Insulin-like growth factor 2 in spermatogenesis dysfunction (Review)

PINGPING TANG[1], JIALE WANG[1], XIAOHAN TANG[1], YICHUN LI[2] and SUYUN LI[1]

[1]Clinical Anatomy and Reproductive Medicine Application Institute, Hengyang Medical School, University of South China, Hengyang, Hunan 421001, P.R. China; [2]Department of Obstetrics and Gynecology, The Second Affiliated Hospital University of South China, Hengyang, Hunan 421001, P.R. China

Received November 4, 2024; Accepted February 21, 2025

DOI: 10.3892/mmr.2025.13494

Abstract. Spermatogenesis dysfunction is characterized by abnormal morphology, destruction, atrophy of seminiferous tubules, blocked differentiation of spermatogenic cells, decreased sperm count and increased sperm abnormalities. Inflammation, oxidative stress, endoplasmic reticulum stress and obesity are important factors leading to spermatogenesis dysfunction. It has been demonstrated that insulin-like growth factor 2 (IGF2) is closely related to the aforementioned factors. In the present review, the relationship between IGF2 and inflammation, oxidative stress, ER stress and obesity was investigated, providing theoretical and experimental evidence on the role of IGF2 in the prevention and treatment of spermatogenesis dysfunction of male infertility.

Contents

1. Introduction
2. IGF2 and inflammation
3. IGF2 and oxidative stress
4. IGF2 and ER stress
5. IGF2 and obesity
6. Conclusions and future perspectives

1. Introduction

The World Health Organization (WHO) defines infertility as the inability to conceive spontaneously within a year of engaging in frequent, unprotected sexual activity. It is estimated that 8-12% of couples worldwide are unable to conceive normally due to infertility (1); male fertility factors are known to contribute to ~50% of these cases (2) and >50 million men worldwide are infertile (3). Spermatogenic dysfunction is a major cause of male infertility. Dysfunction of spermatogenesis, referred to as spermatogenic disorder, includes non-obstructive azoospermia, cryptospermia and severe oligospermia. Patients with spermatogenic dysfunction present clinically with sperm number defects (oligospermia or azoospermia), reduced sperm motility (hypospermia), abnormal sperm morphology (dyszoospermia), or a combination of these abnormalities (4). Spermatogenic dysfunction is caused by multiple causes and contributing factors. Genetics constitute a significant congenital factor. One prominent example of a complex phenotype influenced by genetics is spermatogenesis with spermatogenesis dysfunction being involved in 10-15% of infertility cases including conditions such as Kirschner's syndrome and Y-chromosome microdeletions, as well as abnormalities of testicular development, such as congenital cryptorchidism. Endocrine factors such as hypogonadotropic hypogonadism and hyperprolactinemia are also congenital factors (5-7). The patient's family history is important for understanding spermatogenesis dysfunction; it can help to identify possible genetic disorders, assess the genetic risk of the patient and his family members, provide appropriate genetic testing and counseling, develop a personalized treatment plan as well help to interrupt hereditary birth defects at the source and improve the quality of the birth population. Secondary factors (acquired factors) encompass a wide range of conditions, including neoplastic diseases, particularly male reproductive system tumors and systemic tumors requiring radiotherapy. Additional secondary factors include testicular torsion and trauma resulting in ischemic and inflammatory damage to the testes, varicocele, exposure to toxic chemicals, prolonged high-temperature environments, infectious diseases such as epididymitis and unhealthy lifestyle choices including smoking and alcohol consumption and other external factors (8-13). The detrimental effects of male infertility are extensive, adversely affecting the psychological and physiological well-being of the individual, as well as potentially disrupting the stability

Correspondence to: Professor Suyun Li, Clinical Anatomy and Reproductive Medicine Application Institute, Hengyang Medical School, University of South China, 28 Changsheng West Road, Hengyang, Hunan 421001, P.R. China
E-mail: lsy1631632021@163.com

Key words: insulin-like growth factor 2, spermatogenesis dysfunction, inflammation, oxidative stress, endoplasmic reticulum stress, obesity

of social connections and familial harmony, making male infertility an emerging major and escalating global health issue (14).

Abnormalities in chromosome number or structure have long been associated with male infertility. Mutations in specific genes involved in meiosis, mitosis, or spermatogenesis result in spermatogenesis dysfunction. The main genes associated with spermatogenic disorders include DMC1 which is associated with spermatogenic failure and is located on the human chromosome 22q13.1 with the protein encoded by the DMC1 gene containing the domain II region of the highly conserved RecA-like family of proteins. DMC1 plays an important role in meiotic homologous recombination, which Mlh1-Mlh3 endonuclease physically interacts with and facilitates meiotic crossover function. DMC1 is expressed in testicular germ cells, especially during meiosis and gene deletion or mutation results in defective meiotic recombination and chromosome association and the cell cycle is arrested in prophase, leading to sterility (15). SYCE1 is located on the human chromosome 10q26.3; it has five transcripts and encodes a member of the association complex that joins homologous chromosomes during prophase I of meiosis. Its protein is localized to the centromeric element and is required for the initiation and lengthening of synapses. SYCE1 interacts with the synaptonemal complex central element protein 3 (SYCE3). SYCE1 is specifically expressed in spermatocytes and allelic variants of this gene are associated with spermatogenic failure (16). BRDT is located on the human chromosome 1p22.1 and functions as a key epigenetic reader, binding to acetylated histones to modulate transcription, chromatin structure and organization. It is crucial for chromosome organization and reprogramming during prophase I of meiosis and loss of function leads to disruptions in the epigenetic state of meiotic chromosomes. This gene is primarily expressed in the testes, notably during late prophase I spermatogonia and spermatocytes. Polymorphisms in the BRDT gene are markedly linked to compromised spermatogenesis and male infertility (17).

The main methods of identification to determine the presence of dysfunction of spermatogenesis are as follows: i) Knowledge of past medical history and patient's family history; ii) ultrasound testing to detect abnormal testicular volume; iii) semen therapy to evaluate sperm concentration; iv) abnormal reproductive hormone levels; v) abnormal testicular histopathologic evaluation; vi) testicular micro sperm retrieval; and vii) whole exome sequencing (11,18-22). Disease management for patients with spermatogenic dysfunction includes the following: i) Genetic evaluation and management; ii) endocrine neoadjuvant therapy; iii) targeted therapy; iv) establishment of a multifaceted and precise diagnostic and treatment system; v) physiotherapy interventions; vi) pharmacological treatment; and vii) assisted reproductive technology (23,24). Treatment for spermatogenesis dysfunction depends on the causes so there is a variety of treatment options. Patients with spermatogenic dysfunction caused by unhealthy lifestyle choices can change their lifestyle, such as reducing smoking, drinking and drug intake. Obese patients may benefit from anti-estrogens and aromatase inhibitors and weight loss should also be encouraged. Gene editing techniques may provide a treatment for dysfunctional spermatogenesis due to hereditary factors; assisted reproductive techniques such as *in vitro* fertilization and intrasperm injection of oocyte cytoplasm are commonly used for patients who are unable to regain spermatogenesis through pharmacological or surgical treatment (4,25-27).

A previous study revealed that the involvement of inflammation in spermatogenesis plays a fundamental role in male reproductive function (28). Therefore, there is a close association between male infertility and inflammation (29). In addition, a number of other factors including endoplasmic reticulum (ER) stress, oxidative stress, obesity and others can also contribute to the development of spermatogenesis dysfunction (30-33). The insulin-like growth factor (IGF) family, a subtype of the growth factor family, includes IFG1 and 2 and the sequence of IGF is highly similar to that of insulin (34). IGF1 mainly secreted by the liver, plays an important role in normal physiology (35). IGF2, as a hormone that is secreted by the liver, is absorbed into the bloodstream and enters the circulation and has a variety of physiological functions known to be involved in female fertility (36). IGFs exert spatiotemporal-specific regulation in the hypothalamic-pituitary-testicular axis and are involved in testicular development, puberty initiation and spermatogenesis in males (37). In peripheral reproductive organs, IGFs are involved in testicular development and sex differentiation during embryonic development, as well as in the proliferation and differentiation of testicular mesenchymal cells, supporting cells and spermatogenic cells (38). IGF-1-knockout mice have reduced testicular volume and decreased supporting cell and sperm concentrations in adulthood (39). IGF-2 plays an important role in spermatogenesis; it is a key factor in embryonic and placental growth and is a key gene in the context of male infertility; methylation modifications of IGF2, particularly at the imprinted control region 1 motif of IGF2/long noncoding RNA H19 (H19), are strongly associated with sperm health (40,41). IGF2 is also involved in numerous processes such as inflammation, oxidative stress, ER stress and obesity which have been associated with spermatogenesis dysfunction (42-45). This suggests that IGF2 may have a potential link to spermatogenesis dysfunction, however, a systematic and comprehensive review of the relationship between IGF2 and spermatogenesis dysfunction has not been performed. Consequently, it is urgently required to overview recent studies on the relationships between IGF2 and spermatogenesis dysfunction to identify the roles of IGF2 in the pathophysiology of male infertility. In the present review, using the key words IGF2, male infertility, inflammation, oxidative stress, ER stress, obesity and insulin resistance (IR), the relationship between IGF2 and the development of spermatogenesis dysfunction was systematically summarized, providing compelling evidence for the role of IGF2 as a potential candidate target of action for the treatment of spermatogenesis dysfunction.

2. IGF2 and inflammation

Spermatogenesis dysfunction is known to be notably influenced by infections (46). Various inflammatory factors, such as interleukin (IL)-6, tumor necrosis factor α (TNFα), IL-1 and nitric oxide (NO) are involved in spermatogenesis (47). Disruption of the dynamic balance between inflammatory/anti-inflammatory factors during spermatogenesis may

cause male infertility (48). Inflammation can be caused by a number of factors, but the main cause is infection by gram-negative bacteria (49). Lipopolysaccharides (LPS) are essential for maintaining both structural and functional integrity. LPS not only induce proinflammatory cytokines such as IL-1 and TNFα but also act through the Toll-like receptor 4 (TLR4) complex; TLR4 is expressed by rat macrophages, Sertoli and Leydig cells (50,51). In addition, Shen *et al* (52) report that male fertility was compromised with lower testosterone levels, impaired spermatogenesis and disruption of the blood-testis barrier (BTB) in the testes under LPS intraperitoneal injection-induced acute systemic inflammation (53). The potential mechanism for this includes creation of an inflammatory-oxidative milieu that causes spermatocytes and spermatids to undergo temporal apoptosis and activate the apoptotic mitochondrial pathway (51,54). Reproductive tract infections are known to increase proinflammatory cytokines such as IL-1β, which can also generate inflammatory damage to the testes and reduce sperm quality (46,48). It has been estimated that uropathogenic *Escherichia coli* (UPEC) is the major pathogen causing genitourinary tract infections (55). Clinical and pathologic evidence suggest that a chronic inflammatory condition in the testis can impair spermatogenesis and irreversibly alter sperm quantity and quality (46). In a mouse model of experimentally induced UPEC epididymo-orchitis, testicles of mice injected with *Escherichia coli* displayed acute histological damage accompanied by severe testicular atrophy and impaired spermatogenesis (56). The aforementioned results indicate the pivotal role of inflammation in the progress of spermatogenesis dysfunction.

The complex relationship between inflammation and sperm quality is a key aspect of current findings. Street *et al* (57) report that compared with age-matched healthy individuals, the serum concentrations of IL-1β, IL-6 and TNFα are markedly, raised and the concentration of IGF2 was notably reduced, in young patients with cystic fibrosis. It is hypothesized that IGF2 bioactivities are reduced in the presence of chronic inflammation-induced conditions (58). The relationship between IGF2 protein concentration, inflammation and sperm parameters was identified in 320 patients with spermatogenic dysfunction and downregulation of the IGF2 protein exacerbated the existing inflammation state by interrupting the fine balance of proinflammatory and anti-inflammatory signaling, which further contributed to sperm quality decline (59). These findings are consistent with the existing literature suggesting that inflammation responses and DNA damage lead to impaired sperm function and reduced fertilization rates (60). Monocytes found in the bloodstream migrate to neighboring tissues, then mature into macrophages and acquire a proinflammatory or anti-inflammatory phenotype (61), whereas the energy requirements of anti-inflammatory macrophages are largely dependent on oxidative phosphorylation (OXPHOS) (62). Testicular macrophages may be crucial to the development of orchitis caused by inflammation and infection. According to a study, during orchitis, these inflammatory macrophages predominantly derived from circulating monocytes, contribute to tissue destruction and negatively affect the process of spermatogenesis (63). However, IGF2 regulates macrophage phenotype through IGF2R and IGF1R in a dose range (64). Cells with high levels of IGF2 co-ordinate the creation of an anti-inflammatory environment that promotes tissue regeneration and repair (65). One possible explanation could be that the nucleus of IGF2R is translocated in response to low doses of IGF2, activating glycogensynthase kinase 3 α/β and promoting Dnmt3a-mediated DNA methylation. IGF2R signaling also causes proton rechanneling to the mitochondria, which results in the preferential use of OXPHOS for energy generation and pre-programs maturing macrophages to adopt an anti-inflammatory phenotype (66). Evidence suggests that IGF2 may play a role in the treatment of testicular inflammation by modulating the inflammatory response. In addition, studies have also demonstrated the anti-inflammatory effects of IGF2 in other diseases through different pathways (42,67-74).

Inflammation is an important factor in spermatogenesis dysfunction and IGF2 has a degree of anti-inflammatory properties. In conclusion, the current review suggested that there is a notable association between reduced seminal plasma IGF2 protein levels and inflammation in patients with spermatogenic dysfunction and that IGF2 plays a crucial role in protecting spermatozoa from inflammatory stress and DNA damage which in turn affects male reproductive health. The current review provided new perspectives for the treatment of male infertility caused by inflammation.

3. IGF2 and oxidative stress

There is growing evidence that male infertility is strongly associated with oxidative stress (75-77). Infertile men with varicocele have elevated expression of reactive oxygen species (ROS). At the cell level, researchers have also underlined the notable contribution of oxidative stress (31). The byproducts of regular cellular metabolism are ROS (78). Numerous studies indicate that in 30-80% of infertile men, ROS-mediated spermatozoa damage is a marked factor in the pathophysiology of infertility (79). Oxidative stress is caused by an imbalance between ROS production and the body's antioxidant defense mechanisms which leads to cellular function disruption (80). Oxidative stress can be an important mediator of damage to cell structures (81), it may affect the integrity of nuclear and mitochondrial DNA (mtDNA) (82). It has been demonstrated that low levels of ROS play an essential role in sperm capacitation, acrosome reaction and sperm-oocyte fusion, but supraphysiological ROS levels obstruct sperm membrane fluidity and permeability (83). In addition, spermatozoa have limited antioxidant defenses so they are highly susceptible to oxidative stress (60). Spermatozoa are abundant in mitochondria, which contribute to a variety of spermatozoa physiological functions by producing ATP. This process inevitably produces ROS, but mitochondria are a major source of ROS so they are also targets of ROS attacks (84). ROS also has the ability to harm the inner mitochondrial membrane, which directly damages mtDNA and impairs the ability of spermatozoa to function physiologically (85). Furthermore, the increase of apoptosis is linked to oxidative stress (86) and excessive ROS levels have the ability to split the mitochondrial membrane which triggers the family of caspases and initiates the apoptotic cascade in spermatozoa (87). In addition, cytochrome *c* release is encouraged by mitochondrial membrane fragmentation which results in mitochondria-dependent apoptosis (88). The aforementioned results suggest that oxidative stress plays a pivotal role in the development of spermatogenesis dysfunction.

IGF2 deficiency is both a consequence and a contributing factor to the pathologic mechanisms that undermine sperm health. A key aspect of this interrelationship lies in the adverse effects of IGF2 deficiency on mitochondrial function. Mitochondria are key to energy metabolism and ROS regulation and when IGF2 levels are deficient, mitochondria become dysfunctional (89,90). Inflammation, obesity, unhealthy diet and unhealthy lifestyles contribute to an environment of increased oxidative stress (91). ROS levels are markedly associated with H19-Igf2 gene methylation and semen parameters, high ROS levels activated the H19 gene and repressed the Igf2 gene leading to impaired spermatogenesis and sperm maturation (92) The accumulation of oxidative damage directly damages mtDNA and promotes nuclear DNA damage which further disrupts sperm function and viability (85). Emerging research reveals that IGF2 has anti-apoptotic characteristics (93). This suggests that IGF2 induces cellular resistance to oxidative stress-induced apoptosis through mitochondrial protective ATP production (94). Castilla-Cortázar *et al* (95) found that aged rats without treatment had lower serum total antioxidant status, IGF1 and testosterone levels. On the other hand, IGF2 treatment increased serum antioxidant capacity and enhanced mitochondrial function and antioxidant enzyme activities while it lowered oxidative damage. In a similar study, increased oxidative damage in isolated mitochondria and reduced mitochondrial membrane potential (MMP) and ATP synthesis were identified in untreated aged mice consistent with overexpression of cysteine aspartate protease 3 and 9 active fragments in their liver homogenates. However, IGF2-treated old mice had reversed all of these parameters of mitochondrial dysfunction and had reduced activation of caspases (94).

IGF2 acts not only by regulating the synthesis or activity of antioxidant enzymes, but also by restoring mitochondrial cytochrome *c* oxidase activity and MMP. This potential mechanism may be due to after an oxidative damage, IGF2 promotes improved mitochondrial function and increases manganese superoxide dismutase, cyclooxygenase activity and MMP levels by IGFRs (96). In addition, IGF2 boosts mitochondrial functional activity by decreasing oxidative stress and raising the intensity of mitochondrial immunofluorescence staining (97). Increasing IGF2 improves mitochondrial function and reduces oxidative stress supporting a positive role for IGF2 in improving male infertility. High ROS levels affect the hypothalamic hormone-releasing axes, such as the hypothalamic-pituitary-testicular and hypothalamic-pituitary-gonadal (HPG) axes, increasing the release of cortisol hormones, decreasing luteinizing hormone (LH) secretion via HPA and testosterone synthesis via crosstalk, leading to infertility indirectly (98). A study by Martín-Montañez *et al* (99) showed that treating cells with IGF2 reverses the attenuation of corticosteroid-induced oxidative damage. IGF2 also promotes the synthesis and secretion of LH by pituitary gonadotropin cells (100).

All of the aforementioned studies emphasize the critical role of IGF2 in maintaining the integrity of spermatogenesis indicating that IGF2 plays an integral role in oxidative stress-induced male infertility.

4. IGF2 and ER stress

Protein quality control is essential to maintain intracellular protein biosynthesis, folding, transport and degradation and ultimately protein and cellular homeostasis (101). The primary site of protein folding and maturation is the ER and overaccumulation of unfolded or misfolded proteins leads to ER stress (102). The ER chaperones, folding enzymes and proteases identify misfolded proteins in order to prevent inappropriate molecular interactions (103). Nevertheless, in order to protect the organism, apoptosis will be initiated if homeostasis cannot be restored (104). There is growing evidence that abnormal ER stress-induced expression of chaperonin is a major contributor to altered sperm protein content in a number of male infertility conditions (105). Chronic activation of ER stress inhibits the Akt/mTORC1 pathway and dysregulation of the mTOR signaling pathway triggers cell death, apoptosis and autophagy and impairs protein synthesis in vital organs (106). It has been demonstrated that mTORC1 inhibition prevents the activation of mRNA translation triggered by retinoic acid which causes an accumulation of progenitor spermatogonia without differentiation and can lead to infertility (107). Furthermore, low dose and combined exposure to bisphenol A and diethylstilbestrol may have toxic effects on male fertility in the adult population, however, this damaging process is mainly induced through ER stress (108). Huang *et al* (109) performed a study on testicular injury after torsion/detorsion (T/D) in rat model and showed that the ER stress-related apoptotic pathway is involved in testicular injury after testicular T/D likely through the PERK-eIF2α signaling pathway. Oxidative stress in the epididymal microenvironment induces ER stress in the epididymal epithelial cells. This process modifies the composition, amount and profile of the differentially expressed ER proteins in exosomes derived from epididymal tissue. Ultimately, this results in irregularities in sperm maturation and fertility (110). Protein palmitoylation-mediated palmitic acid sensing causes BTB damage by inducing ER stress (111). These studies suggest that ER stress signaling is an important signaling pathway regulating apoptosis in male germ cells.

A growing number of studies have indicated the indispensable role of IGF2 in regulating ER stress. Indicating that IGF2 is closely related to ER stress (112,113). A study showed that the PI3K/Akt signaling pathway could be activated by upregulation of IGF2, ultimately activating mTOR1 (114). During spermatogenesis, the mTOR signaling pathway regulates the proliferation, differentiation and self-renewal of spermatogonia and may be involved in the regulation of spermatogonial meiosis (115). ER stress inhibits the Akt/mTORC1 pathway and enhances autophagy (116). Therefore, upregulation of IGF2 activates the mTOR signaling pathway, thereby inhibiting autophagy and apoptosis induced by ER stress may be an effective treatment for patients with spermatogenesis dysfunction. In addition, a strong association is observed between the metabolic levels of the proteins and their subcellular localization, as demonstrated by the study of Yuan *et al* (117) and comparisons regarding the metabolism of cell surface membrane proteins. In the lumen of the ER, the mitotic retardation factor of IGF2R levels are notably higher. The ability of IGF2R to bind IGF2 with specificity is used in an additional research study as a powerful ligand for cell surface receptors

targeted by lysosomes, resulting in the transmembrane delivery of extracellular and membrane proteins as well as lysosomal lysis (118). This further supports the potential role of IGF2 in ameliorating ER stress-induced protein folding disorders. The development of oligospermia in men has been found to be associated with reduced IGF2 gene expression (119) and Cannarella *et al* (120) discovered that human spermatozoa contain varying levels of the IGF2 protein, which seems to play a role in downregulating mitogen signaling, thereby facilitating the proliferation of secondary germ cells and guiding the differentiation of spermatogonial cells. Paternally derived H19 hypomethylation may contribute to H19 bi-allelic expression and IGF2 downregulation, as found in oligospermia-associated male reproductive systems (121,122). In other diseases, IGF2 has also been shown to differentially reduce aberrant protein aggregation and reduce its misfolding thereby alleviating ER stress (113,123).

Taken together, IGF2 may play a part in treating ER stress-induced spermatogenesis dysfunction since it inhibits aberrant protein aggregation; imbalance of protein homeostasis is a common cause of both ER stress and male infertility.

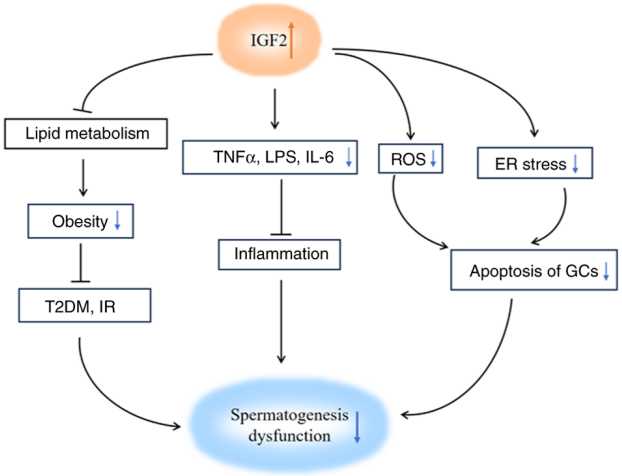

Figure 1. Diagram demonstrating the potential link between IGF2 and spermatogenesis dysfunction. Blue arrows represent a decrease, red arrows represent an increase, solid arrows represent an effect on downstream factors, t-shaped arrows represent an inhibitory effect. IGF2, insulin-like growth factor 2; TNFα, tumor necrosis factor α; LPS, lipopolysaccharides; IL-6, interleukin-6; ROS, reactive oxygen species; ER, endoplasmic reticulum; T2DM, type II diabetes mellitus; IR, insulin resistance; GCs, germ cells.

5. IGF2 and obesity

Obesity has detrimental effects on the physical and mental well-being of individuals and it is a complicated condition. The WHO defines it as abnormal or excessive accumulation of fat that may impair health (124). Obesity has become an urgent public health issue in recent decades, related to the decline in reproductive potential (32). There is a growing body of evidence that obesity disrupts the male reproductive potential and causes male infertility (125,126). Obesity impairs male sexual health and fertility by affecting erectile function and semen parameters, respectively (127). The increase in obesity incidence is parallel to poor sperm quality and an increase in male infertility (128), as it may affects sperm development and maturation, leading to a decrease in semen quality including vitality, survival ability and morphology (129). Previous studies have shown that diet-induced obesity in animal models results in decreased testosterone levels and aberrant sperm parameters such as sperm motility, count and deformity, all of which reduce fertility (130,131). In addition, mice on a high-fat diet (HFD) demonstrated increased body weight and epididymal fat weight, along with elevated blood glucose, serum total cholesterol, high density lipoprotein and low density lipoprotein levels, decreased follicle-stimulating hormone, testosterone levels and notable lipid deposition in the testicular interstitium (132,133). Furthermore, Han *et al* (32) report that the expression of glycolysis-related proteins in the testes of obese male mice is markedly reduced, indicating that obesity impairs the energy supply for spermatogenesis. Previous studies suggest that obesity is strongly associated with other negative factors leading to spermatogenic dysfunction (134-136). Excessive adipose tissue can cause male infertility by inhibiting the HPG axis, interfering with hormone balance and raising inflammatory cytokines and ROS (137). Additionally, it has been shown that obesity leads to a number of diseases, commonly metabolic disorders, hyperinsulinemia and hyperglycemia. Obesity and diabetes have a negative effect on both the quantity and quality of sperm in men (138). The effect of obesity on sperm DNA damage is amplified in obese diabetic mice (139). These results suggest a strong association between obesity and male infertility. Therefore, reducing obesity is one of the possible strategies to restore male infertility caused by spermatogenesis dysfunction.

Recently, Faienza *et al* (140) discovered that HFD-induced obesity is inherited and was associated with the expression of Igf2 genes; increasing IGF2 improves glucose metabolism and obesity in HFD-fed mice, while downregulating IGF2 in adipocytes promotes diet-induced obesity and obesity-related symptoms. In adults, Igf2 gene variants are strongly associated with weight, body mass index and metabolic characteristics. In a prospective adult study, it was found that low serum IGF2 concentrations in both type 2 diabetic and normal subjects predicted future weight gain (141). By contrast, elevated IGF2 was markedly linked to a subsequent decrease in weight over a 9-year period, supporting the hypothesis that IGF2 controls fat mass (142). In addition, obesity affects spermatogenesis and quality through a variety of mechanisms and IGF2 may promote normal spermatogenesis and development by improving the testicular microenvironment and its role in cell proliferation and differentiation (120,143,144). Murphy *et al* (145) found that IR may be a specific manifestation of IGF2 expression loss caused by IGF2/H19 methylation deficiency. Similarly, the deficiency of IGF2 has been shown to be associated with the occurrence of spontaneous type II diabetes mellitus phenotype in Goto-Kawasaki rats (146). Since the proliferation of islet cells is fueled by IGF2-derived cystic protein, this can counteract IR, preserve glycemic control and stop disease progression (147). This suggests that IGF2 can influence insulin sensitivity, which may indirectly improve IR and sex hormone imbalance associated with obesity. This regulatory effect could contribute to enhanced fertility in men with obesity. All of the aforementioned studies suggest a potential role of IGF2 in the regulation of adipose

tissue (148) and in the development of obesity-related IR (149). However, a study shows that the Igf2 gene may play a more important role in lipid metabolism (150). Furthermore, Alfares *et al* (151) show that IGF2 functions as a differential modulator of fat accumulation, favoring less visceral fat deposition and regulating preadipocyte differentiation and metabolism. Transgenic mice overexpressing IGF2 in the liver exhibit increased insulin-stimulated glucose uptake and lower fat content (152).

Consequently, IGF2 is associated with the development of obesity through mechanisms that affect body weight regulation, gene polymorphisms, adipocyte function and IR. It increases glucose metabolism, promotes the growth of pancreatic islet cells to increase insulin sensitivity and regulates preadipocyte differentiation and metabolism to improve obesity, the testicular microenvironment and its role in cell proliferation and differentiation to promote normal spermatogenesis and development. These findings set the scene for future research and emphasize the importance of IGF2 in the broader context of male reproductive health.

6. Conclusions and future perspectives

Spermatogenesis dysfunction is caused by inflammation, oxidative stress, ER stress, obesity and others (46,153) and IGF2 can improve spermatogenesis dysfunction induced by these factors (154-156). The present review summarized the relationship between IGF2 and the etiology of spermatogenic dysfunction (Fig. 1) and described the ameliorative effect of IGF2 on spermatogenesis dysfunction. IGF2 may shed a new light on the development of new treatment approaches for infertile males. Nonetheless, there are several issues to be addressed in future studies. First, in obese individuals, although IGF2 is mainly secreted in the liver and serum, IGF2 levels are closely linked to IR; IGF2 levels are positively associated with the types of metabolic syndrome and gain weight and it is not clear whether IGF2 is involved in the pathophysiology of the metabolic syndrome (146). Second, spermatogenesis dysfunction caused by inflammation, oxidative stress, ER stress and obesity has improved due to IGF2, but the specific mechanism remains unclear. Finally, there is an important association between IGF2 genetic polymorphisms and differences in lipid metabolism (150) and the role of IGF2 in other causes of spermatogenesis dysfunction need to be further explored. Consequently, it is expected that research on IGF2 will pave the way for novel clinical approaches for infertility diagnosis and treatment.

Acknowledgements

Not applicable.

Funding

The present review was supported by the Natural Science Foundation of Hunan Province (grant no. 2023JJ60358)

Availability of data and materials

Not applicable.

Authors' contributions

PT drafted the manuscript. PT, JW, XT, YL and SL performed the literature search and revised the manuscript. YL and SL conceived the review idea and critically revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Vander Borght M and Wyns C: Fertility and infertility: Definition and epidemiology. Clin Biochem 62: 2-10, 2018.
2. Sharlip ID, Jarow JP, Belker AM, Lipshultz LI, Sigman M, Thomas AJ, Schlegel PN, Howards SS, Nehra A, Damewood MD, *et al*: Best practice policies for male infertility. Fertil Steril 77: 873-882, 2002.
3. Agarwal A, Mulgund A, Hamada A and Chyatte MR: A unique view on male infertility around the globe. Reprod Biol Endocrinol 13: 37, 2015.
4. Leaver RB: Male infertility: An overview of causes and treatment options. Br J Nurs 25: S35-S40, 2016.
5. Gunes S and Esteves SC: Role of genetics and epigenetics in male infertility. Andrologia 53: e13586, 2021.
6. Tiepolo L and Zuffardi O: Localization of factors controlling spermatogenesis in the nonfluorescent portion of the human Y chromosome long arm. Hum Genet 34: 119-124, 1976.
7. Umino S, Kitamura M, Katoh-Fukui Y, Fukami M, Usui T, Yatsuga S and Koga Y: A case of combined 21-hydroxylase deficiency and CHARGE syndrome featuring micropenis and cryptorchidism. Mol Genet Genomic Med 7: e730, 2019.
8. Cocuzza M, Cocuzza MA, Bragais FMP and Agarwal A: The role of varicocele repair in the new era of assisted reproductive technology. Clinics 63: 395-404, 2008.
9. Cocuzza M, Athayde KS, Agarwal A, Pagani R, Sikka SC, Lucon AM, Srougi M and Hallak J: Impact of clinical varicocele and testis size on seminal reactive oxygen species levels in a fertile population: A prospective controlled study. Fertil Steril 90: 1103-1108, 2008.
10. Cho CL, Esteves SC and Agarwal A: Indications and outcomes of varicocele repair. Panminerva Med 61: 152-163, 2019.
11. Achermann APP and Esteves SC: Diagnosis and management of infertility due to ejaculatory duct obstruction: summary evidence. Int Braz J Urol 47: 868-881, 2021.
12. Juul A, Almstrup K, Andersson AM, Jensen TK, Jørgensen N, Main KM, Rajpert-De Meyts E, Toppari J and Skakkebæk NE: Possible fetal determinants of male infertility. Nat Rev Endocrinol 10: 553-562, 2014.
13. Esteves SC: Evolution of the World Health Organization semen analysis manual: Where are we? Nat Rev Urol 19: 439-446, 2022.
14. Baskaran S, Agarwal A, Leisegang K, Pushparaj PN, Panner Selvam MK and Henkel R: An in-depth bibliometric analysis and current perspective on male infertility research. World J Mens Health 39: 302, 2021.
15. Jiang Y, Zhang HY, Lin Z, Zhu YZ, Yu C, Sha QQ, Tong MH, Shen L and Fan HY: CXXC finger protein 1-mediated histone H3 lysine-4 trimethylation is essential for proper meiotic crossover formation in mice. Development 147: dev183764, 2020.
16. Maor-Sagie E, Cinnamon Y, Yaacov B, Shaag A, Goldsmidt H, Zenvirt S, Laufer N, Richler C and Frumkin A: Deleterious mutation in SYCE1 is associated with non-obstructive azoospermia. J Assist Reprod Genet 32: 887-891, 2015.

17. Li L, Sha Y, Wang X, Li P, Wang J, Kee K and Wang B: Whole-exome sequencing identified a homozygous BRDT mutation in a patient with acephalic spermatozoa. Oncotarget 8: 19914-19922, 2017.
18. Guler I, Erdem M, Erdem A, Demirdağ E, Tunc L, Bozkurt N, Mutlu MF and Oktem M: Impact of testicular histopathology as a predictor of sperm retrieval and pregnancy outcome in patients with nonobstructive azoospermia: Correlation with clinical and hormonal factors. Andrologia 48: 765-773, 2016.
19. Ramasamy R, Padilla WO, Osterberg EC, Srivastava A, Reifsnyder JE, Niederberger C and Schlegel PN: A comparison of models for predicting sperm retrieval before microdissection testicular sperm extraction in men with nonobstructive azoospermia. J Urol 189: 638-642, 2013.
20. Pozzi E, Raffo M, Negri F, Boeri L, Saccà A, Belladelli F, Cilio S, Ventimiglia E, d'Arma A, Pagliardini L, *et al*: Anti-Müllerian hormone predicts positive sperm retrieval in men with idiopathic non-obstructive azoospermia-findings from a multi-centric cross-sectional study. Hum Reprod 38: 1464-1472, 2023.
21. Yildirim ME, Koc A, Kaygusuz IC, Badem H, Karatas OF, Cimentepe E and Unal D: The association between serum follicle-stimulating hormone levels and the success of microdissection testicular sperm extraction in patients with azoospermia. Urol J 11: 1825-1828, 2014.
22. Sharma A, Minhas S, Dhillo WS and Jayasena CN: Male infertility due to testicular disorders. J Clin Endocrinol Metab 106: e442-e459, 2021.
23. Minhas S, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, Cocci A, Corona G, Dimitropoulos K, Gül M, *et al*: European association of urology guidelines on male sexual and reproductive health: 2021 update on male infertility. Eur Urol 80: 603-620, 2021.
24. Sciorio R, Thong KJ and Pickering SJ: Single blastocyst transfer (SET) and pregnancy outcome of day 5 and day 6 human blastocysts vitrified using a closed device. Cryobiology 84: 40-45, 2018.
25. Halpern JA, Davis AM and Brannigan RE: Diagnosis and treatment of infertility in men. JAMA 328: 2056, 2022.
26. Huyghe E, Faix A, Bouker A and Methorst C: Testicular and epididymal sperm extraction surgery. Prog Urol 33: 697-709, 2023 (In French).
27. Sharma R, Biedenharn KR, Fedor JM and Agarwal A: Lifestyle factors and reproductive health: Taking control of your fertility. Reprod Biol Endocrinol 11: 66, 2013.
28. Tavalaee M, Rahmani M, Drevet JR and Nasr-Esfahani MH: The NLRP3 inflammasome: Molecular activation and regulation in spermatogenesis and male infertility; a systematic review. Basic Clin Androl 32: 8, 2022.
29. De Rivero Vaccari JP: The Inflammasome in reproductive biology: A promising target for novel therapies. Front Endocrinol 11: 8, 2020.
30. Karna KK, Shin YS, Choi BR, Kim HK and Park JK: The role of endoplasmic reticulum stress response in male reproductive physiology and pathology: A review. World J Mens Health 38: 484-494, 2020.
31. Agarwal A, Rana M, Qiu E, AlBunni H, Bui AD and Henkel R: Role of oxidative stress, infection and inflammation in male infertility. Andrologia 50: e13126, 2018.
32. Han J, Zhao C, Guo H, Liu T, Li Y, Qi Y, Deussing JM, Zhang Y, Tan J, Han H and Ma X: Obesity induces male mice infertility via oxidative stress, apoptosis, and glycolysis. Reproduction 166: 27-36, 2023.
33. Rodprasert W, Toppari J and Virtanen HE: Environmental toxicants and male fertility. Best Pract Res Clin Obstet Gynaecol 86: 102298, 2023.
34. Martin JL and Baxter RC: Signalling pathways of insulin-like growth factors (IGFs) and IGF binding protein-3. Growth Factors 29: 235-244, 2011.
35. Harris LK and Westwood M: Biology and significance of signalling pathways activated by IGF-II. Growth Factors 30: 1-12, 2012.
36. Livingstone C and Borai A: Insulin-like growth factor-II: Its role in metabolic and endocrine disease. Clin Endocrinol (Oxf) 80: 773-781, 2014.
37. Koskenniemi JJ, Virtanen HE, Wohlfahrt-Veje C, Löyttyniemi E, Skakkebaek NE, Juul A, Andersson AM, Main KM and Toppari J: Postnatal changes in testicular position are associated with IGF-I and function of sertoli and leydig cells. J Clin Endocrinol Metab 103: 1429-1437, 2018.
38. Nef S, Verma-Kurvari S, Merenmies J, Vassalli JD, Efstratiadis A, Accili D and Parada LF: Testis determination requires insulin receptor family function in mice. Nature 426: 291-295, 2003.
39. Pitetti JL, Calvel P, Zimmermann C, Conne B, Papaioannou MD, Aubry F, Cederroth CR, Urner F, Fumel B, Crausaz M, *et al*: An essential role for insulin and IGF1 receptors in regulating sertoli cell proliferation, testis size, and FSH action in mice. Mol Endocrinol 27: 814-827, 2013.
40. Cannarella R, Condorelli RA, La Vignera S, Bellucci C, Luca G, Calafiore R and Calogero AE: IGF2 and IGF1R mRNAs are detectable in human spermatozoa. World J Mens Health 38: 545-551, 2020.
41. Constância M, Hemberger M, Hughes J, Dean W, Ferguson-Smith A, Fundele R, Stewart F, Kelsey G, Fowden A, Sibley C and Reik W: Placental-specific IGF-II is a major modulator of placental and fetal growth. Nature 417: 945-948, 2002.
42. Guo D, Xu Y, Liu Z, Wang Y, Xu X, Li C, Li S, Zhang J, Xiong T, Cao W and Liang J: IGF2 inhibits hippocampal over-activated microglia and alleviates depression-like behavior in LPS-treated male mice. Brain Res Bull 194: 1-12, 2023.
43. Muhammad T, Wan Y, Sha Q, Wang J, Huang T, Cao Y, Li M, Yu X, Yin Y, Chan WY, *et al*: IGF2 improves the developmental competency and meiotic structure of oocytes from aged mice. Aging (Milano) 13: 2118-2134, 2021.
44. Fitzgerald GS, Chuchta TG and McNay EC: Insulin-like growth factor-2 is a promising candidate for the treatment and prevention of Alzheimer's disease. CNS Neurosci Ther 29: 1449-1469, 2023.
45. Roth S, Schrager M, Metter E, Riechman S, Fleg J, Hurley B and Ferrell R: IGF2 genotype and obesity in men and women across the adult age span. Int J Obes 26: 585-587, 2002.
46. Schuppe HC, Meinhardt A, Allam JP, Bergmann M, Weidner W and Haidl G: Chronic orchitis: A neglected cause of male infertility? Andrologia 40: 84-91, 2008.
47. Loveland KL, Klein B, Pueschl D, Indumathy S, Bergmann M, Loveland BE, Hedger MP and Schuppe HC: Cytokines in male fertility and reproductive pathologies: Immunoregulation and beyond. Front Endocrinol (Lausanne) 8: 307, 2017.
48. Li Y, Su Y, Zhou T, Hu Z, Wei J, Wang W, Liu C, Zhang H and Zhao K: Activation of the NLRP3 inflammasome pathway by Prokineticin 2 in testicular macrophages of uropathogenic *Escherichia coli*-Induced orchitis. Front Immunol 10: 1872, 2019.
49. Singh AK and Jiang Y: How does peripheral lipopolysaccharide induce gene expression in the brain of rats? Toxicology 201: 197-207, 2004.
50. Cartmell T, Luheshi GN and Rothwell NJ: Brain sites of action of endogenous interleukin-1 in the febrile response to localized inflammation in the rat. J Physiol 518: 585-594, 1999.
51. Metukuri MR, Reddy CMT, Reddy PRK and Reddanna P: Bacterial LPS-mediated acute inflammation-induced spermatogenic failure in rats: Role of stress response proteins and mitochondrial dysfunction. Inflammation 33: 235-243, 2010.
52. Shen P, Ji S, Li X, Yang Q, Xu B, Wong CKC, Wang L and Li L: LPS-induced systemic inflammation caused mPOA-FSH/LH disturbance and impaired testicular function. Front Endocrinol 13: 886085, 2022.
53. Jangula A and Murphy EJ: Lipopolysaccharide-induced blood brain barrier permeability is enhanced by alpha-synuclein expression. Neurosci Lett 551: 23-27, 2013.
54. Reddy MM, Mahipal SVK, Subhashini J, Reddy MC, Roy KR, Reddy GV, Reddy PR and Reddanna P: Bacterial lipopolysaccharide-induced oxidative stress in the impairment of steroidogenesis and spermatogenesis in rats. Reprod Toxicol 22: 493-500, 2006.
55. Virtanen HE, Jørgensen N and Toppari J: Semen quality in the 21st century. Nat Rev Urol 14: 120-130, 2017.
56. Demir A, Türker P, Önol FF, Sirvanci S, Findik A and Tarcan T: Effect of experimentally induced *Escherichia coli* epididymo-orchitis and ciprofloxacin treatment on rat spermatogenesis. Int J Urol 14: 268-272, 2007.
57. Street ME, Ziveri MA, Spaggiari C, Viani I, Volta C, Grzincich GL, Virdis R and Bernasconi S: Inflammation is a modulator of the insulin-like growth factor (IGF)/IGF-binding protein system inducing reduced bioactivity of IGFs in cystic fibrosis. Eur J Endocrinol 154: 47-52, 2006.
58. Street ME, Spaggiari C, Volta C, Ziveri MA, Viani I, Rossi M, Pisi G, Grzincich G and Bernasconi S: The IGF system and cytokine interactions and relationships with longitudinal growth in prepubertal patients with cystic fibrosis. Clin Endocrinol (Oxf) 70: 593-598, 2009.
59. Wu JG, Zhou CP, Gui WW, Liang ZY, Zhang FB, Fu YG, Li R, Wu F and Lin XH: Correlation of IGF2 levels with sperm quality, inflammation, and DNA damage in infertile patients. Asian J Androl 27: 204-210, 2025.
60. Bisht S, Faiq M, Tolahunase M and Dada R: Oxidative stress and male infertility. Nat Rev Urol 14: 470-485, 2017.

61. Priller J and Böttcher C: Patrolling monocytes sense peripheral infection and induce cytokine-mediated neuronal dysfunction. Nat Med 23: 659-661, 2017.
62. Huang SCC, Smith AM, Everts B, Colonna M, Pearce EL, Schilling JD and Pearce EJ: Metabolic reprogramming mediated by the mTORC2-IRF4 signaling axis is essential for macrophage alternative activation. Immunity 45: 817-830, 2016.
63. Wang M, Yang Y, Cansever D, Wang Y, Kantores C, Messiaen S, Moison D, Livera G, Chakarov S, Weinberger T, *et al*: Two populations of self-maintaining monocyte-independent macrophages exist in adult epididymis and testis. Proc Natl Acad Sci 118: e2013686117, 2021.
64. Clausen BE, Burkhardt C, Reith W, Renkawitz R and Förster I: Conditional gene targeting in macrophages and granulocytes using LysMcre mice. Transgenic Res 8: 265-277, 1999.
65. Charville GW, Cheung TH, Yoo B, Santos PJ, Lee GK, Shrager JB and Rando TA: Ex vivo expansion and in vivo Self-renewal of human muscle stem cells. Stem Cell Rep 5: 621-632, 2015.
66. Wang X, Lin L, Lan B, Wang Y, Du L, Chen X, Li Q, Liu K, Hu M, Xue Y, *et al*: IGF2R-initiated proton rechanneling dictates an anti-inflammatory property in macrophages. Sci Adv 6: eabb7389, 2020.
67. Hao K, Zhai Q, Gu Y, Chen YQ, Wang YN, Liu R, Yan SP, Wang Y, Shi YF, Lei W, *et al*: Disturbance of suprachiasmatic nucleus function improves cardiac repair after myocardial infarction by IGF2-mediated macrophage transition. Acta Pharmacol Sin 44: 1612-1624, 2023.
68. Morita S, Horii T, Kimura M, Arai Y, Kamei Y, Ogawa Y and Hatada I: Paternal allele influences high fat diet-induced obesity. PLoS One 9: e85477, 2014.
69. Gawronska-Kozak B, Walendzik K, Machcinska S, Padzik A, Kopcewicz M and Wiśniewska J: Dermal white adipose tissue (dWAT) is regulated by foxn1 and Hif-1α during the early phase of skin wound healing. Int J Mol Sci 23: 257, 2021.
70. D'Souza A, Fordjour L, Ahmad A, Cai C, Kumar D, Valencia G, Aranda JV and Beharry KD: Effects of probiotics, prebiotics, and synbiotics on messenger RNA expression of caveolin-1, NOS, and genes regulating oxidative stress in the terminal ileum of formula-fed neonatal rats. Pediatr Res 67: 526-531, 2010.
71. Kooijman R, Van Buul-Offers S, Scholtens L, Reijnen-Gresnigt R and Zegers B: T and B cell development in pituitary deficient insulin-like growth factor-II transgenic dwarf mice. J Endocrinol 155: 165-170, 1997.
72. Yang G, Geng XR, Song JP, Wu Y, Yan H, Zhan Z, Yang L, He W, Liu ZQ, Qiu S, *et al*: Insulin-like growth factor 2 enhances regulatory T-cell functions and suppresses food allergy in an experimental model. J Allergy Clin Immunol 133: 1702-1708.e5, 2014.
73. Machhi J, Kevadiya BD, Muhammad IK, Herskovitz J, Olson KE, Mosley RL and Gendelman HE: Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. Mol Neurodegener 15: 32, 2020.
74. Geng XR, Yang G, Li M, Song JP, Liu ZQ, Qiu S, Liu Z and Yang PC: Insulin-like growth factor-2 enhances functions of antigen (Ag)-specific regulatory B cells. J Biol Chem 289: 17941-17950, 2014.
75. Kaltsas A: Oxidative Stress and Male Infertility: The protective role of antioxidants. Medicina (Kaunas) 59: 1769, 2023.
76. Malik J, Choudhary S, Mandal SC, Sarup P and Pahuja S: Oxidative stress and male infertility: Role of herbal drugs. Adv Exp Med Biol 1391: 137-159, 2022.
77. Das S, Roychoudhury S, Dey A, Jha NK, Kumar D, Roychoudhury S, Slama P and Kesari KK: Bacteriospermia and male infertility: Role of oxidative stress. Adv Exp Med Biol 1358: 141-163, 2022.
78. Tremellen K: Oxidative stress and male infertility-a clinical perspective. Hum Reprod Update 14: 243-258, 2008.
79. Agarwal A, Prabakaran S and Allamaneni S: What an andrologist/urologist should know about free radicals and why. Urology 67: 2-8, 2006.
80. Li YR and Trush M: Defining ROS in biology and medicine. React Oxyg Species 1: 9-21, 2016.
81. Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M and Telser J: Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39: 44-84, 2007.
82. Dorostghoal M, Kazeminejad SR, Shahbazian N, Pourmehdi M and Jabbari A: Oxidative stress status and sperm DNA fragmentation in fertile and infertile men. Andrologia 49: e12762, 2017.
83. Aitken RJ, Gibb Z, Mitchell LA, Lambourne SR, Connaughton HS and De Iuliis GN: Sperm motility is lost in vitro as a consequence of mitochondrial free radical production and the generation of electrophilic aldehydes but can be significantly rescued by the presence of nucleophilic thiols. Biol Reprod 87: 110, 2012.
84. Bui AD, Sharma R, Henkel R and Agarwal A: Reactive oxygen species impact on sperm DNA and its role in male infertility. Andrologia 50: e13012, 2018.
85. Aitken RJ, De Iuliis GN, Finnie JM, Hedges A and McLachlan RI: Analysis of the relationships between oxidative stress, DNA damage and sperm vitality in a patient population: Development of diagnostic criteria. Hum Reprod 25: 2415-2426, 2010.
86. Muratori M, Tamburrino L, Marchiani S, Cambi M, Olivito B, Azzari C, Forti G and Baldi E: Investigation on the origin of Sperm DNA fragmentation: Role of apoptosis, immaturity and oxidative stress. Mol Med 21: 109-122, 2015.
87. Scorrano L and Korsmeyer SJ: Mechanisms of cytochrome c release by proapoptotic BCL-2 family members. Biochem Biophys Res Commun 304: 437-444, 2003.
88. Morse PT, Arroum T, Wan J, Pham L, Vaishnav A, Bell J, Pavelich L, Malek MH, Sanderson TH, Edwards BFP and Hüttemann M: Phosphorylations and acetylations of cytochrome c control mitochondrial respiration, mitochondrial membrane potential, energy, ROS, and apoptosis. Cells 13: 493, 2024.
89. Gui W, Zhu Y, Sun S, Zhu W, Tan B, Zhao H, Shang C, Zheng F, Lin X and Li H: Knockdown of insulin-like growth factor 2 gene disrupts mitochondrial functions in the liver. J Mol Cell Biol 13: 543-555, 2021.
90. Zhu Y, Gui W, Tan B, Du Y, Zhou J, Wu F, Li H and Lin X: IGF2 deficiency causes mitochondrial defects in skeletal muscle. Clin Sci (Lond) 135: 979-990, 2021.
91. Ni W, Pan C, Pan Q, Fei Q, Huang X and Zhang C: Methylation levels of IGF2 and KCNQ1 in spermatozoa from infertile men are associated with sperm DNA damage. Andrologia 51: e13239, 2019.
92. Darbandi M, Darbandi S, Agarwal A, Baskaran S, Dutta S, Sengupta P, Khorram Khorshid HR, Esteves S, Gilany K, Hedayati M, *et al*: Reactive oxygen species-induced alterations in H19-Igf2 methylation patterns, seminal plasma metabolites, and semen quality. J Assist Reprod Genet 36: 241-253, 2019.
93. Ness JK, Scaduto RC and Wood TL: IGF-I prevents glutamate-mediated bax translocation and cytochrome C release in O4+ oligodendrocyte progenitors. Glia 46: 183-194, 2004.
94. Garcia-Fernandez M, Sierra I, Puche JE, Guerra L and Castilla-Cortazar I: Liver mitochondrial dysfunction is reverted by insulin-like growth factor II (IGF-II) in aging rats. J Transl Med 9: 123, 2011.
95. Castilla-Cortázar I, García-Fernández M, Delgado G, Puche JE, Sierra I, Barhoum R and González-Barón S: Hepatoprotection and neuroprotection induced by low doses of IGF-II in aging rats. J Transl Med 9: 103, 2011.
96. Martin-Montañez E, Pavia J, Santin LJ, Boraldi F, Estivill-Torrus G, Aguirre JA and Garcia-Fernandez M: Involvement of IGF-II receptors in the antioxidant and neuroprotective effects of IGF-II on adult cortical neuronal cultures. Biochim Biophys Acta 1842: 1041-1051, 2014.
97. Pagan ML, Radhakrishnan VK and Leon DD: Abstract 4421: IGF2 regulates mitochondrial cell energy phenotype and biogenesis in TNBC cells. Cancer Res 77: 4421, 2017.
98. Darbandi M, Darbandi S, Agarwal A, Sengupta P, Durairajanayagam D, Henkel R and Sadeghi MR: Reactive oxygen species and male reproductive hormones. Reprod Biol Endocrinol 16: 87, 2018.
99. Martín-Montañez E, Millon C, Boraldi F, Garcia-Guirado F, Pedraza C, Lara E, Santin LJ, Pavia J and Garcia-Fernandez M: IGF-II promotes neuroprotection and neuroplasticity recovery in a long-lasting model of oxidative damage induced by glucocorticoids. Redox Biol 13: 69-81, 2017.
100. Soldani R, Cagnacci A and Yen SS: Insulin, insulin-like growth factor I (IGF-I) and IGF-II enhance basal and gonadotrophin-releasing hormone-stimulated luteinizing hormone release from rat anterior pituitary cells in vitro. Eur J Endocrinol 131: 641-645, 1994.
101. Santiago J, Santos MAS, Fardilha M and Silva JV: Stress response pathways in the male germ cells and gametes. Mol Hum Reprod 26: 1-13, 2020.
102. Liu M, Chen Z and Chen L: Endoplasmic reticulum stress: A novel mechanism and therapeutic target for cardiovascular diseases. Acta Pharmacol Sin 37: 425-443, 2016.

103. Hwang J and Qi L: Quality control in the endoplasmic reticulum: Crosstalk between ERAD and UPR pathways. Trends Biochem Sci 43: 593-605, 2018.
104. Ron D and Walter P: Signal integration in the endoplasmic reticulum unfolded protein response. Nat Rev Mol Cell Biol 8: 519-529, 2007.
105. Samanta L, Sharma R, Cui Z and Agarwal A: Proteomic analysis reveals dysregulated cell signaling in ejaculated spermatozoa from infertile men. Asian J Androl 21: 121-130, 2019.
106. Wang J, Yang X and Zhang J: Bridges between mitochondrial oxidative stress, ER stress and mTOR signaling in pancreatic β cells. Cell Signal 28: 1099-1104, 2016.
107. Busada JT, Niedenberger BA, Velte EK, Keiper BD and Geyer CB: Mammalian target of rapamycin complex 1 (mTORC1) Is required for mouse spermatogonial differentiation in vivo. Dev Biol 407: 90-102, 2015.
108. Jiang X, Chen H, Cui Z, Yin L, Zhang WL, Liu WB, Han F, Ao L, Cao J and Liu JY: Low-dose and combined effects of oral exposure to bisphenol A and diethylstilbestrol on the male reproductive system in adult Sprague-Dawley rats. Environ Toxicol Pharmacol 43: 94-102, 2016.
109. Huang KH, Weng TI, Huang HY, Huang KD, Lin WC, Chen SC and Liu SH: Honokiol attenuates torsion/detorsion-induced testicular injury in rat testis by way of suppressing endoplasmic reticulum stress-related apoptosis. Urology 79: 967.e5-967.e11, 2012.
110. Li Y, Zhao W, Fu R, Ma Z, Hu Y, Liu Y and Ding Z: Endoplasmic reticulum stress increases exosome biogenesis and packaging relevant to sperm maturation in response to oxidative stress in obese mice. Reprod Biol Endocrinol 20: 161, 2022.
111. Ge X, He Z, Cao C, Xue T, Jing J, Ma R, Zhao W, Liu L, Jueraitetibaike K, Ma J, *et al*: Protein palmitoylation-mediated palmitic acid sensing causes blood-testis barrier damage via inducing ER stress. Redox Biol 54: 102380, 2022.
112. García-Huerta P, Troncoso-Escudero P, Wu D, Thiruvalluvan A, Cisternas-Olmedo M, Henríquez DR, Plate L, Chana-Cuevas P, Saquel C, Thielen P, *et al*: Insulin-like growth factor 2 (IGF2) protects against Huntington's disease through the extracellular disposal of protein aggregates. Acta Neuropathol 140: 737-764, 2020.
113. Fertan E, Gendron WH, Wong AA, Hanson GM, Brown RE and Weaver ICG: Noncanonical regulation of imprinted gene Igf2 by amyloid-beta 1-42 in Alzheimer's disease. Sci Rep 13: 2043, 2023.
114. Dunlop EA and Tee AR: Mammalian target of rapamycin complex 1: Signalling inputs, substrates and feedback mechanisms. Cell Signal 21: 827-835, 2009.
115. Xu H, Shen L, Chen X, Ding Y, He J, Zhu J, Wang Y and Liu X: mTOR/P70S6K promotes spermatogonia proliferation and spermatogenesis in Sprague Dawley rats. Reprod Biomed Online 32: 207-217, 2016.
116. Qin L, Wang Z, Tao L and Wang Y: ER stress negatively regulates AKT/TSC/mTOR pathway to enhance autophagy. Autophagy 6: 239-247, 2010.
117. Yuan F, Li Y, Zhou X, Meng P and Zou P: Spatially resolved mapping of proteome turnover dynamics with subcellular precision. Nat Commun 14: 7217, 2023.
118. Zhang B, Brahma RK, Zhu L, Feng J, Hu S, Qian L, Du S, Yao SQ and Ge J: Insulin-like Growth Factor 2 (IGF2)-fused lysosomal targeting chimeras for degradation of extracellular and membrane proteins. J Am Chem Soc 145: 24272-24283, 2023.
119. Marques CJ, Carvalho F, Sousa M and Barros A: Genomic imprinting in disruptive spermatogenesis. Lancet 363: 1700-1702, 2004.
120. Cannarella R, Mancuso F, Arato I, Lilli C, Bellucci C, Gargaro M, Curto R, Aglietti MC, La Vignera S, Condorelli RA, *et al*: Sperm-carried IGF2 downregulated the expression of mitogens produced by Sertoli cells: A paracrine mechanism for regulating spermatogenesis? Front Endocrinol 13: 1010796, 2022.
121. Marques CJ, Costa P, Vaz B, Carvalho F, Fernandes S, Barros A and Sousa M: Abnormal methylation of imprinted genes in human sperm is associated with oligozoospermia. Mol Hum Reprod 14: 67-74, 2008.
122. Kobayashi H, Sato A, Otsu E, Hiura H, Tomatsu C, Utsunomiya T, Sasaki H, Yaegashi N and Arima T: Aberrant DNA methylation of imprinted loci in sperm from oligospermic patients. Hum Mol Genet 16: 2542-2551, 2007.
123. Mellott TJ, Pender SM, Burke RM, Langley EA and Blusztajn JK: IGF2 ameliorates amyloidosis, increases cholinergic marker expression and raises BMP9 and neurotrophin levels in the hippocampus of the APPswePS1dE9 Alzheimer's disease model mice. PLoS One 9: e94287, 2014.
124. Santi D, Lotti F, Sparano C, Rastrelli G, Isidori AM, Pivonello R, Barbonetti A, Salonia A, Minhas S, Krausz C, *et al*: Does an increase in adipose tissue 'weight' affect male fertility? A systematic review and meta-analysis based on semen analysis performed using the WHO 2010 criteria. Andrology 12: 123-136, 2024.
125. Reverchon M, Maillard V, Froment P, Ramé C and Dupont J: Adiponectin and resistin: a role in the reproductive functions? Med Sci (Paris) 29: 417-424, 2013 (In French).
126. Lu JC, Jing J, Yao Q, Fan K, Wang GH, Feng RX, Liang YJ, Chen L, Ge YF and Yao B: Relationship between lipids levels of serum and seminal plasma and semen parameters in 631 Chinese subfertile men. PLoS One 11: e0146304, 2016.
127. Ameratunga D, Gebeh A and Amoako A: Obesity and male infertility. Best Pract Res Clin Obstet Gynaecol 90: 102393, 2023.
128. Katib A: Mechanisms linking obesity to male infertility. Cent Eur J Urol 68: 79-85, 2015.
129. Leisegang K, Sengupta P, Agarwal A and Henkel R: Obesity and male infertility: Mechanisms and management. Andrologia 53: e13617, 2021.
130. Erdemir F, Atilgan D, Markoc F, Boztepe O, Suha-Parlaktas B and Sahin S: The effect of diet induced obesity on testicular tissue and serum oxidative stress parameters. Actas Urol Esp 36: 153-159, 2012 (In Spanish).
131. Fan Y, Liu Y, Xue K, Gu G, Fan W, Xu Y and Ding Z: Diet-induced obesity in male C57BL/6 mice decreases fertility as a consequence of disrupted blood-testis barrier. PLoS One 10: e0120775, 2015.
132. Maghsoumi-Norouzabad L, Zare Javid A, Aiiashi S, Hosseini SA, Dadfar M, Bazyar H and Dastoorpur M: The impact of obesity on various semen parameters and sex hormones in iranian men with infertility: A Cross-Sectional study. Res Rep Urol Volume 12: 357-365, 2020.
133. Zhang W, Tian Z, Qi X, Chen P, Yang Q, Guan Q, Ye J and Yu C: Switching from high-fat diet to normal diet ameliorate BTB integrity and improve fertility potential in obese male mice. Sci Rep 13: 14152, 2023.
134. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS and Obin MS: Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J Lipid Res 46: 2347-2355, 2005.
135. Demirci T and Sahin E: The effect of chronic stress and obesity on sperm quality and testis histology in male rats; a morphometric and immunohistochemical study. Histol Histopathol 34: 287-302, 2018.
136. Zhou X and You S: Rosiglitazone inhibits hepatic insulin resistance induced by chronic pancreatitis and IKK-β/NF-κB expression in liver. Pancreas 43: 1291-1298, 2014.
137. Odle AK, Akhter N, Syed MM, Allensworth-James ML, Beneš H, Melgar Castillo AI, MacNicol MC, MacNicol AM and Childs GV: Leptin regulation of gonadotrope Gonadotropin-releasing hormone receptors as a metabolic checkpoint and gateway to reproductive competence. Front Endocrinol (Lausanne) 8: 367, 2018.
138. Alves MG, Martins AD, Cavaco JE, Socorro S and Oliveira PF: Diabetes, insulin-mediated glucose metabolism and Sertoli/blood-testis barrier function. Tissue Barriers 1: e23992, 2013.
139. Alfarhan MW, Al-Hussaini H and Kilarkaje N: Role of PPAR-γ in diabetes-induced testicular dysfunction, oxidative DNA damage and repair in leptin receptor-deficient obese type 2 diabetic mice. Chem-Biol Interact 361: 109958, 2022.
140. Faienza MF, Santoro N, Lauciello R, Calabrò R, Giordani L, Di Salvo G, Ventura A, Delvecchio M, Perrone L, Del Giudice EM and Cavallo L: IGF2 gene variants and risk of hypertension in obese children and adolescents. Pediatr Res 67: 340-344, 2010.
141. Sandhu MS, Gibson JM, Heald AH, Dunger DB and Wareham NJ: Low Circulating IGF-II concentrations predict weight gain and obesity in humans. Diabetes 52: 1403-1408, 2003.
142. Heald AH, Kärvestedt L, Anderson SG, McLaughlin J, Knowles A, Wong L, Grill V, Cruickshank JK, White A, Gibson JM and Brismar K: Low Insulin-like Growth Factor-II levels predict weight gain in normal weight subjects with type 2 diabetes. Am J Med 119: 167.e9-e15, 2006.
143. Miyaso H, Ogawa Y and Itoh M: Microenvironment for spermatogenesis and sperm maturation. Histochem Cell Biol 157: 273-285, 2022.

144. Griffeth RJ, Bianda V and Nef S: The emerging role of insulin-like growth factors in testis development and function. Basic Clin Androl 24: 12, 2014.
145. Murphy R, Ibáñez L, Hattersley A and Tost J: IGF2/H19 hypomethylation in a patient with very low birthweight, precocious pubarche and insulin resistance. BMC Med Genet 13: 42, 2012.
146. Calderari S, Gangnerau MN, Thibault M, Meile MJ, Kassis N, Alvarez C, Portha B and Serradas P: Defective IGF2 and IGF1R protein production in embryonic pancreas precedes beta cell mass anomaly in the Goto-Kakizaki rat model of type 2 diabetes. Diabetologia 50: 1463-1471, 2007.
147. Lee KL, Aitken JF, Li X, Montgomery K, Hsu HL, Williams GM, Brimble MA and Cooper GJS: Vesiculin derived from IGF-II drives increased islet cell mass in a mouse model of pre-diabetes. Islets 14: 14-22, 2022.
148. Feinberg AP, Koldobskiy MA and Göndör A: Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. Nat Rev Genet 17: 284-299, 2016.
149. Gaunt TR: Positive associations between single nucleotide polymorphisms in the IGF2 gene region and body mass index in adult males. Hum Mol Genet 10: 1491-1501, 2001.
150. Kadlecová M, Dobešová Z, Zicha J and Kuneš J: Abnormal Igf2 gene in Prague hereditary hypertriglyceridemic rats: Its relation to blood pressure and plasma lipids. Mol Cell Biochem 314: 37-43, 2008.
151. Alfares MN, Perks CM, Hamilton-Shield JP and Holly JMP: Insulin-like growth factor-II in adipocyte regulation: Depot-specific actions suggest a potential role limiting excess visceral adiposity. Am J Physiol Endocrinol Metab 315: E1098-E1107, 2018.
152. Rossetti L, Barzilai N, Chen W, Harris T, Yang D and Rogler CE: Hepatic overexpression of insulin-like growth factor-II in adulthood increases basal and insulin-stimulated glucose disposal in conscious mice. J Biol Chem 271: 203-208, 1996.
153. Back N, Cohen IR, Lajtha A, Lambris JD, Paoletti R, O'Bryan MK and Hedger MP: Inflammatory networks in the control of spermatogenesis: Chronic inflammation in an immunologically privileged tissue? Adv Exp Med Biol 636: 92-114, 2009.
154. Okabayashi Y, Maddux BA, McDonald AR, Logsdon CD, Williams JA and Goldfine ID: Mechanisms of insulin-induced insulin-receptor downregulation. Decrease of receptor biosynthesis and mRNA levels. Diabetes 38: 182-187, 1989.
155. Suh HS, Zhao ML, Derico L, Choi N and Lee SC: Insulin-like growth factor 1 and 2 (IGF1, IGF2) expression in human microglia: Differential regulation by inflammatory mediators. J Neuroinflamm 10: 805, 2013.
156. Martin-Montañez E, Pavia J, Santin LJ, Boraldi F, Estivill-Torrus G, Aguirre JA and Garcia-Fernandez M: Involvement of IGF-II receptors in the antioxidant and neuroprotective effects of IGF-II on adult cortical neuronal cultures. Biochim Biophys Acta 1842: 1041-1051, 2014.