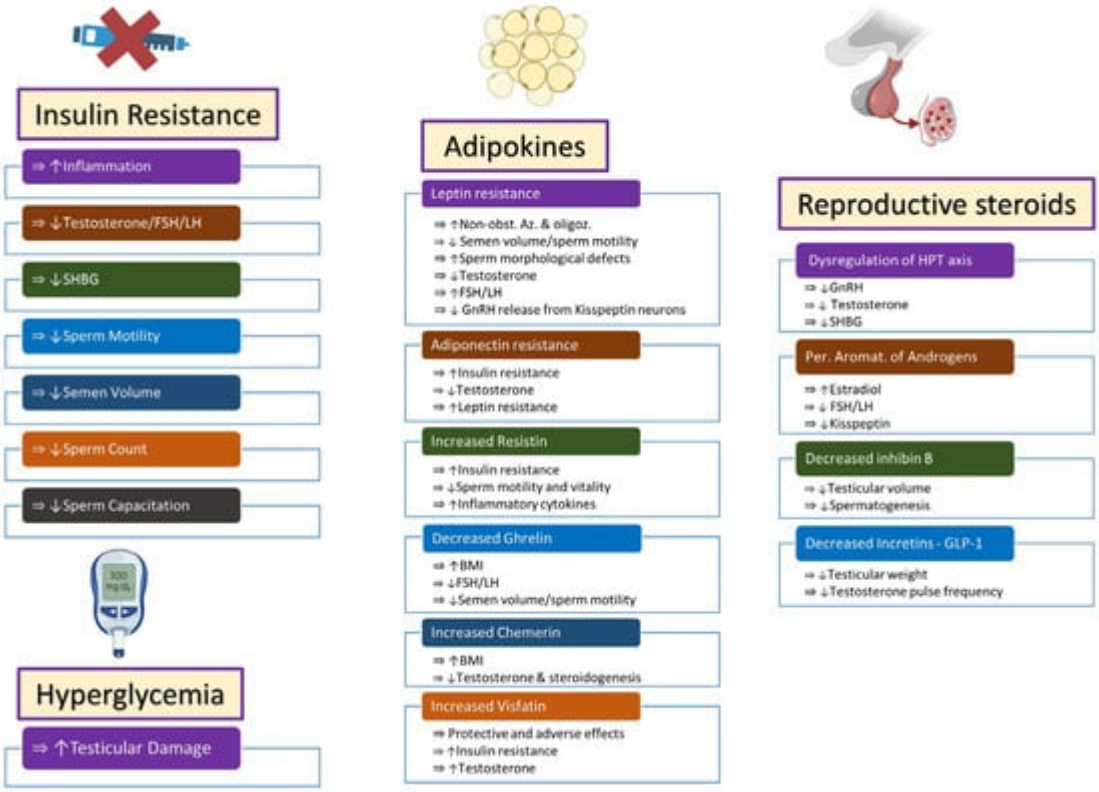


Figure 1. Endocrine changes in obese males lead to infertility via multiple pathways. Increased insulin resistance and hyperglycemia affect fertility via effects on inflammatory molecules, steroidogenesis, and semen quality. Adipokines behave like endocrine organs and secrete multiple hormones that have protective or adverse effects on semen and sperm quality, steroidogenesis, insulin resistance, and inflammatory mechanisms. Dysregulation of steroidogenesis occurs and leads to alterations in steroidogenesis through central and peripheral pathways. Symbols: (⇒): is associated with/is correlated with; (↑): increased; (↓): decreased. Abbreviations: FSH: follicle-stimulating hormone; LH: luteinizing hormone; SHBG: sex hormone-binding globulin; Non-obst. Az: non-obstructive azoospermia; Oligoz: oligozoospermia; GnRH: gonadotropin-releasing hormone; BMI: body mass index; HPT axis: hypothalamus–pituitary–testicular axis; Per. Aromat.: peripheral aromatization; GLP-1: glucagon-like peptide-1.

2. Insulin Resistance and Hyperglycemia

2.1. Insulin Resistance

The term “metabolic syndrome” encompasses a range of related conditions, including diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, and obesity [17]. Insulin resistance is the inability of a known

dose of exogenous or endogenous insulin to stimulate glucose uptake and metabolism in an individual to the same extent that it does in the general population in good health [18][19]. Increased insulin resistance has been noted in males with unexplained infertility [20].

Insulin resistance increases inflammation, lowers male sex hormone release, lowers sex hormone binding globulin levels, and aggravates obesity [14][18][21][22]. Insulin resistance has been shown to independently influence sperm motility and, when associated with obesity, decrease semen volume and sperm count [17][19][23].

Freshly ejaculated sperm are still without progressive motility or the capacity to fertilize. They first need to go through a process called capacitation, which entails a progression of biochemical and physiological alterations. A key requirement for fertilization is capacitation [24][25]. Insulin has been found to be secreted by sperm. It has been shown that there is a significant difference between insulin release in capacitated and non-capacitated sperm, pointing to a possible active role for insulin in capacitation. Insulin resistance could interfere with the distal effects of autocrine insulin secretion from the sperm and negatively affect capacitation [26].

Extra-pancreatic insulin receptors have been demonstrated to be present in sperm cells in mammals. The activation of these receptors has been shown to enhance sperm motility. It is also noted that the male germ cell line is capable of producing insulin itself [27][28][29]. Whether insulin resistance seen in obesity affects these receptors is not known.

2.2. Hyperglycemia

Hyperglycemia has been shown to negatively affect male fertility, both in Type 1 and Type 2 diabetes mellitus [30][31][32]. Hyperglycemia has been demonstrated to induce testicular damage via diacylglycerol–protein kinase C and the polyol pathways in the Type 1 diabetes mellitus mouse model [33]. Advanced glycation end-products (AGE) are the result of non-enzymatic glycosylation pathways [34]. AGE receptors are expressed throughout testicular tissue. The excess binding of AGE to these receptors is postulated to play a role in the development of infertility. Hyperglycemia is also shown to affect fertility by stimulating the inflammatory pathways and increasing the production of interleukin-1 and tumor necrosis factor-α [22][30][31][33][34].

3. Adipokines

Up until the 1980s, adipose tissue was thought to be an inert reservoir of energy stored as triglycerides [3]. However, adipose tissue is now understood to be a significant endocrine organ that produces several peptide hormones called adipokines, such as leptin, adiponectin, resistin, and many others [3][35][36]. Other chemicals secreted by adipose tissue include molecules such as cytokines and chemokines [3].

Adipokines regulate a variety of physiologic functions, including hunger, metabolism, cardiovascular function, immunity, and reproduction [12]. Adipokines like leptin, adiponectin, resistin, ghrelin, orexin, and obestatin interfere with normal reproductive hormonal regulation in obese male adults [9]. It has been theorized that adipokines are

significantly implicated in the pathophysiology of poor reproductive outcomes in these individuals, directly or indirectly [12]. However, some studies have failed to show any major effect of adipokines on peripheral sites in the male reproductive system [13]. The expression of various steroidogenic genes is directly impacted by adipokines [35].

3.1. Leptin

Leptin is a non-glycosylated peptide that is largely secreted by adipocytes [11]. It is a key regulatory adipokine that plays a fundamental role in a variety of metabolic processes, including reproductive performance [9][37].

Childhood obesity has been reported in families with congenital leptin deficiency [35]. Leptin has powerful anorexigenic effects, decreasing appetite by inhibiting the orexigenic factors neuropeptide Y and agouti-related peptide and augmenting the effects of the anorexigenic peptides alpha-MSH/pro-opiomelanocortin and cocaine- and amphetamine-related transcript (CART). It also raises calorie expenditure. The Janus kinase/signal transducer and activator of the transcription complex is activated by leptin, which, in turn, affects sex hormone expression [36].

Numerous studies have reported a significant correlation between the levels of leptin, obesity, and infertility with respect to the hypothalamic–pituitary–testicular axis, the regulation of androgen levels, and the production of sperm. Elevated levels of leptin have been observed in obese infertile male individuals with disorders affecting the parenchyma of the testicles, such as nonobstructive azoospermia and oligozoospermia.

Furthermore, elevated serum leptin levels are associated with decreases in serum testosterone and sperm parameters and increases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, and it can cause abnormal sperm morphology [9][11][13][35][38].

Leptin operates in a narrow range of optimum functions. Excess or deficits in the level of leptins adversely affect reproductive functions. Leptin acts directly on the kisspeptin neurons in the hypothalamus to stimulate the release of gonadotropin-releasing hormone (GnRH). Poor reproductive status, which is associated with increasing obesity, is postulated to be due to the effect of leptin on the kisspeptin-GnRH pathway [37][39].

Excessive levels of leptins are paradoxically found in obese adults [22]. A leptin resistance pathway has been hypothesized, similar to the insulin resistance pathway, whereby the excessive level of leptin has an inhibitory effect on the kisspeptin neurons, the function of the testes, and spermatogenesis [9][22][36][39].

Elevated levels of leptin also seem to weaken the nutritional function of Sertoli cells in spermatogenesis. Hyperleptinemia can impair testosterone production in the Leydig cells. It is also associated with mitochondrial dysfunction, increasing oxidative stress and affecting spermatozoal function [3].

It is probable that measuring leptin and FSH levels is a sensitive biomarker in predicting the successful retrieval of sperm in obese adult males with non-obstructive azoospermia [36].

3.2. Adiponectin

The most abundant adipose-tissue-secreted hormone is adiponectin, which plays important functions in glucose regulation and lipid metabolism. Adiponectin has two distinctive receptors, namely, AdipoR1, which is universally expressed in skeletal muscle, and AdipoR2, which is principally expressed in the liver and adipose tissue. Both receptors are also expressed by Leydig cells, spermatozoa, and the epididymis. Adiponectin shields Leydig cells from the injurious effects of cytokines by inhibiting nuclear factor-KB signaling through the stimulation of testicular 5′ AMP-activated protein kinase [36].

The production of adiponectin by adipose tissue increases during starvation and is inversely related in obese individuals to visceral adiposity and BMI [35][36][40]. Furthermore, adiponectin increases insulin sensitivity. Decreases in adiponectin levels result in insulin resistance and metabolic syndrome. Adiponectin levels have been found to be low in obese females [40].

Adiponectin has been found in circulation in various molecular isoforms. Four-fifths of circulating adiponectin is the high-molecular-weight isoform. The level of adiponectin is nearly double in serum when compared with that in human seminal plasma. This is hypothesized to be due to the blood–testis barrier. The measured adiponectin level in semen is lower in overweight and obese patients when compared with patients with normal BMIs [3][41][42].

The level of circulating adiponectin is inversely proportional to the level of circulating testosterone [43]. Possibly because of the low serum concentrations of testosterone seen in obese males, levels of serum adiponectin have been shown to be paradoxically elevated in obese males. This suggests a resistance phenomenon similar to insulin and leptin in obese males [9].

3.3. Resistin

Resistin is a polypeptide that is involved in the development of insulin resistance. The modulation of insulin sensitivity and the differentiation of adipocytes are among the known functions of resistin [35]. Increased concentrations of resistin have been correlated with low sperm motility and vitality. However, other studies have not shown any effect of resistin on sperm function [42].

Resistin is also associated with increased levels of cytokines such as interleukin-6 and elastase in seminal fluid and is implicated in the inflammation of the reproductive organs noted in obese males [3][44]. Apart from the peripheral effects of resistin on the reproductive system in obese males, resistin has also been isolated from the pituitary gland and hypothalamus in humans, suggesting a central action too [3][45].

3.4. Ghrelin

Ghrelin is an orexigenic peptide released from the stomach during fasting states and has been called the “hunger hormone” [9][11]. Circulating levels of ghrelin have been shown to be inversely correlated with BMI. When administered centrally, ghrelin has been shown to increase the utilization of glucose in adipose tissue. It has been

shown to protect the testes and sperm from endoplasmic reticulum stress and inhibit the inflammatory response to stress and apoptosis [46].

Ghrelin in association with leptin is involved in the control of adiposity in obese individuals. Ghrelin has been found in Leydig and Sertoli cells in the testes and inhibits testosterone secretion. It also plays a role in the regulation of spermatogenesis, and decreased levels may suppress the secretion of FSH and LH in adult men [11][47][48][49][50]. Low serum concentrations of ghrelin have been found to adversely decrease semen volume, sperm motility, and morphology [51].

3.5. Chemerin

Chemerin is another peptide secreted by adipocytes that modulates insulin [3]. Concentrations of chemerin are elevated in obese individuals when compared with normal-weight individuals, and its levels are directly correlated with increases in BMI and inversely correlated with levels of testosterone [42]. Chemerin and its receptors have been found in the testes and adipose tissue and have adverse effects on testicular steroidogenesis. Chemerin effects the release of gonadotropins from the hypothalamus and is concentrated in the Leydig cells. Anti-androgens have been demonstrated to inhibit the expression of chemerin in Leydig cells [52][53][54]. Adiponectin and chemerin are called “contrary adipokines”, as they display opposing functions, where adiponectin promotes insulin sensitivity while chemerin inhibits the signaling of insulin. A high-adiponectin-to-low-chemerin ratio is suggested to play an important role in the development of metabolic syndrome in obesity, and this might be a target of therapeutic interventions meant to treat infertility in obese males [55].

3.6. Visfatin

Visfatin, which is also known as a pre-B-cell colony-enhancing factor or phosphoribosyltransferase, is a protein whose role in obesity is uncertain [3]. It has been theorized to be an insulin-like adipocytokine secreted from adipose cells. Protective and adverse roles in obese individuals have both been reported. More recently, it has been reported to produce proinflammatory expression in genes, including the *CD68* and *tumor necrosis factor-alpha (TNF-α) genes* in adipose tissue, and is associated with insulin resistance and hyperlipidemia [56][57][58]. Visfatin is found in seminal fluid, Leydig cells, and spermatozoa and has been shown to increase testosterone levels [59][60].

3.7. Apelin, Omentin, Hepcidin, and Vaspin

Apelin increases with adiposity and with increased insulin levels. It modulates insulin resistance by increasing the expression of uncoupling proteins in adipose tissue and decreasing the levels of adiponectin [61][62]. Omentin-1 seems to have an anti-inflammatory and antioxidative action [63]. Levels of omentin-1/intelectin, like adiponectin, decrease with insulin resistance, BMI, and adiposity [61][64]. Hepcidin seems to modulate inflammatory cytokines like TNF-α and C-reactive protein, and its concentrations have been found to increase in obese individuals [65]. Vaspin is a serine protease inhibitor that is also an insulin sensitizer and has increased concentrations in adipose individuals, especially those with increased glucose tolerance [61].

4. Reproductive Steroids

4.1. Hypothalamic–Pituitary–Testicular Axis

Normal reproductive hormone secretion is imperative for normal male fertility. Infertility may result from any interference with the intricately balanced interplay between the constituents of the hypothalamic–pituitary–testicular axis [66][67].

The hypothalamic–pituitary–testicular axis regulates the production of testosterone, which, in turn, is influenced by direct negative feedback from testosterone. LH and FSH are secreted in response to the pulsatile release of gonadotropin-releasing hormone (GnRH). LH stimulates testosterone secretion by acting on Leydig cells, and FSH induces spermatogenesis by acting on Sertoli cells in the testes [3][5].

The effects of obesity and hypogonadism form a vicious cycle, whereby dysregulation of the hypothalamic–pituitary–testicular axis—due to the effect of the release of multiple mediators, thus decreasing GnRH release from the GnRH neurons of the hypothalamus—causes decreases in LH and FSH levels. This leads to lower levels of testosterone, which further increases adiposity because of increased lipogenesis [68].

Since the 1970s, researchers have identified hormonal differences between obese and non-obese adult males in the hypothalamic–pituitary–testicular axis. Adult obese males have been found to have decreased peripheral levels of total testosterone and sex hormone-binding globulin (SHBG). Lower levels of SHBG are mostly mediated by elevated levels of circulating insulin linked to the insulin resistance of obesity [23]. The significantly decreased SHBG concentration is the primary cause of the concurrent decrease in total testosterone [69]. There is a negative correlation between the degree of obesity, as measured by the BMI, and levels of total testosterone and SHBG [5][15][66][70][71]. The typical reproductive hormonal profile in obese adult males is that of hyperestrogenic hypogonadotropic hypoandrogenemia [23].

4.2. Estrogens

The peripheral aromatization of androgens leads to elevated levels of estrogens. Increased adiposity in obese males boosts conversion rates of testosterone into estradiol [9][23][35]. Estradiol blunts GnRH pulses in the hypothalamus and, therefore, FSH and LH secretion in the pituitary. The rise in estradiol levels in obese men reduces the production of FSH and LH, which impairs testicular function and lowers levels of testosterone [23].

Kisspeptin neurons in the hypothalamus act as a center for the regulation of reproductive hormones. Numerous regulatory factors govern the release of kisspeptin from these neurons, which, in turn, affects the release of GnRH from GnRH neurons that control the reproductive axis. Estrogens produce negative feedback in the arcuate nucleus of the hypothalamus, which specifically decreases the production of kisspeptin, thereby inhibiting the pulsatile release of GnRH, resulting in decreased production of FSH and LH from the pituitary gland [9][72][73].

4.3. Inhibin B

Inhibin B is a protein dimer composed of an alpha and a beta subunit produced primarily by Sertoli cells in the prepubertal testes. The site of secretion in adult males is still not clear. Inhibin B regulates FSH production via a negative feedback mechanism and, in turn, is regulated by FSH and LH levels. There is a positive correlation between testicular volume and sperm production with the level of circulating inhibin B. This makes the measurement of inhibin B a good marker of male reproductive function [74][75][76]. Inhibin B is considered to be a marker for “nurse” Sertoli cells, which are primarily involved in the nutrition and physical support of spermatogenesis [11].

5. Incretins

Glucagon-like peptide-1 (GLP-1), which is an incretin hormone, is responsible for the control of insulin release from the pancreatic islet in response to meal ingestion and consequent glucose loading. It has a very short half-life of 1.5 to 5 min and is rapidly cleared by the kidney [77]. It crosses the blood–brain barrier and induces satiety, thereby reducing food intake. Low levels of GLP-1 have been shown to reduce the testosterone pulse frequency and reduce testicular weight [11]. The administration of GLP-1 receptor antagonists has been demonstrated to increase testosterone levels and increase testicular weight [78].

References

1. Meldrum, D.R.; Morris, M.A.; Gambone, J.C. Obesity pandemic: Causes, consequences, and solutions-but do we have the will? Fertil. Steril. 2017, 107, 833–839.
2. Obesity and Overweight. Available online: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on 18 October 2023).
3. Barbagallo, F.; Condorelli, R.A.; Mongioì, L.M.; Cannarella, R.; Cimino, L.; Magagnini, M.C.; Crafa, A.; La Vignera, S.; Calogero, A.E. Molecular Mechanisms Underlying the Relationship between Obesity and Male Infertility. Metabolites 2021, 11, 840.
4. Chambers, T.J.; Richard, R.A. The impact of obesity on male fertility. Hormones 2015, 14, 563–568.
5. Kahn, B.E.; Brannigan, R.E. Obesity and male infertility. Curr. Opin. Urol. 2017, 27, 441–445.
6. Swan, S.H.; Elkin, E.P.; Fenster, L. The question of declining sperm density revisited: An analysis of 101 studies published 1934–1996. Environ. Health Perspect. 2000, 108, 961–966.
7. Sermondade, N.; Faure, C.; Fezeu, L.; Lévy, R.; Czernichow, S. Obesity and increased risk for oligozoospermia and azoospermia. Arch. Intern. Med. 2012, 172, 440–442.
8. Ellulu, M.S.; Patimah, I.; Khaza’ai, H.; Rahmat, A.; Abed, Y. Obesity and inflammation: The linking mechanism and the complications. Arch. Med. Sci. 2017, 13, 851–863.

9. Leisegang, K.; Sengupta, P.; Agarwal, A.; Henkel, R. Obesity and male infertility: Mechanisms and management. Andrologia 2021, 53, e13617.
10. Craig, J.R.; Jenkins, T.G.; Carrell, D.T.; Hotaling, J.M. Obesity, male infertility, and the sperm epigenome. Fertil. Steril. 2017, 107, 848–859.
11. Alves, M.G.; Jesus, T.T.; Sousa, M.; Goldberg, E.; Silva, B.M.; Oliveira, P.F. Male fertility and obesity: Are ghrelin, leptin and glucagon-like peptide-1 pharmacologically relevant? Curr. Pharm. Des. 2016, 22, 783–791.
12. Dupont, J.; Pollet-Villard, X.; Reverchon, M.; Mellouk, N.; Levy, R. Adipokines in human reproduction. Horm. Mol. Biol. Clin. Investig. 2015, 24, 11–24.
13. Kawwass, J.F.; Summer, R.; Kallen, C.B. Direct effects of leptin and adiponectin on peripheral reproductive tissues: A critical review. Mol. Hum. Reprod. 2015, 21, 617–632.
14. Fushimi, H.; Horie, H.; Inoue, T.; Kameyama, M.; Kanao, K.; Ishihara, S.; Tsujimura, T.; Nunotani, H.; Minami, T.; Okazaki, Y.; et al. Low testosterone levels in diabetic men and animals: A possible role in testicular impotence. Diabetes Res. Clin. Pract. 1989, 6, 297–301.
15. Carrageta, D.F.; Oliveira, P.F.; Alves, M.G.; Monteiro, M.P. Obesity and male hypogonadism: Tales of a vicious cycle. Obes. Rev. 2019, 20, 1148–1158.
16. Barbagallo, F.; La Vignera, S.; Cannarella, R.; Mongioì, L.M.; Garofalo, V.; Leanza, C.; Marino, M.; Calogero, A.E.; Condorelli, R.A. Obesity and Male Reproduction: Do Sirtuins Play a Role? Int. J. Mol. Sci. 2022, 23, 973.
17. Martins, A.D.; Majzoub, A.; Agawal, A. Metabolic Syndrome and Male Fertility. World J. Mens. Health 2019, 37, 113–127.
18. Zańko, A.; Siewko, K.; Krętowski, A.J.; Milewski, R. Lifestyle, Insulin Resistance and Semen Quality as Co-Dependent Factors of Male Infertility. Int. J. Environ. Res. Public Health 2022, 20, 732.
19. Ma, J.; Han, R.Y.; Mei, X.A.; Qi, Y.N.; Ma, J.Y.; Liu, W.J.; Wang, S.S. Correlation of insulin resistance with male reproductive hormone levels and semen parameters. Zhonghua Nan Ke Xue 2018, 24, 695–699.
20. Mansour, R.; El-Faissal, Y.; Kamel, A.; Kamal, O.; Aboulserour, G.; Aboulghar, M.; Fahmy, I. Increased insulin resistance in men with unexplained infertility. Reprod. Biomed. Online 2017, 35, 571–575.
21. Morrison, C.D.; Brannigan, R.E. Metabolic syndrome and infertility in men. Best Pract. Res. Clin. Obstet. Gynaecol. 2015, 29, 507–515.
22. AbbasiHormozi, S.; Kouhkan, A.; Shahverdi, A.; Parikar, A.; Shirin, A.; Vesali, S. How much obesity and diabetes do impair male fertility? Reprod. Biol. Endocrinol. 2023, 21, 48.

23. Hammoud, A.O.; Gibson, M.; Peterson, C.M.; Meikle, A.W.; Carrell, D.T. Impact of male obesity on infertility: A critical review of the current literature. Fertil. Steril. 2008, 90, 897–904.
24. Jin, S.K.; Yang, W.X. Factors and pathways involved in capacitation: How are they regulated? Oncotarget 2017, 8, 3600–3627.
25. Okabe, M. Sperm-egg interaction and fertilization: Past, present, and future. Biol. Reprod. 2018, 99, 134–146.
26. Aquila, S.; Gentile, M.; Middea, E.; Catalano, S.; Andò, S. Autocrine regulation of insulin secretion in human ejaculated spermatozoa. Endocrinology 2005, 146, 552–557.
27. Aitken, R.J.; Curry, B.J.; Shokri, S.; Pujianto, D.A.; Gavriliouk, D.; Gibb, Z.; Whiting, S.; Connaughton, H.S.; Nixon, B.; Salamonsen, L.A.; et al. Evidence that extrapancreatic insulin production is involved in the mediation of sperm survival. Mol. Cell. Endocrinol. 2021, 526, 111193.
28. Pasquali, R.; Patton, L.; Gambineri, A. Obesity and infertility. Curr. Opin. Endocrinol. Diabetes Obes. 2007, 14, 482–487.
29. Lampiao, F.; Agarwal, A.; du Plessis, S.S. Invited review The role of insulin and leptin in male reproduction. Arch. Med. Sci. Spec. Issues 2009, 5, S48–S54.
30. Maresch, C.C.; Stute, D.C.; Alves, M.G.; Oliveira, P.F.; de Kretser, D.M.; Linn, T. Diabetes-induced hyperglycemia impairs male reproductive function: A systematic review. Hum. Reprod. Update 2018, 24, 86–105.
31. Facondo, P.; Di Lodovico, E.; Delbarba, A.; Anelli, V.; Pezzaioli, L.C.; Filippini, E.; Cappelli, C.; Corona, G.; Ferlin, A. The impact of diabetes mellitus type 1 on male fertility: Systematic review and meta-analysis. Andrology 2022, 10, 426–440.
32. Ding, G.L.; Liu, Y.; Liu, M.E.; Pan, J.X.; Guo, M.X.; Sheng, J.Z.; Huang, H.F. The effects of diabetes on male fertility and epigenetic regulation during spermatogenesis. Asian J. Androl. 2015, 17, 948–953.
33. Maresch, C.C.; Stute, D.C.; Fleming, T.; Lin, J.; Hammes, H.P.; Linn, T. Hyperglycemia induces spermatogenic disruption via major pathways of diabetes pathogenesis. Sci. Rep. 2019, 9, 13074.
34. Omolaoye, T.S.; du Plessis, S.S. Male infertility: A proximate look at the advanced glycation end products. Reprod. Toxicol. 2020, 93, 169–177.
35. Roumaud, P.; Martin, L.J. Roles of leptin, adiponectin and resistin in the transcriptional regulation of steroidogenic genes contributing to decreased Leydig cells function in obesity. Horm. Mol. Biol. Clin. Investig. 2015, 24, 25–45.
36. Tsatsanis, C.; Dermitzaki, E.; Avgoustinaki, P.; Malliaraki, N.; Mytaras, V.; Margioris, A.N. The impact of adipose tissue-derived factors on the hypothalamic-pituitary-gonadal (HPG) axis.

Hormones 2015, 14, 549–562.

37. Childs, G.V.; Odle, A.K.; MacNicol, M.C.; MacNicol, A.M. The Importance of Leptin to Reproduction. Endocrinology 2021, 162, bqaa204.
38. Khodamoradi, K.; Parmar, M.; Khosravizadeh, Z.; Kuchakulla, M.; Manoharan, M.; Arora, H. The role of leptin and obesity on male infertility. Curr. Opin. Urol. 2020, 30, 334–339.
39. Ghaderpour, S.; Ghiasi, R.; Heydari, H.; Keyhanmanesh, R. The relation between obesity, kisspeptin, leptin, and male fertility. Horm. Mol. Biol. Clin. Investig. 2021, 43, 235–247.
40. Ahmad, R.; Haque, M. Obesity: A Doorway to a Molecular Path Leading to Infertility. Cureus 2022, 14, e30770.
41. Isidori, A.M.; Caprio, M.; Strollo, F.; Moretti, C.; Frajese, G.; Isidori, A.; Fabbri, A. Leptin and androgens in male obesity: Evidence for leptin contribution to reduced androgen levels. J. Clin. Endocrinol. Metab. 1999, 84, 3673–3680.
42. Thomas, S.; Kratzsch, D.; Schaab, M.; Scholz, M.; Grunewald, S.; Thiery, J.; Paasch, U.; Kratzsch, J. Seminal plasma adipokine levels are correlated with functional characteristics of spermatozoa. Fertil. Steril. 2013, 99, 1256–1263.e3.
43. Page, S.T.; Herbst, K.L.; Amory, J.K.; Coviello, A.D.; Anawalt, B.D.; Matsumoto, A.M.; Bremner, W.J. Testosterone administration suppresses adiponectin levels in men. J. Androl. 2005, 26, 85–92.
44. Wilkinson, M.; Brown, R.; Imran, S.A.; Ur, E. Adipokine gene expression in brain and pituitary gland. Neuroendocrinology 2007, 86, 191–209.
45. Heydari, H.; Ghiasi, R.; Ghaderpour, S.; Keyhanmanesh, R. The Mechanisms Involved in Obesity-Induced Male Infertility. Curr. Diabetes Rev. 2021, 17, 259–267.
46. Wang, Y.; Cao, L.; Liu, X. Ghrelin alleviates endoplasmic reticulum stress and inflammation-mediated reproductive dysfunction induced by stress. J. Assist. Reprod. Genet. 2019, 36, 2357–2366.
47. Kheradmand, A.; Dezfoulian, O.; Alirezaei, M.; Rasoulian, B. Ghrelin modulates testicular germ cells apoptosis and proliferation in adult normal rats. Biochem. Biophys. Res. Commun. 2012, 419, 299–304.
48. Kluge, M.; Schussler, P.; Uhr, M.; Yassouridis, A.; Steiger, A. Ghrelin suppresses secretion of luteinizing hormone in humans. J. Clin. Endocrinol. Metab. 2007, 92, 3202–3205.
49. Kluge, M.; Uhr, M.; Bleninger, P.; Yassouridis, A.; Steiger, A. Ghrelin suppresses secretion of FSH in males. Clin. Endocrinol. 2009, 70, 920–923.

50. Wang, C.; Jackson, G.; Jones, T.H.; Matsumoto, A.M.; Nehra, A.; Perelman, M.A.; Swerdloff, R.S.; Traish, A.; Zitzmann, M.; Cunningham, G. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. Diabetes Care 2011, 34, 1669–1675.
51. Kısa, Ü.; Başar, M.M.; Şipal, T.; Ceylan, Ö.D. Ghrelin and orexin levels in infertile male: Evaluation of effects on varicocele pathophysiology, relationship seminal and hormonal parameter. Turk. J. Biochem. 2020, 45, 877–882.
52. Li, L.; Huang, C.; Zhang, X.; Wang, J.; Ma, P.; Liu, Y.; Xiao, T.; Zabel, B.A.; Zhang, J.V. Chemerin-derived peptide C-20 suppressed gonadal steroidogenesis. Am. J. Reprod. Immunol. 2014, 71, 265–277.
53. Li, L.; Ma, P.; Huang, C.; Liu, Y.; Zhang, Y.; Gao, C.; Xiao, T.; Ren, P.G.; Zabel, B.A.; Zhang, J.V. Expression of chemerin and its receptors in rat testes and its action on testosterone secretion. J. Endocrinol. 2014, 220, 155–163.
54. Yu, M.; Yang, Y.; Huang, C.; Ge, L.; Xue, L.; Xiao, Z.; Xiao, T.; Zhao, H.; Ren, P.; Zhang, J.V. Chemerin: A Functional Adipokine in Reproductive Health and Diseases. Biomedicines 2022, 10, 1910.
55. Singh, A.; Choubey, M.; Bora, P.; Krishna, A. Adiponectin and Chemerin: Contrary Adipokines in Regulating Reproduction and Metabolic Disorders. Reprod. Sci. 2018, 25, 1462–1473.
56. Zorena, K.; Jachimowicz-Duda, O.; Slezak, D.; Robakowska, M.; Mrugacz, M. Adipokines and Obesity. Potential Link to Metabolic Disorders and Chronic Complications. Int. J. Mol. Sci. 2020, 21, 3570.
57. Wang, W.D.; Xing, L.; Teng, J.R.; Li, S.; Mi, N.A. Effects of basal insulin application on serum visfatin and adiponectin levels in type 2 diabetes. Exp. Ther. Med. 2015, 9, 2219–2224.
58. Chang, Y.C.; Chang, T.J.; Lee, W.J.; Chuang, L.M. The relationship of visfatin/pre-B-cell colony-enhancing factor/nicotinamide phosphoribosyltransferase in adipose tissue with inflammation, insulin resistance, and plasma lipids. Metabolism 2010, 59, 93–99.
59. Hameed, W.; Yousaf, I.; Latif, R.; Aslam, M. Effect of visfatin on testicular steroidogenesis in purified Leydig cells. J. Ayub. Med. Coll. Abbottabad 2012, 24, 62–64.
60. Elfassy, Y.; Bastard, J.P.; McAvoy, C.; Fellahi, S.; Dupont, J.; Levy, R. Adipokines in Semen: Physiopathology and Effects on Spermatozoas. Int. J. Endocrinol. 2018, 2018, 3906490.
61. Wozniak, S.E.; Gee, L.L.; Wachtel, M.S.; Frezza, E.E. Adipose tissue: The new endocrine organ? A review article. Dig. Dis. Sci. 2009, 54, 1847–1856.
62. Higuchi, K.; Masaki, T.; Gotoh, K.; Chiba, S.; Katsuragi, I.; Tanaka, K.; Kakuma, T.; Yoshimatsu, H. Apelin, an APJ receptor ligand, regulates body adiposity and favors the messenger ribonucleic

acid expression of uncoupling proteins in mice. Endocrinology 2007, 148, 2690–2697.

63. Moretti, E.; Signorini, C.; Noto, D.; Tripodi, S.A.; Menchiari, A.; Sorrentino, E.; Collodel, G. Seminal Levels of Omentin-1/ITLN1 in Inflammatory Conditions Related to Male Infertility and Localization in Spermatozoa and Tissues of Male Reproductive System. J. Inflamm. Res. 2022, 15, 2019–2031.
64. de Souza Batista, C.M.; Yang, R.Z.; Lee, M.J.; Glynn, N.M.; Yu, D.Z.; Pray, J.; Ndubuizu, K.; Patil, S.; Schwartz, A.; Kligman, M.; et al. Omentin plasma levels and gene expression are decreased in obesity. Diabetes 2007, 56, 1655–1661.
65. Bekri, S.; Gual, P.; Anty, R.; Luciani, N.; Dahman, M.; Ramesh, B.; Iannelli, A.; Staccini-Myx, A.; Casanova, D.; Ben Amor, I.; et al. Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. Gastroenterology 2006, 131, 788–796.
66. Sokol, R.Z. Endocrinology of male infertility: Evaluation and treatment. Semin. Reprod. Med. 2009, 27, 149–158.
67. Anawalt, B.D. Approach to Male Infertility and Induction of Spermatogenesis. J. Clin. Endocrinol. Metab. 2013, 98, 3532–3542.
68. Genchi, V.A.; Rossi, E.; Lauriola, C.; D'Oria, R.; Palma, G.; Borrelli, A.; Caccioppoli, C.; Giorgino, F.; Cignarelli, A. Adipose Tissue Dysfunction and Obesity-Related Male Hypogonadism. Int. J. Mol. Sci. 2022, 23, 8194.
69. Salas-Huetos, A.; Maghsoumi-Norouzabad, L.; James, E.R.; Carrell, D.T.; Aston, K.I.; Jenkins, T.G.; Becerra-Tomás, N.; Javid, A.Z.; Abed, R.; Torres, P.J.; et al. Male adiposity, sperm parameters and reproductive hormones: An updated systematic review and collaborative meta-analysis. Obes. Rev. 2021, 22, e13082.
70. Giagulli, V.A.; Kaufman, J.M.; Vermeulen, A. Pathogenesis of the decreased androgen levels in obese men. J. Clin. Endocrinol. Metab. 1994, 79, 997–1000.
71. Tchernof, A.; Després, J.P.; Bélanger, A.; Dupont, A.; Prud'homme, D.; Moorjani, S.; Lupien, P.J.; Labrie, F. Reduced testosterone and adrenal C19 steroid levels in obese men. Metabolism 1995, 44, 513–519.
72. Navarro, V.M. Metabolic regulation of kisspeptin—The link between energy balance and reproduction. Nat. Rev. Endocrinol. 2020, 16, 407–420.
73. Harter, C.J.L.; Kavanagh, G.S.; Smith, J.T. The role of kisspeptin neurons in reproduction and metabolism. J. Endocrinol. 2018, 238, R173–R183.
74. Kolb, B.A.; Stanczyk, F.Z.; Sokol, R.Z. Serum inhibin B levels in males with gonadal dysfunction. Fertil. Steril. 2000, 74, 234–238.

75. Meachem, S.J.; Nieschlag, E.; Simoni, M. Inhibin B in male reproduction: Pathophysiology and clinical relevance. Eur. J. Endocrinol. 2001, 145, 561–571.
76. Andersson, A.M.; Skakkebaek, N.E. Serum inhibin B levels during male childhood and puberty. Mol. Cell. Endocrinol. 2001, 180, 103–107.
77. Hui, H.; Farilla, L.; Merkel, P.; Perfetti, R. The short half-life of glucagon-like peptide-1 in plasma does not reflect its long-lasting beneficial effects. Eur. J. Endocrinol. 2002, 146, 863–869.
78. Cannarella, R.; Calogero, A.E.; Condorelli, R.A.; Greco, E.A.; Aversa, A.; La Vignera, S. Is there a role for glucagon-like peptide-1 receptor agonists in the treatment of male infertility? Andrology 2021, 9, 1499–1503.

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