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# BASIC PRINCIPLES AND METHODS OF MODELING HYPOGONADISM: A LITERATURE REVIEW

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**ABSTRACT** — Purpose: To consider the basic principles and methods of experimental modeling of hypogonadism in laboratory animals, to define the main benefits and drawbacks of each separate method in hypogonadism modeling.
Materials and methods: We analyzed modern foreign and domestic literature using the following databases: PubMed / Medline, Embase, Google Scholar.
Results: Presently, there are three main principles of modeling hypogonadism: surgical, genetic, and pharmacological. The principle of surgical modeling of hypogonadism is based on the removal of the gonads, or on the temporary imposition of a suture on the distal section of the spermatic cord, which leads to occlusion of the testicular artery that feeds the gonads. The principle of genetic modeling of hypogonadism is to induce mutations in the genes encoding the most important regulatory molecules, in particular kisspeptin, neurokinin B, and their receptors in laboratory animals. The principle of pharmacological modeling of hypogonadism is based on the administration of streptozocin to laboratory animals, which has a toxic effect on the gonads and pancreas.
Conclusion: Hypogonadism represents a very common pathological condition that affects many organs and tissues. Therefore, the use of experimental models of hypogonadism to study fundamental pathophysiological and pathomorphological processes is a relevant research area. Each principle of hypogonadism modeling is unique in its own way, exhibits advantages and disadvantages, and allows the creation of specific conditions necessary for the development of hypogonadism in laboratory animals. Taking into account the numerous beneficial effects of testosterone on many cells and tissues of the human body, it becomes obvious that experimental models of hypogonadism can be in demand for many medical spheres.

## INTRODUCTION

Hypogonadism is a clinical and laboratory syndrome that develops as a result of a decrease in the production of the hormone testosterone by the sexual glands of men [5, 21, 31]. Biosynthesis of testosterone by Leydig's cells is controlled by the hypothalamus and pituitary gland, forming the gonadal-pituitary hypothalamic system: gonadotropin-releasing hormone → luteinizing hormone → testosterone. In hypogonadism, the formation of the gonadotropin-releasing hormone and the luteinizing hormone is enhanced by the negative regulatory feedback mechanism [5, 21].

Hypogonadism is classified into several types depending on the level at which the disorder takes place. In primary hypogonadism, testosterone production in the male gonads is disturbed, most often affected by inflammatory or tumor processes, removal, and decrease in activity with age. Primary hypogonadism is also called hypergonadotropic hypogonadism, since low androgen levels through long and short negative regulatory feedback mechanisms stimulate the synthesis of gonadotropin-releasing hormone and luteinizing hormone by the hypothalamus and pituitary gland, respectively. Whereas secondary hypogonadism is caused by the insufficient formation of gonadotropin-releasing hormone and luteinizing hormone as a result of damage to the hypothalamus and pituitary gland, and consequently, insufficient stimulation of the gonads to produce androgens [5, 21, 31].

The clinical picture of hypogonadism depends on the age at which the disease occurs, as well as the form and degree of testosterone deficiency. The testosterone molecule in the human body performs many important functions, so low testosterone levels lead to numerous disorders. To a greater extent, hypogonadism affects the musculoskeletal system, reproductive, nervous, and cardiovascular systems [5, 8, 11, 16–18, 21, 31, 35, 38]. Methods of experimental modeling of hypogonadism in animals are widely used to study the structural and functional disorders of various organs and systems that arise during hypogonadism. Review articles that fully summarize the basic principles and methods of experimental modeling of hypogonadism are not available.

*The purpose* of this review is to discuss the principles and methods of experimental modeling of hypogonadism, to analyze the advantages and drawbacks of certain modeling methods.

An ideal model of hypogonadism should meet the following criteria: persistent impairment of hormonogenic and reproductive functions, technical availability, and low cost of maintenance, as well as the absence of nonspecific (toxic and adverse) effects on other organs and systems when modeling hypogonadism [19]. Currently, there are three main principles of modeling hypogonadism: surgical, pharmacological, and genetic, however, none of them meets all of the above criteria for an ideal model. Below we will take a look at the principles of modeling hypogonadism.

## THE PRINCIPLE OF SURGICAL MODELING OF HYPOGONADISM

Surgical models of hypogonadism are among the most commonly used and are based on surgical removal of the gonads (unilateral or bilateral orchiectomy/gonadectomy) from male animals [7, 13, 15, 25, 43]. Animals are usually anesthetized with xylazine (10 mg/kg body weight) and ketamine (70 mg/kg body weight). The surgical access is achieved through the midsection of the scrotum about 1 cm long. During the operation, the testicles are removed after the spermatic cords are crossed [13]. The disadvantage of this model is the complexity of implementation and the need for qualified surgical personnel. To confirm the simulated conditions, the levels of hormones that make up the gonadal-pituitary hypothalamic system (namely, testosterone, luteinizing hormone) are assessed; evaluation of the mass and size of the gonads, and reproduction capability test are implemented [19].

Native researchers P. Kulikova et al. developed another surgical model of hypogonadism [19]. The principle of this model is based on the temporary ligation of the distal section of the spermatic cord, which leads to partial occlusion of the testicular artery. To establish the optimal time for clamping the spermatic cord, the researchers applied a suture using a surgical needle and thread for a period of one, two, three, and four days (four experimental groups of animals). Serum testosterone concentration was determined using an automatic enzyme-linked immunosorbent assay. A month after the temporary ligation of the spermatic cord, all groups of animals showed a decrease in the weight and linear dimensions of the gonads by 1.5–7 times in comparison with the control group ($p < 0.05$). The minimum time required for the development of persistent hypogonadism, according to the study, comprised 3 days. The testosterone level in these animals was lower than that in the group of intact males, however, the degree of decrease was not significant, which, most likely, was because the suture was applied to only one spermatic cord. The reproduction capability test showed negative results. Ligation for more than 3 days can be dangerous due to the development of pronounced necrotic changes in the testes [19].

## THE PRINCIPLE OF GENETIC MODELING OF HYPOGONADISM

As noted earlier, the production of testosterone by the gonads is inextricably linked to the optimal activity of the hypothalamus and pituitary gland. Deficiency of gonadotropin-releasing hormone or luteinizing hormone leads to decreased testosterone production and is termed hypogonadotropic hypogonadism. Congenital or idiopathic hypogonadotropic hypogonadism, the causes, and mechanisms of which have been unknown for a long time, is most often based on genetic disorders. Over the past few decades, genetic studies have been carried out on patients with idiopathic hypogonadotropic hypogonadism, which have revealed several pathways that affect the migration of neurons that produce the gonadotropin-releasing hormone, as well as the secretion and activity of this hormone [3]. In patients with idiopathic hypogonadotropic hypogonadism, mutations were found in the genes encoding kisspeptin (KISS-1), neurokinin B (TAC3), and their respective receptors (GPR54 and TACR3) [10, 14, 39, 40]. The neuropeptides kisspeptin and neurokinin B, in addition to the third peptide hormone, dynorphin, are co-expressed in a specific cell population of hypothalamic neurons and appear to be critical components that regulate the release of gonadotropin-releasing hormone. The expression of genes encoding the formation of these peptides increases during puberty. It was found that the deficiency of kisspeptin and neurokinin B leads to various manifestations of hypogonadotropic hypogonadism, in particular to the absence of puberty and infertility, both in humans and in animals, which indicates the important role of these hormones in the regulation of puberty [20, 44]. Experimental studies have shown that the administration of kisspeptin stimulates the secretion of gonadotropin-releasing hormone and luteinizing hormone [34].

The use of kisspeptin and neurokinin B-deficient mice models allows for a more in-depth study of the mechanisms by which these neuropeptides regulate hypothalamic control of reproduction. KISS-1 gene knockout in mice led to a sharp drop in the level of free testosterone in blood plasma compared to wild-type mice (<0.17 pg/ml versus 4.1 ± 1.8 pg/ml, respectively). Similarly, plasma levels of luteinizing hormone were significantly lower in KISS-1 knockout male mice than in wild-type mice (0.28 ± 0.01 and 0.42 ± 0.03 ng/ml, respectively) [9]. A key advantage of genetic models of hypogonadism is the ability to

study the role of a particular gene and its product (peptide compound) in the development of this disease. Moreover, these models are indispensable for the study of hereditary hypogonadism and preclinical assessment of the effectiveness of medications under development. At the same time, high-tech and expensive equipment are needed to model idiopathic hypogonadotropic hypogonadism, which becomes a drawback of genetic models.

## THE PRINCIPLE OF PHARMACOLOGICAL MODELING OF HYPOGONADISM

The syndrome of hypogonadism develops in several different ICDs: kidney diseases [41], hepatic and thyroid diseases [30], and very often in diabetes mellitus [22, 23, 42]. The mechanisms of the development of hypogonadism in these diseases are different. Due to the high prevalence and steady increase in the incidence of diabetes mellitus [6], and hypogonadism syndrome in diabetes mellitus, as well as the possibilities of using such data in experimental studies, in this article, we will focus on the mechanisms of hypogonadism development in diabetes mellitus.

The prevalence of hypogonadism in patients with diabetes mellitus averages 37–57% [1]. It is reported that approximately 50% of men with diabetes mellitus have reproductive disorders, including hypogonadism, impaired spermatogenesis, psychosexual dysfunction due to depression associated with chronic disease, and erectile dysfunction [42]. According to a study by Al Hayek et al., 36.5% of men with diabetes mellitus have low testosterone levels. Among these patients with diabetes mellitus and low testosterone levels, 16.9% had symptoms of primary hypogonadism, and 83.1% had secondary hypogonadism [1].

Based on clinical observations on the frequent occurrence of hypogonadism in patients with diabetes mellitus, experimental models of hypogonadism have been developed [33, 37]. To simulate diabetes mellitus and hypogonadism, laboratory animals are injected with streptozocin, an alkylating chemotherapeutic medication. It is seldom used in clinical practice due to its high toxicity to the beta cells of the pancreas. In the experimental study of L. Seethalakshmi, after the administration of streptozocin to rats, a pronounced decrease in body weight and size of reproductive organs, a decrease in the number and motility of spermatozoa, and a decrease in the concentration of serum testosterone and luteinizing hormone were noted. While the introduction of insulin or testosterone led to the restoration of the abovementioned indicators [33]. It is assumed that diabetes mellitus can cause hypogonadism through many mechanisms, affecting various links of the gonadal-pituitary hypothalamic system, including suppression of the secretion of gonadotropin-releasing hormone, testosterone, or direct impairment of spermatogenesis. The introduction of insulin and streptozocin significantly affects the functioning of the gonadal-pituitary hypothalamic system. Normally, the gonadotropin-releasing hormone is secreted by the cells of the median elevation of the hypothalamus into the portal circulation by impulses every 1–2 hours, causing the corresponding impulse secretion of luteinizing hormone by pituitary gonadotropic cells. Since the gonadotropin-releasing hormone is not secreted into the peripheral circulation, the assessment of pulsatile luteinizing hormone secretion is the gold standard for measuring gonadotropin-releasing hormone secretion. The study showed that in diabetes mellitus caused by the administration of streptozocin, the pulsatile secretion of LH in mature male rats is significantly reduced [12]. R Steger and colleague comprehensively studied endocrine and sexual function in adult male rats which undergone insulin therapy twice daily after simulating streptozocin-induced diabetes mellitus. With the introduction of streptozocin (50 mg/kg of animal weight), there is a decrease in the level of testosterone in the blood plasma of laboratory animals by 4 times compared with the control. The introduction of insulin led to the normalization of the pulsatile secretion of luteinizing hormone and testosterone concentration [36].

It is noteworthy that the restoration of ejaculatory function depends on the time of initiation of insulin therapy. Thus, the ejaculatory function in rats was almost completely restored to normal when insulin therapy was carried out timely, but only partially recovered when insulin therapy was carried out 4 weeks after streptozocin injection [36]. These data suggest that insulin signaling plays a critical role in maintaining the reproductive function of the hypothalamus. And a more prolonged inhibition of sexual function by streptozocin injections can reduce the effectiveness of the subsequent normalizing effect of insulin treatment.

Interesting are the observations of researchers regarding the fact that the pulsatile secretion of luteinizing hormone is significantly lower in castrated rats with streptozocin-induced diabetes mellitus compared to castrated rats without the same. There was also a significant decrease in the sensitivity of the pituitary gland to the exogenous gonadotropin-releasing hormone by about 67% in castrated rats with diabetes mellitus compared to control ($p = 0.001$) [12]. This indicates that hypogonadism caused by diabetes mellitus may lead to dysfunction of the pituitary gonadotropic cells.

In addition to disrupting the secretory function of the hypothalamus and pituitary gland, there

is evidence that diabetes mellitus can directly disrupt the endocrine function of the gonads. The administration of large doses (100–200 mg/kg) of streptozocin to male rats causes a decrease in testosterone production in the male gonads [32]. Streptozocin-induced diabetes mellitus is accompanied by hypogonadism due to a reduced number of functioning Leydig's cells in the gonads and impaired androgen biosynthesis in the remaining Leydig's cells [29].

Insulin is expressed in the gonads and regulates normal Leydig cell function by stimulating deoxyribonucleic acid synthesis and steroidogenesis during puberty. Also, insulin is of great importance for the functioning of Sertoli's cells, since it provides the transport of glucose and the synthesis of lactate, which is an important energy substrate for maintaining the vital functions of germ cells. Therefore, diabetes-related effects on male sex gland function may result from decreased insulin signaling and impaired energy metabolism [24]. In another study, the number and function of Leydig's cells were markedly reduced in rats with streptozocin-induced diabetes mellitus compared to control. Besides, some diabetic rats showed a decrease in insulin-like growth factor-1, androgen receptors after streptozocin injection compared to a control group of animals [4]. The mechanisms, by which insulin regulates the function of cells of the hypothalamus and gonads, in particular the biosynthesis of hormones, have not been completely established.

Researchers J Orth et al. described morphological ultrastructural changes taking place in Leydig's cells in streptozocin-induced diabetes mellitus [28]. Morphological changes in Leydig's cells caused by diabetes mellitus in adult male rats were not profound and included basically the accumulation of lipid droplets and a decrease in the size (atrophy) of the smooth endoplasmic reticulum. Secondary lysosomes and autophagic vacuoles-like structures were also found in the cytoplasm of Leydig's cells in rats with diabetes mellitus [28].

According to J O'Neill et al., Streptozocin can have a cytotoxic effect on Sertoli's cells, cause oxidative stress and DNA damage [27].

Diabetic models of hypogonadism have an advantage over surgical and genetic models in a way they are relatively easy to perform. As a disadvantage, it should be noted that persistent impairment of reproductive functions and hypogonadism does not occur in all animals, and streptozocin, being a highly toxic compound, causes several additional disorders that can affect the results of the experiment. Although, given the high prevalence of diabetes mellitus accompanied by the syndrome of hypogonadism, experimental diabetic models of hypogonadism are practically indispensable for the study of pathogenetic mechanisms and preclinical assessment of the effectiveness of therapeutic and prophylactic effects. Thus, N Ayuob et al. recently studied the effectiveness of oral antidiabetic medications (metformin, pioglitazone, and sitagliptin) on the sexual function of rodents with streptozocin-induced diabetes mellitus. After treatment with metformin, an increase in testosterone levels and a normalization of the sexual function of animals were observed. The group of mice treated with metformin restored the mass of the gonads to values similar to those in the control group. In contrast, rats receiving other hypoglycemic medications (pioglitazone and sitagliptin) had significantly lower testosterone levels compared with the control group, and there was no restoration of gonads [2]. These data suggest that metformin may be the best antidiabetic treatment option for young patients with diabetes mellitus (especially with a decline in sexual function) compared with pioglitazone and sitagliptin.

Low testosterone levels were also observed in the group of diabetic mice deprived of oral hypoglycemic agents. In the gonads and epididymis of male diabetic rats, unfavorable histopathological changes caused by lipid peroxidation and DNA damage due to the accumulation of reactive oxygen species were found [2]. In this regard, the study of the role of oxidative stress in the pathophysiology and pathomorphology of hypogonadism in diabetes mellitus is a very interesting direction in terms of developing supplementary therapy.

Exercise can also be considered as one of the complementary treatments to restore testosterone levels, erectile function, and improve insulin sensitivity in animal models of metabolic syndrome. Rabbits on a high-fat diet develop glucose intolerance and reduction of testosterone levels similar to how humans do. After running on a treadmill specifically designed for use in rabbits, testosterone levels were found to be negatively related to glucose levels and positively related to distance traveled [26].

## CONCLUSION

Thus, for the simulation of hypogonadism in experimental conditions, there are three main principles available to researchers: surgical, genetic, and pharmacological. Each method of experimental modeling has certain benefits and drawbacks that must be taken into account when planning an experimental study. Given the high prevalence of hypogonadism syndrome and the involvement of many organs and tissues in the pathological process, the principles of experimental modeling of hypogonadism can be useful for researchers of various medical specialties and may enable

studying the necessary aspects of its manifestations and conducting a preclinical assessment of the effectiveness of the developed medications.

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