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

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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.

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1. Introduction

The World Health Organization (WHO) defines infertility as the inability to conceive spontaneously within a year

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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

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.

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
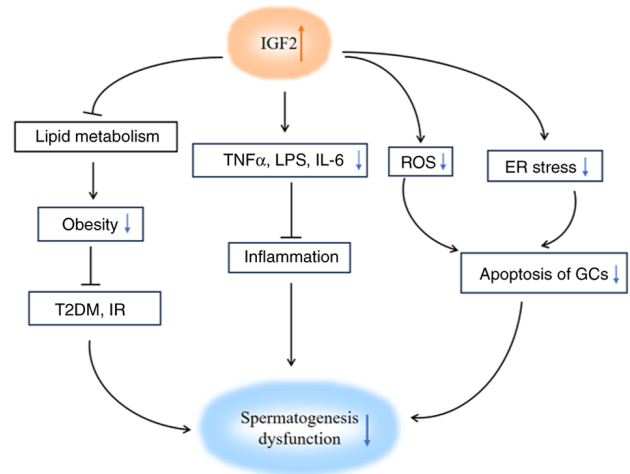

Figure 1. Diagram demonstrating the potential link between IGF2 and spermatogenesis dysfunction. Blue arrows represent a decrease, red arrows represent an increase, solid arrows represent an effect on downstream factors, t-shaped arrows represent an inhibitory effect. IGF2, insulin-like growth factor 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.

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.

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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.

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Competing interests

The authors declare that they have no competing interests.

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