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Review article / обзорная статья

Functional hypogonadism in men: key causes and neuroendocrine mechanisms of its development

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Abstract
Modern concepts of hypogonadism in men are undergoing significant transformation. The concept of functional hypogonadism, which is gaining increasing support among expert communities today, is based on the reversibility of symptomatic hypotestosteronemia after eliminating the causal factor or disease in men with an intact hypothalamic-pituitary-gonadal system. This makes the diagnosis of functional hypogonadism an exclusion diagnosis of organic hypogonadism, which can be congenital (genetic) or acquired (destructive or structural) irreversible disorder occurring at any level of the hypothalamic-pituitary-gonadal axis. Functional hypogonadism in men is becoming more common, attributed to its association with non-infectious pandemics such as obesity, type 2 diabetes, and other comorbid pathologies. Additionally, age-related hypogonadism meets the criteria of functional hypogonadism, as accumulating age-associated comorbidities have been shown to play a significant role in testosterone decline in aging men. Moreover, excessive physical activity, drastic calorie restriction, high psycho-emotional stress, injuries, surgeries, and the use of certain medications can also be causes of functional hypogonadism. Despite the wide range and heterogeneity of diseases and conditions underlying functional hypogonadism, the mechanisms driving its development are quite similar since in most cases, this androgen deficiency is secondary hypogonadotropic (central). However, in some cases, functional hypogonadism can be primary or mixed. Therefore, understanding the pathogenesis of functional hypogonadism is crucial as it involves a variety of biological pathways depending on the etiological factor or disease, which is detailed through a literature review. The article pays special attention to the evolutionary significance of the phenomenon of functional hypogonadism, an adapted classification of its causes, and describes the achievements of Russian researchers who have studied the impact of acute conditions and extreme influences on the hypothalamic-pituitary-gonadal system in men.

Keywords: testosterone; obesity, type 2 diabetes, injuries; relative energy deficiency, hypothalamic-pituitary-gonadal axis

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Функциональный гипогонадизм у мужчин: основные причины и нейроэндокринные механизмы его развития

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Резюме
Современные представления о гипогонадизме у мужчин претерпевают существенную трансформацию. Концепция функционального гипогонадизма, которая сегодня находит все большую поддержку среди экспертного сообщества, базируется на обратимости симптоматической гипотестостеронемии после устранения причинного фактора или заболевания у мужчины с неповрежденной гипоталамо-гипофизарно-гонадной (ГГГ) системой. Функциональный гипогонадизм у мужчин встречается все чаще, что обусловлено его ассоциацией с такими неинфекционными пандемиями, как ожирение, сахарный диабет 2-го типа, и другой коморбидной патологией. С другой стороны, и возрастной гипогонадизм отвечает критериям функционального гипогонадизма, поскольку, как установлено, именно накопление возраст-ассоциированных сопутствующих заболеваний определяет решающий вклад в снижение тестостерона у стареющих мужчин. Кроме того, чрезмерная физическая активность, резкое сокращение потребления калорий, высокая психоэмоциональная нагрузка, травмы, операции и прием некоторых лекарственных препаратов также могут стать причинами функционального гипогонадизма. Несмотря на широкий диапазон и гетерогенность заболеваний и состояний, лежащих в основе функционального гипогонадизма, механизмы, определяющие его развитие, довольно схожи, поскольку в большинстве случаев этот андрогенодефицит является вторичным гипогонадотропным (центральным), существенно реже встречается первичный или смешанный варианты. Таким

образом, в патогенезе функционального гипогонадизма задействовано множество разнообразных биологических путей, описание которых на основе подробного анализа литературы стало содержанием обзора. Особое внимание в статье уделено эволюционному значению феномена функционального гипогонадизма, адаптированной классификации его причин, а также описанию достижений отечественной школы исследователей, изучавших влияние острых состояний и экстремальных воздействий на гипоталамо-гипофизарно-гонадную систему мужчин.

Ключевые слова: тестостерон, ожирение, сахарный диабет 2-го типа, травмы, относительный энергетический дефицит, гипоталамо-гипофизарно-гонадная ось

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INTRODUCTION

The role of androgens in the human body is multifaceted. Testosterone is the main male sex steroid, the main its task is to regulate and maintain reproductive function. However, being an anabolic hormone, testosterone has multiple effects on the body, participating in the regulation of reparative and plastic processes in the body, affecting the metabolism of carbohydrates, lipids and proteins. In the brain, it stimulates libido and assertiveness, and is associated with the process of cognition and memory functioning. There is convincing evidence of a decrease in the structure of hypogonadism and the protective effect of testosterone in anxiety and depression. The results of the effect of testrosterone therapy on men's social behavior and decision-making in various situations are also described. In addition, testosterone influences bone development, muscle tissue growth, and lipogenesis processes and it stimulates erythropoiesis. In the skin, it supports collagen production, stimulates hair growth and sebum production. In the heart, it has a positive effect on cardiac output and coronary and peripheral blood flow, reduces the QTc interval and reperfusion damage. Thus, to a large extent, men's health in a wide range of manifestations is determined by testosterone level [1].

The self-regulation of the pituitary-gonadal system is based on the principle of feedback, first discovered by the Russian scientist M.M. Zavadovsky. The hypothalamus produces gonadotropin-releasing hormone (GnRH), which is secreted into the portal bloodstream by pulse waves every 60-120 minutes.

GnRH is under the powerful stimulating influence of kisspeptin, which is secreted in KNDy neurons in the arcuate nucleus of the mediobasal hypothalamus and implements GnRH release through its KISS-1R receptor. Neurokinin B and leptin are involved in activating the transmission of kisspeptin signals to KISS-1R, while dynorphin, also produced in KNDy neurons, on the contrary, blocks this transmission.

GnRH, acting on the anterior lobe of the pituitary gland, leads to the production of luteinizing hormone (LH). According to modern concepts, there is also a negative feedback mechanism in the regulatory system, where only estradiol, but not testosterone, provides the release of LH under certain pathophysiological conditions, for example, castration or hypogonadism [2]. In turn, the Leydig cells in the testicles respond to the action of LH by producing testosterone in an amount of 5-10 mg daily. Testosterone is synthesized from cholesterol through several intermediate metabolites, including dehydroepiandrosterone (DHEA) and androstenedione. Most of the testosterone in the systemic bloodstream is associated with transport proteins: about 40% has a strong connection with sex hormone binding globulin (SHBG), and 58% has a weak connection with albumin. Thus, only about 2% of circulating testosterone is bioavailable for the realization of its basic functions. In target tissues with the participation of the enzyme 5-alpha-reductase, about 70% testosterone is converted into the more active metabolite dihydrotestosterone (DHT).

Disorders in the hypothalamic-pituitary-gonadal (HPG) system are described by a classification that etiologically divides male hypogonadism into primary, secondary and mixed forms. Primary (hypergonadotropic) hypogonadism occurs due to a violation of the function of the testicles due to a defect in the tissue of the testicles themselves. In the pathogenesis of the development of secondary (hypogonadotropic or central) hypogonadism, there is a violation of the structure of the pituitary gland, a decrease in its gonadotropic function or damage to the hypothalamic centers that regulate the activity of the pituitary gland. If it is impaired as hypothalamic pituitary both the function and the function of the testicles and/or the insensitivity of the receptor apparatus is observed, then such hypogonadism is mixed.

In 2017, M. Grossmann and A. Matsumoto proposed a new classification of adult male hypogonadism, distinguishing between organic and functional hypogonadism (FHH) [3]. According to this classification approach, "organic" (or classical) hypogonadism is an irreversible form of hypogonadism caused by an innate (genetic) or acquired (destructive or structural) disorder occurring at any level of the HPG axis [4, 5], which implies traditional therapy (for example, gonadotropins or testosterone). "Functional" hypogonadism occurs in the absence of an established organic pathology in the HPG system and is a potentially reversible disorder after the elimination of the influencing cause. In other words, functional

hypogonadism is a diagnosis of the exclusion of organic causes of hypogonadism.

So, hypogonadism in men is a clinical and biochemical syndrome associated with a permanent or temporary inability of the gonads to produce physiological concentrations of testosterone and/ or insensitivity of the receptor apparatus to it and its metabolites, which has a negative impact on organs and systems, as well as quality of life.

Currently, the pathophysiological mechanisms of the development of organic hypogonadism have been studied in sufficient detail, but the causes of functional hypogonadism remain the subject of lively scientific discussion.

Most often, such violations occur against the background of exposure to endogenous or exogenous modifiable factors [6]. The main reasons for the functional decrease in testosterone production include obesity and metabolic syndrome in general, the presence of concomitant acute and chronic diseases that indirectly affect testosterone synthesis, taking medications that affect its production, intense exposure to physical factors such as vibration, radiation, noise, temperature, as well as sleep disorders, intense physical activity and psycho - emotional stress, etc. (*Fig. 1*).

According to some scientists, age-related androgen deficiency can also be attributed to functional hypogonadism, since there are a considerable number of men over 80 years old with normal testosterone levels and an adequately functioning HPG system [7]. Thus, in the European Study Male Aging Study (EMAS), it was found that the decisive contribution to the age-related decrease in testosterone levels is determined not by biological aging as such, but rather by the accumulation of age-associated concomitant diseases such as obesity, type 2 diabetes mellitus, etc., leading to suppression of LH secretion [8].

Figure 1. Main causes of functional hypogonadism (adapted [9])
Рисунок 1. Основные причины функционального гипогонадизма (адаптировано из[9])

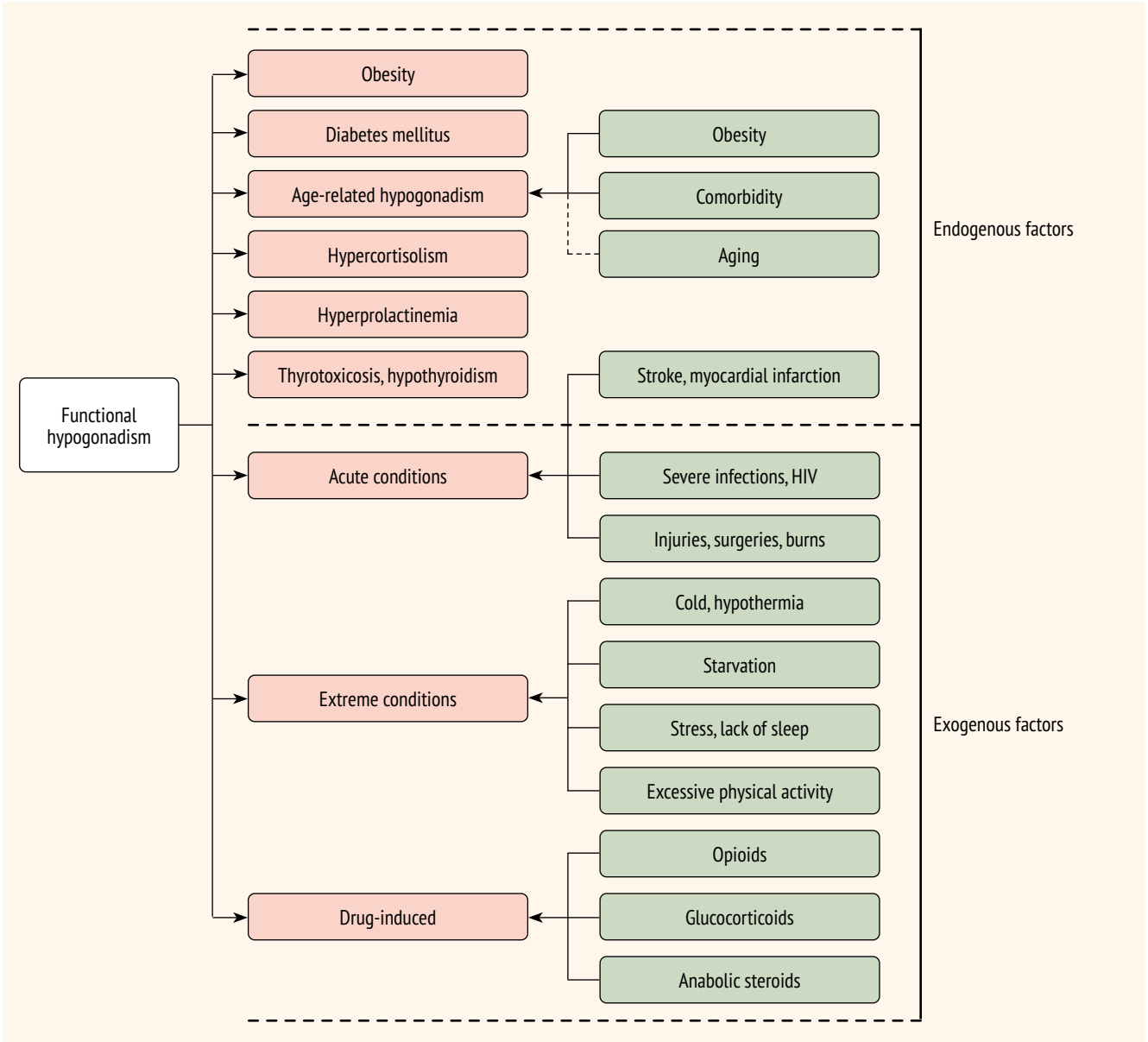


Table. Diseases and conditions causing various forms of functional hypogonadism (adapted from [10])
Таблица. Заболевания и состояния, вызывающие различные формы функционального гипогонадизма (адаптировано из [10])

Form of functional hypogonadism	Diseases and conditions
Primary	• Getting old • Drug-induced: ketoconazole, aminoglutetimide, mitotan, methirapone • Chronic systemic diseases • Organ failure • Alcohol
Secondary	• Acute or critical desease • Drug-induced: opioids, glucocorticoids, androgens/anabolic androgenic steroids, GnRH analogues, cyproterone acetate, psychotropic drugs that cause hyperprolactinemia • Non-sufficient nutrition, excessive physical activity • HIV/AIDS • Abuse of cannabinoids • Obesity, DM2, accompanying diseases, obstructive sleep apnea
Androgen resistance / decreased biological activity of testosterone	• Drug-induced blockade of androgenic receptors: steroid antiandrogen • (e.g., cyproterone acetate, spironolactone), • nonsteroidal antiandrogen (e.g., flutamide, bicalutamide, nilutamide) • Drug-induced blockade of 5α-reductase activity: finasteride, dutasteride • Increased contents of sex hormone binding globulin

For both organic hypogonadism and functional hypogonadism, the differential diagnosis between primary and secondary hypogonadism is important (see the *Table 1*).

Most cases of FHH should be attributed to secondary or mixed hypogonadism with low or lownormal values of luteinizing hormone. However, primary FHH with elevated LH levels is also found, although infrequently, in older men (>70 years old), especially in combination with accompanying diseases [4].

The purpose of this review will be to highlight the most common conditions that lead to functional hypogonadism in men, as well as the mechanisms that determine this.

ENDOGENOUS MODIFIABLE FACTORS

Obesity

Obesity, in addition to metabolic syndrome and cardiovascular diseases, can not only cause PH, but is also one of its leading causes. This proves the prevalence of hypogonadism in people with morbid obesity (BMI > 40 kg/m2), which reaches 75%. The effect of obesity on testosterone levels is realized through several mechanisms, which are mainly associated with an excessive amount of adipose tissue, including visceral fat, as well as with a violation of its properties [10].

I. *Direct effect of adipose tissue*. Testosterone, being a lipophilic molecule, is retained in the fat depot, which in the case of obesity leads to a decrease in its concentration in the systemic bloodstream. Thus, adipocytes from subcutaneous adipose tissue in obese men have higher concentrations of intracellular testosterone compared with adipocytes obtained from lean men [11]. In addition, adipose tissue in obese individuals shows an increase in aromatase expression, which is proportional to body fat mass and converts testosterone into estrogens. The increased content of estrogens, in turn, reduces the amplitude of pulsating LH release and can directly enhance lipogenesis and increase subcutaneous, ectopic and visceral fat. Thus, an excessive amount of dysfunctional adipose tissue can directly participate in androgenic deprivation by removing testosterone from the systemic bloodstream, as well as by converting it to estradiol and indirectly by reducing stimulation of testosterone synthesis by the hypothalamus [12].

II. *Effects of adipokines*. Obesity increases the production of adipokines from adipose tissue, the most important of which is leptin. Leptin released from adipocytes is commensurate with the volume of adipose tissue, acting as a useful biomarker of fat reserve in the body, which provides an important peripheral signal to the normal functioning of the reproductive HPG axis. However, increased secretion of leptin with a large volume of fat leads to dysfunction of the HPG axis, androgen deficiency, and a decrease in the number of spermatozoa and their mobility [13].

Apparently, leptin regulates the functioning of the HPG system through indirect control of hypothalamic neurons, on the other hand, if its level exceeds a certain threshold, it suppresses the function of the gonads. In particular, an increased level of leptin is able to suppress the expression of the kisspeptin-1 gene and its receptors in the arched nuclei of the hypothalamus, which reduces the production of kisspeptin and leads to inhibition of GnRH secretion, followed by a decrease in steroidogenesis at the testicular level and the development of a hypogonadal state [14].

The role of adiponectin is also significant, the decrease of which in obesity has been documented in numerous studies. Thus, the use of adiponectin in high doses stimulated cell proliferation and survival in the testes of mice, enhanced the transport of energy substrates,

on the contrary, blockade of adiponectin receptors AdipoR2 led to an increase in obesity and caused atrophy of the seminal tubules and aspermia [15]. Given these results, it can be concluded that adiponectin is necessary to maintain the eugonadal state, and a decrease in its secretion, usually observed in dysfunctional adipose tissue, contributes to hypoandrogenism.

III. *The effect of meta-inflammation*. Obesity is accompanied by low-intensity inflammation (metainflammation), which is characterized by excessive production of such proinflammatory cytokines as IL-6, IL-1, TNF-α, mainly from visceral adipose tissue. Accumulating data indicate that overproduction of inflammatory mediators is associated with a decrease in testosterone levels, and administration of proinflammatory cytokines or endotoxins to men or treatment of Leydig cells in culture with proinflammatory cytokines reduces testosterone production [16].

The inhibitory effect of proinflammatory cytokines on the reproductive axis is due to a decrease in the sensitivity of hypothalamic neurons to kisspeptin through suppression of the expression of kisspeptin receptor genes (KISS1R). The significance of the resulting resistance to kisspeptin, which leads to a decrease in GnRH production, is indirectly confirmed by a study in which the administration of exogenous kisspeptin-54 to healthy men stimulated a significant increase in serum concentrations of LH, FSH and testosterone [17].

IV. *The effect of oxidative stress*. An increase in adipose tissue requires not only the development of collateral blood flow, but also neovascularization, ensuring adequate blood supply. If the rate of its increase does not match with a sufficient increase in blood flow, hypoxia of adipose tissue may occur, which will create prerequisites for the development of oxidative stress with the generation of reactive oxygen species (ROS), leading to its dysfunction. Intense oxidative stress, AFC can disrupt the work of mitochondria in Leydig cells, which, in turn, can affect the steroidogenic cascade, determining a decrease in testosterone production and infertility [18].

In addition, excessive generation of AFC can contribute to the development of FGG through increased secretion of cortisol, which, in turn, has an inhibitory effect on the secretion of LH by the pituitary gland, thereby reducing the production of testosterone by Leydig cells [19].

V. *The effect on globulin, that binds sex hormones*.

Sex Hormone Binding globulin (SHBG) is a glycoprotein that plays a key role in the cross-links between metabolic disorders and testosterone deficiency. Indeed, overweight and obese men tend to have lower concentrations of SHBG compared to lean subjects. This is due to the presence of hyperinsulinemia, which often accompanies visceral obesity, which can reduce the production of SHBG by the liver [20]. Moreover, many data suggest that SHBG production is suppressed by pro-inflammatory cytokines, whose levels are significantly elevated in obese patients. This decrease in SHBG can lead to a temporary increase in free testosterone levels, which contributes to an even greater increase in aromatase activity with increased testosterone-estradiol shunt activity. An increase in the estradiol content by negative feedback suppresses the HPG system, which ultimately leads to a decrease in the level of both total and free testosterone [12].

Summarizing the above, we can conclude that obesity leads to dysfunction of the HPG system, while simultaneously forming a vicious circle in which an increase in the amount of adipose tissue reduces testosterone production, thereby determining further accumulation of adipose tissue.

Confirmation of the crucial importance of obesity in the development of FHH is a serious evidence base on the correction of androgen deficiency by lifestyle modification with a decrease in body weight. Conducted by G. Corona et al. Meta-analysis has shown that dieting and bariatric surgical treatment lead to a significant increase in both total and free testosterone levels [21]. Similar results are demonstrated by another study that included 3,369 men aged 40-79 years with concomitant obesity. Against the background of normalization of body weight, 42.9% of men with secondary hypogonadism had an increase in testosterone levels to the eugonadic parameters [22]. With an extended evaluation of the data in the EMAS study, a decrease in IMT > 15% from the baseline was associated with a significant increase in the level of total and free testosterone [7].

Diabetes mellitus

Diabetes mellitus, primarily type 2 (DM2), is one of the most important determinants of FHH [23]. A significant number of studies show that DM2, especially poorly controlled, can determine disorders in the structure of gonads (degenerative and apoptotic changes), as well as in the synthesis of GnRH [24].

Indeed, insulin, along with leptin and other hormones, regulates the work of the HPG axis, stimulating GnRH secretion through increased expression of kisspeptin and its receptors in the arched nuclei of the hypothalamus. Consequently, both insulinopenia and insulin resistance, which alters the activity of insulin receptors in the brain, can lead to central functional hypogonadotropic hypogonadism. This has been shown in clinical studies and works with experimental models, where it was found that low leptin levels (in patients in a catabolic state with severe DM decompensation) and low insulin levels, or sufficient values of it in conditions of insulin resistance, inhibit the expression of kisspeptin in the central nervous system [25]. In addition, the toxic effect of chronic hyperglycemia on hypothalamic neurons is another likely mechanism for reducing GnRH secretion [26].

A comparative assessment of violations of the HPG system in men with DM1 and DM2 was carried out in an extremely limited number of studies with relatively small and extremely heterogeneous cohorts. These attempts have produced mixed and poorly reproducible results. The effect of the pathophysiological links of diabetes mellitus on the state of the gonads, as well as the characteristics of sperm, including the assessment of sperm motility in men with DM1 and DM2, remains largely unclear [27].

It should be emphasized that a proper lifestyle in combination with adequate pharmacological control is the basis for maintaining reproductive health in patients with diabetes, however, further research is needed to detail the effect of diabetes mellitus on the HPG axis.

Age-related hypogonadism

According to large–scale studies, the level of total testosterone decreases by 0.5–1.5% per year starting from the age of 30, and the rate of decrease in free testosterone reaches 2-3% per year [28]. The difference between the decrease in total and free testosterone is explained by an age-related increase in the circulating concentration of SHBG, which reduces the proportion of free testosterone.

At the same time, combining data from three different stages of the Massachusetts Male Aging Study (MMAS) indicates that, in addition to aging, obesity and some chronic concomitant diseases themselves disrupt the functioning of the HPG system, leading to the development of primary, but more often secondary hypogonadism in older men [29].

The European Male Aging Study (EMAS) has largely confirmed these findings. When examining about 3.5 thousand men aged 40 to 79 years, the prevalence of hypogonadism was 23.3%; of these, 85.5% of men had secondary hypogonadism, the prevalence of which did not increase significantly with age [30]. This allowed us to conclude that in reality, a decrease in testosterone in aging men manifests itself as a cumulative effect of aging, obesity and accumulating comorbid pathology.

Some medical communities, taking into account the potential reversibility of secondary hypogonadism caused by obesity, DM2 and other concomitant diseases, suggest interpreting such disorders as functional hypogonadism [4]. At the same time, in some cases, it is impossible to deny the formation of age-related primary testicular insufficiency in the aging process, which has an irreversible and, thus, organic character [31]. Its causes include age-related cellular degeneration, a decrease in the number of functional Leydig cells, atherosclerosis of the arterial vascular in the channels of the testicles. The dividing criterion for total testosterone < 12 nmol/l, which makes it possible to distinguish primary hypogonadism, according to the EMAS data, is the concentration of LH ⩾ 9.4 IU/l, while a reduced or low-normal LH content determines secondary hypogonadism [32].

EMAS experts suggested classifying men with "compensated hypogonadism" (subclinical – by analogy with thyroid diseases), having a normal content of total testosterone (⩾12.1 nmol/l) and elevated LH levels (⩾9.4 IU/L). 10% of such patients were identified in the EMAS, and they were characterized by a higher risk (16 times) of progression to primary hypogonadism compared with eugonadic individuals [33].

Nevertheless, current data on the long-term clinical significance of compensated (subclinical) hypogonadism are few, which makes it advisable to monitor these patients and study the prospects of the proposed approach.

EXOGENOUS MODIFIABLE FACTORS

Acute conditions and extreme effects

Among our compatriots, the founder of the scientific direction devoted to the study of changes in the pituitary-gonadal system of healthy men under the influence of various extreme factors was Professor D.Ya. Shurygin, who initiated a number of studies at the Military Medical Academy more than half a century ago. D.Ya. Shurygin and his students in this series of works showed that the stay of a healthy man in a complex factor of highlands, high latitudes, when exposed to chemical agents, as well as with traumatic, burn, vibration diseases, acute blood loss, hypokinesia, it has an overwhelming effect on the function of his pituitary-gonadal system. Thus, V. Mazurov's study demonstrated that under the influence of prolonged hypokinesia in the antiorthostasis position, simulating a long-term space flight, as well as under conditions of hyperkinesis and climbing to a mountain height, healthy men's levels of LH and testosterone decrease, i.e. functional (transient) hypogonadism develops with subsequent independent restoration of testosterone levels [34].

When studying the health of participants in several polar expeditions at the Leningradskaya Antarctic station, V.A. Yakovlev revealed signs of restructuring the HPG system in the form of an increase in average LH values in winter, as well as an associated decrease in testosterone levels in autumn, mainly when combining the effects of adverse climatic factors with intense physical exertion [35].

These data allowed us to conclude that healthy men who were exposed to extreme factors in most cases develop functional hypogonadism, which, apparently, is an adaptive reaction and has a transient character, self-limiting after the end of the stressor.

At the same time, D.Ya. Shurygin and his school were engaged in research on the effects of acute conditions and therapeutic diseases on the body and the state of the HPG system. Thus, A.L. Rakov continued to study the effect of stressors on the HPG axis in studies related to the acute condition - burn disease. In his work, it was found that the testosterone content is reduced during all periods of burn disease, and the suppression of gonadotropic function occurs with deep burns over 10% of the body surface and the earlier the greater the severity of the lesion. During the period of reconvalescence, normalization of the gonadotropic functions of the pituitary gland and testosterone is observed, which was confirmed M.I. Pugachev [36].

S.B. Shustov showed that acute myocardial infarction leads to a restructuring of hormonal regulation in men in the form of activation of the pituitary-adrenal system with significant inhibition of the function of the HPG system. When analyzing the recovery period of the HPG system function, it was noted that the restoration of testosterone levels occurs only in a part of men (after 30 days), and the lack of recovery of its level is a predictor of an unfavorable course of the post-infarction period [37].

The authors of these studies concluded that the prolonged nature of hypogonadism in men with acute diseases and conditions may have pathogenetic significance and determine the development of a peculiar premorbid background.

The next stage of the research carried out under the guidance of S. Shustov was the study of the influence of chronic diseases on the development and course of hypogonadism. M. Kharitonov, M. Kuandykova, A. Vydrych, D. Frolov, A. Makarova, V. Kitsyshin and others worked actively in this field. These studies have shown the effect of chronic diseases such as bronchial asthma, pneumonia, coronary heart disease and GB, diabetes mellitus and diabetic nephropathy on the HPG system, as well as the features of their course [38, 39, 40].

A complex of production factors that affect the pituitary-gonadal system of military personnel taking part in the work on the destruction of chemical weapons were investigated in the works of Yu.Sh. Khalimov and V.A. Zaitsev, who revealed gonadotropin disfunction and impaired spermatogenesis against the background of a decrease in testosterone levels [41].

The development of such research has become the work of other Russian scientists. Thus, E.A. Finagina established a connection between a higher rate of age-related decrease in total and free testosterone in locomotive drivers with the influence of a complex of such unfavorable professional factors as inactivity, shift rhythm of work with night shifts and lack of sleep, high stress on attention, exposure to noise and vibration [42]. S.A. Babanov and other researchers proved the negative effect of vibration disease on the reproductive system of men with the development of androgen deficiency and erectile dysfunction that has been established [43].

Despite a long and detailed study of the problem of hypogonadism and the contribution of various diseases and external extreme influences to its formation, the question of the need for testosterone replacement therapy in functional hypogonadism remains unresolved, as well as the degree of influence of hormone replacement therapy with testosterone on the course of the underlying disease.

High-intensity psychoemotional pressure

In the era of progress, high information flow, and multitasking, the modern human body is experiencing enormous loads, while the contribution of constant psycho-emotional pressure in men to the development of hypogonadism is obvious. In this regard, the term "stress-induced hypogonadism" has recently been introduced [44]. The endocrine system is of primary importance in the formation of compensatory mechanisms in response to various extreme factors affecting the body, and the adequacy of adaptation of the entire body under stress depends on the degree of hormonal activity [45]. The end hormones of the hypothalamic-pituitary-adrenal system, when exposed to extreme factors, adapt the body by regulating many central and peripheral functions. Initially, under the influence of stress factors, the content of LH and FSH increases under the influence of corticotropin-releasing hormone (CRH), prolactin and thyrotropin-releasing hormone, which leads to the release of testosterone [30]. But subsequently, against the background of increased activity of the hypothalamic-pituitary-adrenal system, the secretion of LH and FSH is inhibited by blocking gonadoliberin receptors [46]. When the adrenocortical link is turned on, the decrease in tropic hormones is aggravated, and under the action of glucocorticoids, the sensitivity of receptors on Leydig cells decreases, which reduces steroidogenesis [47]. In general, stress-induced dysfunction of the HPG axis largely depends on the duration of its exposure, as well as the initial state of the body, while after the cessation of the stress factor and rest, all indicators normalize [45].

Relative energy deficiency

Relative energy deficiency (low energy availability) causes functional hypogonadism due to the following reasons: high-intensity physical activity with inadequate and/or reduced food intake (starvation) that does not meet energy needs [48].

This concept originates from the "triad of female athletes", identified in 1992 in sports medicine for women, which included disordered nutrition, amenorrhea and osteoporosis. In this case, hypogonadotropic hypogonadism in women acts as a protective mechanism that prevents pregnancy that is "costly" for the body, due to an insufficient supply of adipose tissue necessary to maintain ovulatory function. The male reproductive HPG axis was also vulnerable to intense physical exertion and inadequate food intake in 2014 the International Olympic Committee has changed the term to the gender-neutral "Relative energy deficiency syndrome in sports" (RED - S, Relative Energy Deficiency in Sport) [48].

Today, there are two main explanations for the decrease in testosterone observed during overtraining. In the first case, the justification is a multitude of studies reporting a sharp increase in cortisol and prolactin caused by intense physical activity, which inhibit the production of GnRH and gonadotropins, and also have a direct suppressive effect on Leydig cells [49].

The second mechanism under discussion is related to the short-term or long-term effects of calorie deficiency, which causes a decrease in testosterone in men. It is generally recognized that overtraining often leads to weight loss and appetite suppression/tendency to anorexia. A negative energy balance causes hypoleptinemia, which, in accordance with the above, leads to suppression of GnRH and the entire HPG axis. Such suppression of the reproductive axis has a functional character and will be reversible with an increase in body weight, however, the timing of normalization of testosterone levels is individual [50].

One of the illustrative examples of functional hypogonadism caused by extreme loads when summing up several active factors was the examination of soldiers in field exercises. Intensive training, severe psycho-emotional stress and calorie restriction in the daily diet

led to the decrease in total testosterone in young men below the reference values [51]. At the same time, relative energy deficiency in men may be accompanied by symptoms of manifest hypogonadism (i.e. decreased libido and sexual dysfunction) with rapid recovery of the HPG axis, often within a week after having rest, resumption of nutrition and stress reduction.

Injuries and surgical interventions

One of the most poorly studied and debatable issues in the problem of functional hypogonadism is the impact on the reproductive axis of factors such as trauma, including traumatic brain injury or combat gunshot injury, surgical stress, as well as the effect of transient androgen deficiency on the timing of regeneration.

The probability and severity of functional hypogonadism in this case will be determined by the volume of traumatic injury, the level of psychoemotional stress, as well as the magnitude of catabolic and inflammatory processes caused by the lesion. The most obvious mechanism of suppression of the HPG axis, which determines the development of such functional hypogonadism, is obviously cortisol-mediated with the involvement of the above-described effect of proinflammatory cytokines in the case of the addition of an immuno-inflammatory syndrome [52]. This is confirmed by a recent examination of patients with mine-blast wounds, in whom FHH occurred in 61% of cases, and the level of testosterone decrease was lower the more severe the injury [53].

Traumatic brain injury (TBI) stands somewhat apart, which can predetermine damage to hypothalamic or pituitary structures, leading through suppression of GnRH or gonadotropins to a more significant decrease in testosterone production and/or longer hypogonadism [54]. In addition to direct damage, in this case, secondary effects of TBI are also isolated, which include hypoxia, decreased cerebral blood flow and metabolism, as well as increased intracranial pressure, which can eventually induce ischemic adenohypophyseal infarction [55] and lead to persistent hypopituitarism.

Discussing traumatic illness, it is important to emphasize the uncertainty of modern ideas

regarding the role and significance of functional hypogonadism in the processes of regeneration and general recovery after injury, which requires further research and consideration.

Drug-induced hypogonadism

The relationship between testosterone levels and the intake of certain pharmacological drugs has been proven. Glucocorticoids, tricyclic antidepressants, opioids, cimetidine, nicotine, acting at all levels of the HGH axis, can suppress testosterone production for up to 12 months. After the cessation of their use [56]. Let's focus on the most common of them.

Opioids are widely used for pain relief as well as for detoxification of opioid addiction. They act on the μ-opioid receptors in the hypothalamus and, through the activation of dynorphin, lead to a decrease in the pulsating release of GnRH, a decrease in the frequency of LH production (as well as FSH) and ultimately to a decrease in the level of sex hormones. The prevalence of opioid-induced hypogonadism in men is estimated from 19 to 86% and depends on the duration of treatment with specific opioid drugs and their dosage [57]. Prolonged use of opioids causes FHH, which leads to sexual dysfunction and impaired sperm production, since δ-, κ- and μ-o-pyoid receptors are present in human spermatozoa [58]. Opioids can also increase prolactin levels, thereby further reducing testosterone levels. Opioid withdrawal is usually followed by a restoration of serum testosterone levels within one month [59].

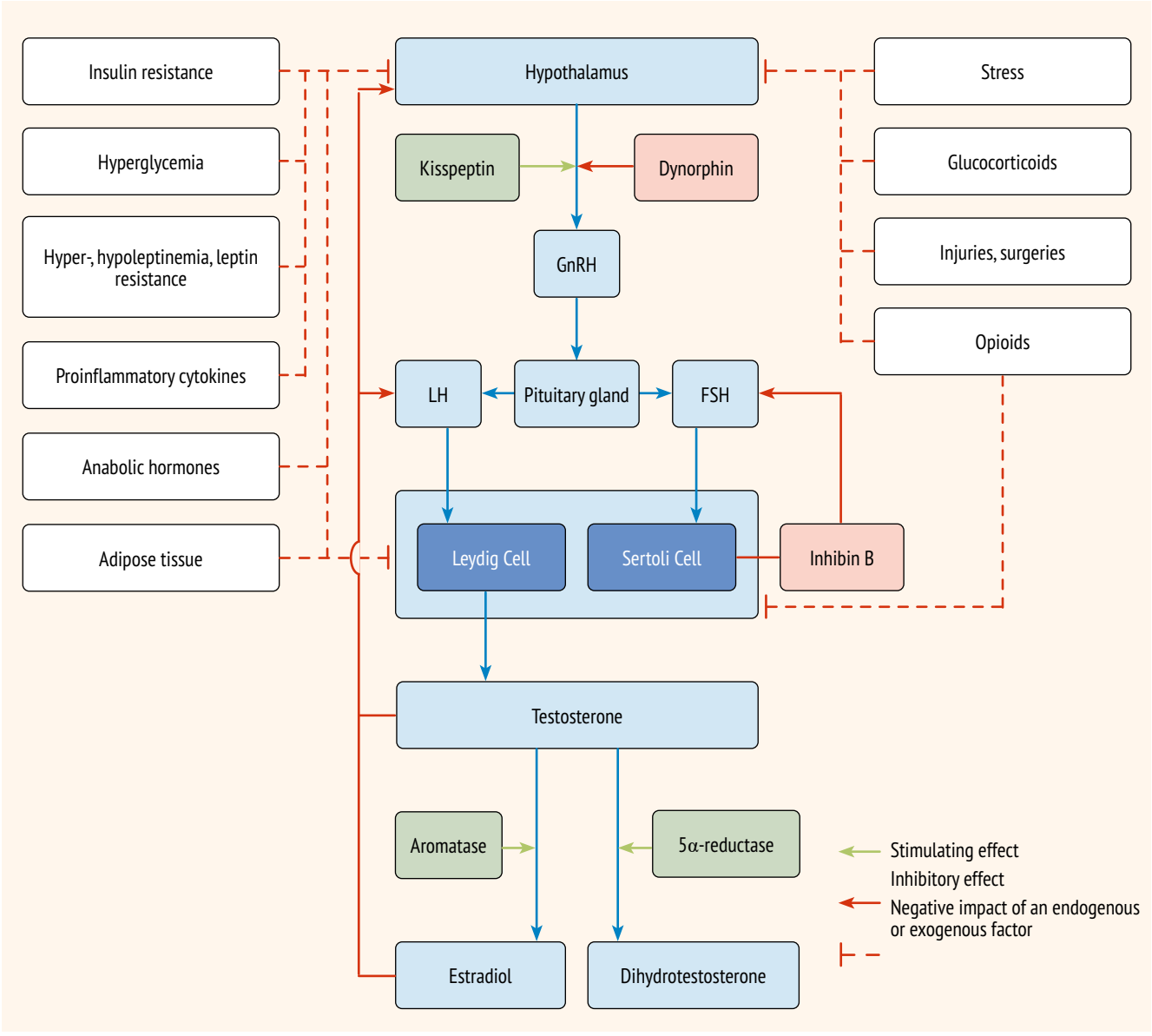
Anabolic steroids, the use of which is common among athletes and bodybuilders, disrupts the functioning of the GGG system, and their chronic use can cause gonadotropin suppression and even testicular hypotrophy with the development of oligozoospermia or azoospermia. Symptoms of hypogonadism during use are usually absent. After discontinuation of the HPG axis, it recovers within a few weeks or months, but sustained suppression can last up to several years [60].

Glucocorticoid drugs with prolonged use determine the development of exogenous hypercorticism, which is a common cause of functional hypogonadism. Glucocorticoids suppress the secretion of GnRH, which leads to a decrease or low-normal gonadotropin level and a subsequent drop in testosterone concentration. However, under certain conditions, they also have a direct suppressive effect on testicular function, thus causing mixed (primary and secondary) hypogonadism, with a marked predominance of cases of secondary hypogonadism. At the same time, glucocorticoid drugs cause a decrease in SHBG, which is important to take into account when diagnosing the biochemical syndrome of hypogonadism [61].

THE BIOLOGICAL SIGNIFICANCE OF THE FUNCTIONAL HYPOGONADISM PHENOMENON

It is well known that the state of the cardiovascular, respiratory, endocrine and other major body systems determines the survival of the body. Thus, in relation to the endocrine system, the hypothalamic-pituitary-adrenal axis [1] or the hypothalamic-pituitary-thyroid axis [2], which regulate the production of cortisol or thyroid hormones, play a crucial role in survival, and therefore the functioning of these systems is stable and, as a rule, maintained despite the development of other diseases or conditions [3,4, 5]. Unlike these systems, the uniqueness of the HPG axis positions it as an important switch between the survival mode of the organism and reproductive function, which is influenced by many endogenous and exogenous factors. That is why the HPG axis in both sexes shows high sensitivity to a huge variety of signals, acting as an early warning system of the body, or a harbinger of illness or distress. Apparently, this is due to the fact that reproduction is an optional process and during illness, serious injury or extreme stress, due to the suppression of the HPG axis, resources are reoriented

● ***Рисунок 2.*** Основные точки приложения нарушений в гипоталамо-гипофизарно-гонадной системе, вызывающих функциональный гипогонадизм у мужчин
● ***Figure 2.*** The main points of application of disorders in the hypothalamic-pituitary-gonadal system, causing functional hypogonadism in men



to a survival mode with a temporary departure from reproductive strategies [7].

The above ideas suggest that it is leptin, apparently, that acts as a kind of gatekeeper between survival and reproductive regime. For optimal reproductive functioning, an ideal metabolic status is required, which allows only euleptinemia (with a narrow range of serum leptin levels). Prolonged restriction in consumption with a decrease in fat reserves is associated with hypoleptinemia, which turns off the reproductive axis and simultaneously increases appetite for food (an important component of the survival regime). Conversely, chronic calorie overabundance with an increase in adipose tissue depot is associated with hyperleptinemia and even leptin resistance, which suppresses the HPG axis and increases appetite in a very similar way to hypoleptinemia [6].

It is important to emphasize at the same time the evolutionarily conditioned susceptibility of the HPG system to suppression, which, apparently, was not designed for the impact of so many "new" factors. Such vulnerability of the HPG axis makes functional hypogonadism a potentially common clinical scenario, especially in the context of obesity, high psychoemotional loads, sleeping disorders, etc. [13]. *Fig. 2* summarizes the disorders at various levels of the HPG axis that cause functional hypogonadism in men.

CONCLUSION

Modern ideas about hypogonadism in men are undergoing a significant transformation. A significant proportion of all cases of decreased testosterone production can

be attributed to functional, reversible conditions that go unnoticed, because unlike women, men do not have a cyclic reproductive equivalent. Temporary suppression of the reproductive HPG axis of a man in the long term may be realized in the negative effects of hypotestosteronemia in relation to the musculoskeletal and cardiovascular systems, may manifest itself in cognitive dysfunction, as well as a decrease in vitality and emotional background.

This actualizes the search for criteria for the timing and methods of correction of functional hypogonadism, depending on the prevailing mechanism of its development, and also requires the differential diagnosis of metabolic dysfunction in men to take into account the causes causing a decrease in testosterone content.

To summarize all said above, we can conclude that functional hypogonadism in men in the modern scientific world is becoming increasingly important as an independent nosological form that requires a more detailed study of its pathophysiology and the need for correction.

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