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Exploring the Rationale of Kidney-Tonifying Method for Spermatogenesis Disorder in Type 2 Diabetes Mellitus from the Hypothalamic-Pituitary-Gonadal Axis: A Postprint

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Abstract

Diabetes mellitus (DM) hyperglycemic pathological state constitutes one of the important factors leading to male spermatogenic dysfunction. The hypothalamic-pituitary-gonadal (HPG) axis serves as a crucial hub for the body' s systemic vegetative functions and neuroendocrine network, physiologically governing human reproduction and growth/development while being pathologically susceptible to DM hyperglycemic pathological states, thereby representing one of the key mechanisms in the pathogenesis of spermatogenic dysfunction in type 2 diabetes mellitus (T2DM). Kidney deficiency represents a common etiology and pathogenesis for both spermatogenic dysfunction and T2DM. The function of "governing reproduction and generating marrow to fill the brain" manifested by kidney storing essence resembles HPG axis function, and kidney-tonifying therapy exerts regulatory and improving effects on HPG axis function, thus establishing the theoretical foundation for treating T2DM-induced spermatogenic dysfunction with kidney-tonifying methods. Classic kidney-tonifying formulas demonstrate complementary therapeutic efficacy in treating both DM and spermatogenic dysfunction, providing approaches and methodologies for the clinical prevention and treatment of infertility resulting from T2DM-induced spermatogenic dysfunction through kidney-tonifying therapy.

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Full Text

The Idea of Kidney Tonifying Therapy for Spermatogenesis Disorder in Type 2 Diabetes Based on the Hypothalamic-Pituitary-Gonadal Axis

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Abstract

Diabetic hyperglycemia in males is a significant contributing factor to the development of spermatogenesis disorder. The hypothalamic-pituitary-gonadal (HPG) axis serves as a crucial center for autonomic sexual function and the neuroendocrine network within the human body. It dominates physiological prominence in human reproduction, growth, and development, while also being susceptible to hyperglycemia, which is one of the key mechanisms in the development of spermatogenic disorder in type 2 diabetes mellitus (T2DM). This mechanism involves kidney deficiency, which is a common etiology and pathogenesis of both spermatogenesis disorder and T2DM. The kidney storing essence, which encompasses the functions of "dominating reproduction, manufacturing marrow to fill up the brain,"bears similarities to the HPG axis. Kidney tonifying therapy can regulate and improve the function of HPG axis, thereby establishing a theoretical basis for the use of kidney tonification therapy in the treatment of spermatogenesis disorder in T2DM. The traditional formula of tonifying the kidney can serve as a complementary treatment for both DM and spermatogenesis disorder. This approach offers a conceptual framework and methodology for the prevention and treatment of T2DM-induced infertility through kidney tonification.

Key words: Hypothalamo-hypophyseal system; Diabetes mellitus, type 2; Dyszoospermia; Reinforcing kidney; Theoretical discussion

Spermatogenesis disorder refers to abnormal spermatogenic function in the

testes, representing the primary mechanism of male infertility and falling under the TCM categories of "childlessness" or "no offspring." Testicular spermatogenic dysfunction denotes a decline in spermatogenic capacity of the germinal epithelium (or spermatogenic tissue) within the testes due to multiple factors, where spermatogenic cell development is obstructed, leading to oligospermia or azoospermia [1]. Diabetes mellitus (DM) is a common chronic metabolic disease clinically, primarily classified into type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with hyperglycemia as its main pathological manifestation, corresponding to the TCM category of "xiao-ke" (consumptive thirst). Research statistics indicate [2] that the number of adults (20-79 years) diagnosed with DM increased from 285 million in 2009 to 463 million in 2019, with T2DM accounting for 95% of cases. Beyond its primary pathology, DM complications can cause varying degrees of pathological changes and damage to multiple organs and systems throughout the body. Studies have confirmed that male reproductive system dysfunction represents a significant complication of DM, leading to decreased semen quality with particularly adverse effects on sperm motility, sperm DNA integrity, and seminal plasma composition [3-4]; it can also damage testicular structure and function [5], resulting in male infertility. Traditional Chinese medicine demonstrates distinctive advantages in preventing and treating both DM and spermatogenesis disorder, yet comprehensive treatment approaches are rarely reported. Modern medicine typically employs separate medications or other methods for DM or spermatogenesis disorder, lacking integrated therapeutic drugs or protocols. Treatment strategies and formulations for DM-induced spermatogenesis disorder urgently require further investigation. Based on TCM theory and modern mechanisms, this paper analyzes the feasibility and effectiveness of kidney-tonifying therapy from the perspective of the hypothalamic-pituitary-gonadal (HPG) axis to provide clinical treatment insights.

1. The HPG Axis as the Most Important Regulatory Center for Human Reproduction

The HPG axis participates in regulating human development, reproduction, and aging [6]. It serves as both the autonomic functional center of the entire body and a hub of the neuroendocrine network. Gonadotropin-releasing hormone (GnRH/LHRH) secreted by the hypothalamus can induce the expression of pituitary gonadotropins, including follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The testes are the most important spermatogenic organ in males, and spermatogenic function is regulated by the HPG axis. FSH promotes sperm production and androgen-binding protein generation by acting on spermatogenic cells and Sertoli cells in the testes, while LH primarily acts on Leydig cells to promote testosterone secretion. The complex inter-regulatory mechanisms among hormones released by the three major organs of the HPG axis constitute a closed-loop negative feedback system to maintain normal reproductive function. Hypogonadism and testicular dysfunction are closely related to the HPG axis, with primary mechanisms including reduced GnRH secretion

from the hypothalamus, disrupted rhythms; diminished pituitary response to GnRH, impaired LH secretory function, disrupted testosterone (T) circadian rhythm, and decreased Leydig cell function [7].

Hormonal regulation plays a crucial role throughout sperm production, development, maturation, and excretion, and this role is mediated through the HPG axis. The HPG axis is a vital regulatory center for maintaining human reproduction and development, with human fertility largely dependent on its regulation. As early as the 1990s, TCM scholars proposed that HPG axis function resembles the role of kidney essence storage and reproduction domination in TCM theory [8].

2. DM-Induced HPG Axis Disorder as an Important Mechanism of Spermatogenesis Disorder

The mechanisms through which DM leads to spermatogenesis disorder are multifaceted and complex. DM-induced spermatogenesis disorder through HPG axis disruption represents a significant mechanism, with numerous studies reported domestically and internationally. Male DM patients exhibit reduced gonadotropin responses to appropriate stimuli, abnormal ejaculation and sperm, likely due to DM directly affecting the testes [9], resulting in severe structural defects in sperm. Hyperglycemia in DM patients can directly adversely affect the HPG axis, leading to reduced sex hormone secretion and gonadal disease, possibly by inhibiting hypothalamic gonadotropin release, thereby decreasing LH pulse frequency and basal testosterone secretion [10]. Clinical studies have also found that most T2DM patients present with insulin resistance and reduced total testosterone levels, which to some extent results from decreased sex hormone-binding globulin caused by insulin resistance and hyperinsulinemia [11]. Regarding spermatogenesis itself, high testosterone concentrations are required, with testosterone secretion regulated by the HPG axis: after hypothalamic LH release, Leydig cells in testicular seminiferous tubules are stimulated to produce and secrete androgens, ensuring proper spermiation for mature sperm [12]. Research has found that hyperlipidemia induced by high-fat diet feeding affects the content of androgen-binding protein secreted by Sertoli cells, leading to insufficient testosterone within seminiferous tubules, obstructing spermatogenesis, while also causing reduced testicular weight and significantly decreased sperm count and motility.

Semen volume, motility, viability, and abnormality rate represent important parameters for assessing spermatogenic function and sperm quality [13]. Human semen studies demonstrate that DM hyperglycemia not only reduces sperm quality but also adversely affects gene expression repair processes in spermatogenic cell DNA, ultimately causing DNA nuclear fragmentation and mitochondrial DNA deletion, with multiple factors directly affecting fertility [14].

Thus, DM hyperglycemia can secondarily cause HPG axis physiological dysfunction, leading to spermatogenesis disorder. The hyperglycemic state itself

can affect testicular structure and spermatogenic function. In a study of clinically commonly used DM medications [15], metformin may improve erectile dysfunction by inhibiting HPG axis function; rosiglitazone can increase T levels in T2DM male patients to enhance ejaculatory pleasure; glimepiride shows no significant effect on prolactin, FSH, LH, or T levels, but patients easily experience decreased libido. Although relevant studies have indicated that oral hypoglycemic agents can affect HPG axis function and sexual function, conclusions remain controversial and require more in-depth research for exploration and verification.

3. Theoretical Basis and Application Research of Kidney-Tonifying Therapy for DM Spermatogenesis Disorder via HPG Axis Regulation

3.1 Kidney Deficiency as a Common Etiology of Spermatogenesis Disorder and Diabetes The TCM theory of kidney governing reproduction originates from the *Huangdi Neijing*. The *Suwen · Liu Jie Cang Xiang Lun* states: "The kidney is the organ of storage, the foundation of containment, and the residence of essence." The *Suwen · Shanggu Tianzhen Lun* notes: "When kidney qi is abundant, tian-gui arrives, essence and qi overflow and are discharged, yin and yang harmonize, thus enabling procreation." The kidney stores essence and governs growth, development, and reproduction, representing the functional manifestation of kidney essence transforming into kidney qi. From a modern TCM clinical perspective, although the etiology and pathogenesis of male spermatogenesis disorder are complex, treatment is primarily approached from kidney deficiency [16]. Furthermore, modern research has confirmed the phenomenon of spermatogenesis disorder in kidney-deficient animals [17]; clinically, treating male infertility patients with oligospermia using TCM kidney-tonifying and essence-generating methods can significantly improve sperm density and quality [18].

Similarly, TCM' s understanding of DM first appears in the *Huangdi Neijing*. The disease name "xiao-ke" (consumptive thirst) first emerged in *Suwen · Qi Bing Lun*: "When the five flavors enter the mouth and are stored in the stomach, the spleen transports their essence and fluid···obesity generates internal heat, sweetness generates central fullness, thus causing qi to overflow upward and transform into xiao-ke." As *Lingshu · Wu Bian* states: "When the five viscera are all weak and soft, they are prone to xiao-dan (consumptive fever)." TCM attributes its etiology and pathogenesis primarily to the lung, spleen, and kidney, with the kidney being particularly critical. Qing dynasty physician Chen Shiduo wrote in *Shishi Milu*: "Although xiao-ke symptoms have upper, middle, and lower distinctions, they all stem from insufficient kidney water." Congenital endowment deficiency represents the key internal cause of xiao-ke onset and development, consistent with Eastern Jin dynasty physician Chen Yanzhi' s statement in *Xiao Pin Fang* that "xiao-ke originates from kidney deficiency." Research on TCM syndrome types in T2DM patients [19] shows common patterns include qi-yin deficiency, phlegm-heat intermingling, blood stasis in collaterals,

and yin-yang deficiency. Xiao-ke initially presents as mixed deficiency-excess, later transforming from excess to deficiency, with yin-yang deficiency as the final stage. Prolonged xiao-ke inevitably damages the kidney, exhausting kidney essence, with yin damage affecting yang, ultimately leading to kidney qi deficiency. Animal experiments demonstrate [20] that long-term chronic hyperglycemia in T2DM causes renal capillary endothelial injury, glomerular basement membrane thickening, and renal interstitial fibrosis, ultimately increasing afferent arteriole resistance and reducing renal blood flow.

Thus, insufficient kidney essence and kidney yin deficiency represent one of the common pathogeneses of male spermatogenesis disorder and DM. Under the guidance of TCM' s "treating the root cause" and "treating different diseases with the same method" principles, addressing both conditions through kidney treatment can comprehensively manage DM hyperglycemia and testicular spermatogenesis disorder, improving sperm quality in DM patients.

3.2 Kidney-Tonifying Therapy' s Regulatory and Improving Effects on HPG Axis Function TCM conceptualizes the "brain-kidney-tian-gui-chong-ren-uterus" axis as the hub of human reproductive function, equivalent to the neuroendocrine network' s "hypothalamic-pituitary-gonadal axis" [21]. The TCM "brain" governs mental activities and sensory functions, similar to the Western medicine "brain." The *Lingshu · Jing Mai* states: "When a human begins life, essence forms first, then the brain marrow generates," leading to the TCM concept that "kidney stores essence, generates marrow, and connects to the brain," and the theory that "all marrow belongs to the brain, and the brain is the sea of marrow" (Zhang Jingyue, *Lei Jing · Jing Luo Lei · Ren Zhi Si Hai*). Insufficient kidney essence and deficient kidney qi result in empty brain marrow. Therefore, kidney deficiency can directly affect brain physiological function, with varying degrees of changes in gonadal axis hormone levels potentially closely related to HPG axis dysfunction.

Research investigating the regulatory mechanisms and effects of kidney-tonifying formulas on neuroendocrine and reproductive functions has revealed that kidney deficiency syndromes (kidney yin deficiency or kidney yang deficiency) primarily manifest as HPG axis functional disorders, leading to hormone secretion disturbances [22]; HPG axis hypofunction can cause exercise-induced low blood testosterone, while application of kidney-tonifying Chinese herbs can increase gonadal hormone content in exercise-induced low testosterone rats, maintaining normal physiological function of the HPG axis and preserving the normal ultrastructure of cells at all levels of the gonadal axis [23]; the kidney yin-yang balancing herb pair "Epimedium-Ligustrum" can upregulate GnRH, T, and serum estradiol (E2) levels while downregulating LH and FSH levels, improving HPG axis function, promoting sex hormone secretion, and regulating reproductive endocrine system function [6]; pharmacological experiments observing Jin Gui Shen Qi Wan' s effects on calmodulin (CaM) ribonucleic acid expression in the hypothalamus, pituitary, and testes of kidney

yang deficiency model rats indicate that Jin Gui Shen Qi Wan can reverse inhibited sex hormone E2 content and stimulate increased hormone T content by regulating calmodulin gene expression in the HPG axis, thereby improving kidney yang deficiency states in rats [24]. Additionally, TCM acupuncture kidney-tonifying methods can correct related hormone disorders in the HPG axis, improve gonadal tissue structure and function, and adjust HPG axis imbalance [25]. Wang Qian et al. [26] found that moxibustion can improve ovarian organ indices, ameliorate ovarian tissue morphology, and effectively restore ovarian function in rats with diminished ovarian reserve, preventing disease progression toward premature ovarian failure. Furthermore, studies on aged male rats [27] revealed that moxibustion can increase cell layers and numbers within testicular seminiferous tubules of naturally aging rat models; compared with the model group, the moxibustion group showed clearer testicular seminiferous tubule tissue structure and more orderly arrangement of cells at various levels within tubules, suggesting that moxibustion therapy can improve testicular structural changes induced by aging.

Thus, whether based on TCM theoretical foundations or scientific research results, kidney-tonifying therapy demonstrates therapeutic efficacy for neurological, reproductive, and endocrine system diseases caused by HPG axis dysfunction, exhibiting overall favorable regulatory and improving effects on HPG axis function.

3.3 Application Research of Classic Kidney-Tonifying Formulas in Treating DM and Spermatogenesis Disorder Zhang Zhongjing first applied kidney-tonifying therapy to treat DM in the Han dynasty. In *Jin Gui Yao Lue · Xiao Ke Xiao Bian Bu Li Lin Bing Mai Zheng Bing Zhi Di Shi San*, he stated: "For male xiao-ke with excessive urination···Shen Qi Wan governs it," providing classical TCM documentation for kidney-tonifying therapy in xiao-ke treatment. This formula fills yin essence, supplements innate original qi, and employs a small amount of acrid-warm medicinals to "generate qi with minimal fire," assisting "essence transforming into qi," with its function residing not in warming yang but in "filling essence to transform qi" [28]. Kidney qi is the qi transformed from kidney essence, with physiological functions primarily manifested in reproduction, growth, and development. Research shows that Jin Gui Shen Qi Wan can significantly reduce fasting blood glucose and 2-hour postprandial blood glucose levels in DM patients while effectively decreasing adverse drug reactions [29]; it can markedly improve blood glucose levels in yin-yang deficiency-type T2DM patients while effectively controlling blood glucose fluctuation amplitude [30].

The classical formulas "Zuo Gui Wan" and "You Gui Wan" recorded in *Jing Yue Quan Shu · Xin Fang Ba Zhen · Bu Zhen* represent famous kidney-tonifying formulas created by Zhang Jingyue based on the mutual transformation concept of "yang can transform yin, yin can transform yang." Zuo Gui Wan is commonly used to treat male infertility with kidney essence insufficiency or kidney yin

deficiency patterns, often presenting as oligospermia or semen non-liquefaction. Clinical application of Zuo Gui Wan in treating kidney yin deficiency-type male infertility has found increased semen volume, improved sperm density, count, and motility, and elevated testosterone and luteinizing hormone levels [31]; research confirms that Zuo Gui Wan can treat DM by regulating serum total cholesterol, tumor necrosis factor-α, and fasting insulin levels to correct glucose metabolism disorders [32].

Zhang Jingyue stated: "For treating insufficient original yang, or innate endowment decline, or excessive taxation and damage, resulting in life gate fire decline ···or yang deficiency without offspring, all should promptly benefit the fire source to cultivate right kidney original yang, thereby naturally strengthening spirit and qi—this formula governs it." This formula is You Gui Wan, commonly used to treat male infertility with kidney yang insufficiency or kidney qi deficiency patterns, often presenting as asthenospermia or low sperm motility. Research confirms that You Gui Wan can regulate calmodulin gene expression in the HPG axis CaM to alter pathological states, possessing kidney-tonifying and essence-filling functions [33]; modified You Gui Wan demonstrates significant efficacy in treating kidney yang deficiency-type T2DM complicated with osteoporosis, with marked reductions in glycated hemoglobin and fasting blood glucose levels, and notable increases in serum type I procollagen carboxy-terminal peptide and osteocalcin content, possibly related to improved glucose and bone metabolism [34].

One study on comprehensive TCM treatment of DM complicated with spermatogenesis disorder indicated that spleen-benefiting and kidney-tonifying formulas could improve testicular morphology and increase sperm quality by promoting glucose uptake and increasing pancreatic function sensitivity, with the phosphatidylinositol 3-kinase/protein kinase B/B-cell lymphoma-2 pathway playing an important role in this process [35]. Kidney-tonifying formulas have demonstrated therapeutic effects in improving spermatogenic function and sperm quality, as well as ameliorating hyperglycemia and secondary pathologies in DM patients, further confirming the feasibility and effectiveness of kidney-tonifying therapy in comprehensively treating T2DM spermatogenesis disorder through multiple pathways of HPG axis regulation.

Conclusion

Both T2DM and spermatogenesis disorder involve complex etiologies, with insufficient kidney essence and kidney yin deficiency representing important pathogenic factors in their occurrence and development. Guided by TCM's "treating the root cause" principle and "treating different diseases with the same method" approach, combined with modern research advances, this paper has explored the HPG axis as a critical regulatory center for human reproduction whose function is affected by DM hyperglycemia, representing an important mechanism leading to spermatogenesis disorder. Through reviewing literature on the theoretical basis and application research of kidney-tonifying

therapy regulating the HPG axis for DM spermatogenesis disorder, we propose that kidney-tonifying therapy exerts regulatory and improving effects on HPG axis function. Classic kidney-tonifying formulas can reduce blood glucose levels, improve sperm quality, and enhance spermatogenic function in T2DM patients, further substantiating that classic kidney-tonifying formulas can comprehensively treat T2DM spermatogenesis disorder through multiple pathways of HPG axis adjustment, providing feasibility and guidance for clinical treatment. Therefore, clinical management of such conditions should emphasize both syndrome differentiation and treatment and addressing the root cause, offering conceptual frameworks and methodologies for scientific experiments and clinical applications of our research team and other scholars in preventing and treating T2DM spermatogenesis disorder-induced infertility through kidney-tonifying therapy.

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