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THYROID GLAND FUNCTION AND MAIL REPRODUCTIVE HEALTH

Over the past few decades, thyroid hormones have been well studied for their significance for male reproductive health. Hyperthyroidism and hypothyroidism affect testicular function and neuroendocrine regulation of reproductive functions, which can lead to decreased testosterone levels and poor sperm quality and compromise male fertility. Understanding these processes is more relevant than ever given the continuous decline in sperm count and quality that has been observed in humans over the past decades. The literature review presents a brief concept of the regulation of male reproductive function by thyroid hormones and a possible mechanism by which thyroid dysfunction affects testicular function.

Keywords: thyroid hormones, hypothyroidism, hyperthyroidism, steroidogenesis, spermatogenesis, infertility.

Thyroid hormones play an important role in the growth, development, and thermogenesis of mammals. The role of thyroid hormones in the development of the central nervous system, in the regulation of metabolism and physiology of the heart has been well studied [1, 12, 20]. However, the presence of receptors for thyroid hormones in most cell types and the effects observed by the researchers indicate a broad effect of these hormones on tissue. Several clinical and experimental studies have shown a close relationship between altered thyroid status and reproductive failure [24, 45].

Many works have been devoted to the study of the effect of thyroid hormones on the development and function of the testes [45], as well as the relationship between the altered status of the thyroid gland and infertility [44]. Normal thyroid function is essential for maintaining the reproductive system. Thyroid hormones, primarily the biologically more active triiodothyronine (T_3), regulate the maturation and growth of testes, controlling the proliferation and differentiation of Sertoli and Leydig cells during testes development, and stimulate steroidogenesis in rats and other mammalian species [28, 41].

Both hypothyroidism and hyperthyroidism are associated with changes in the concentration of sex-hormone-binding globulin (SHBG) and sex hormones (testosterone and estradiol) in both sexes, impaired ovulatory function in women and erectile dysfunction in men [13]. Hyperthyroidism causes disturbances in sperm motility, while hypothyroidism is associated with abnormalities in sperm morphology [24]. At the same time, thyroid hormone replacement therapy in patients with hypothyroidism returns the levels of SHBG and testosterone to normal concentrations [21] and eliminates sexual dysfunction [6].

Since normal thyroid function is important for maintaining male reproductive health, the purpose of this review was to discuss relevant information on the effects of hyper- and hypothyroidism on male fertility.

The mechanism of action of thyroid hormones. For a long time it was believed that the action of iodothyronines is regulated mainly by modulating the concentrations of their free fractions in the blood, the activity of nuclear receptors and intracellular destruction by a deiodinating enzyme. However, in the past decade, there has been some departure from this classic model. It is known that iodothyronines act both centrally, regulating sympathetic output, and peripherally, regulating metabolism in target tissues, while their central action can simultaneously alter the effects on peripheral tissues. At the present stage, scientists recognize that in addition to T3, thyroid hormone derivatives such as reverse T_3 (rT3) and diiodothyronine (T_2) have physiological activity, which can act both through traditional genomic transcription regulation pathways, acting on nuclear receptors, and through a more direct, a fast-acting non-genomic mechanism [25].

As derivatives of amino acid tyrosine, thyroid hormones require plasma membrane transporters to reach nuclear receptors. Thus, T_3 secreted by the thyroid gland into the bloodstream enters the target cell using specific cell membrane transporters, among which the monocarboxylate transporter 8 (MCT8), also present in testicular tissues, shows the highest affinity for T_3 [15]. MCT8 mutations in humans are associated with severe psychomotor retardation and elevated T_3 levels.

It was found that thyroid hormone nuclear receptors are expressed in embryonic and mature Sertoli cells [31]. Binding of triiodothyronine to its receptors in testicular cells activates gene transcription and protein synthesis, as well as proliferation and differentiation of Sertoli cells [16]. In addition to genomic effects, thyroid hormones also demonstrate non-genomic, which include the ability of iodothyronines to bind to non-nuclear receptors, affecting cell structure, metabolic rate and cell proliferation. It has been demonstrated that binding to non-nuclear receptors enhances the synthesis of cyclic adenosine monophosphate, calcium release and improved sperm kinetics [11].

In addition to nuclear receptors and transporters, the regulation of the thyroid hormone action in cells is provided by various patterns of iodothyronine metabolism. Iodothyronine deiodinases are a subfamily of selenoenzymes that selectively remove iodide from thyroxine (T_4) and its derivatives, thus activating or inactivating these hormones [29]. It is known that T_3 can be formed in peripheral tissues from T_4, which is produced by the thyroid gland in greater quantities than T_3 and is considered a prohormone, since its affinity for thyroid hormone receptors is 10 times less than that of T_3. The conversion of T_4 to T_3 is carried out by type 1 and type 2 deiodinases, whose activity determines the local availability of T_3, and also makes a significant contribution to the serum levels of thyroid hormones [17]. Type 2 deiodinase is present in the spermatids of the testes of neonatal and adult rats [43]. Type 3 deiodinase converts both T_3 and T_4 into metabolites with very low affinity for thyroid hormone receptors. Given this enzymatic activity, type 3 deiodinase is intended to reduce the availability of T_3 in the tissues in which it is expressed and, therefore, to reduce the local action of the thyroid hormone [35]. Type 3 deiodinase plays an important role in developing testis by maintaining the thyroid hormone availability within levels that are developmentally appropriate [40].

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Thus, the action of T_3 depends not only on the circulating levels of the hormone, but also on a set of a number of molecular determinants, including transporters, enzymes and receptors present in a particular cell or tissue. This set of factors is critical to the local bioavailability of thyroid hormones and can markedly increase or decrease the local action of thyroid hormones.

Influence of hyperthyroidism on sex hormones and sperm parameters. Thyroid dysfunction is one of the most common endocrine disorders observed in clinical practice. The prevalence of thyroid dysfunction varies by age, gender, ethnicity and area of residence due to differences in dietary iodine intake. Thyroid dysfunction has serious health consequences, including cardiovascular arrhythmias, metabolic and mental health problems [32]. The prevalence of hyperthyroidism in the general population is 1.3%, the *ratio* of *males to females* is 1:7. Infertile men with hyperthyroidism usually have decreased libido, erectile dysfunction, premature ejaculation, or symptoms of increased estrogen such as gynecomastia [10].

The effect of changes in thyroid hormone on the reproductive system has been extensively studied in animals and has generally shown that deviations from normal thyroid function lead to decreased sexual activity and fertility. The induction of hyperthyroidism in adult rats by L-thyroxine caused a significant decrease in serum levels of luteinizing hormone, follicle stimulating hormone and testosterone, along with a significant increase in serum estradiol levels compared to euthyroid rats [5]. In addition, sperm count and motility have decreased. After induction of hyperthyroidism there were also noted the increased concentrations of reduced glutathione, malondialdehyde and nitric oxide, along with a significant decrease in the activity of superoxide dismutase and catalase. The authors have suggested that hyperthyroidism may affect fertility by directly affecting the testes through oxidative stress mechanisms. It was found that hyperthyroidism is associated with increased mitochondrial activity and simultaneous release of electrons from the mitochondrial electron transport chain due to increased production of thyroxine [2].

In another study, conducted on rats after administration of L-thyroxine, it was demonstrated not only an increase in the levels of T_3 and T_4, but also in testosterone level. After that the simultaneous administration of antioxidants such as folic and ascorbic acids showed that the levels of thyroid hormones, testosterone, glutathione, as well as markers of oxidative stress approached values very close to normal ranges [7].

In human studies, hyperthyroidism has been associated with an increase in SHBG levels, which led to an increase in circulating levels of total testosterone and a decrease in the rate of its metabolic clearance [46]. These data are probably explained by the ability of thyroxine to increase the level of mRNA of SHBG by stimulating the transcription of the nuclear factor of hepatocytes 4α (HNF4α) [36]. In men with hyperthyroidism, the concentrations of total and free estradiol were increased; the levels of free testosterone were even lower than normal and below the value of the free testosterone / free estradiol ratio compared with euthyroid subjects [33, 38]. An increase in free estradiol in men with hyperthyroidism may contribute to a decrease in libido and a higher incidence of gynecomastia [27].

Clinical studies of the routine semen analysis have shown that an increase in the level of thyroid hormones is accompanied by astheno-, oligo-, teratozoospermia and a decrease in the volume of semen [17, 22]. Abalovich M. et al. investigating the effect of hyperthyroidism on spermatogenesis in 21 patients revealed the following *incidence* of abnormal semen parameters: asthenospermia 85.7%, hypospermia 61.9%, oligospermia 42.9%, necrospermia 42.9% and teratospermia 19.0% [18].

Krassas G.E. et al. studied semen parameters in a prospective study involving 23 men with hyperthyroidism, comparing data with 15 euthyroid men used as controls. The results showed a slight decrease in sperm density, changes in sperm morphology, and a significant decrease in sperm motility compared to controls. They have demonstrated an improvement in sperm count and sperm motility after treatment with methimazole alone or in combination with radioactive iodine [3].

Influence of hypothyroidism on sex hormones and sperm parameters. Hypothyroidism is a pathological condition of a low level of circulating T_4 and T_3 and an elevated thyroid-stimulating hormone level. Hypothyroidism in men is less common than in women, and has a less pronounced effect on reproductive function [14]. Hypothyroidism affects up to 5% of the general population; more than 99% of patients suffer from primary hypothyroidism. Globally, environmental iodine deficiency is the most common cause of all thyroid diseases, including hypothyroidism [8].

Primary hypothyroidism leads to a decrease in the concentration of SHBG, total and free testosterone [19], whose concentrations may increase after therapy with L-thyroxine [4]. Primary hypothyroidism is also associated with hyperprolactinemia and hypogonadotropic hypogonadism, which is reversible with thyroid hormone replacement therapy [27].

Among men with hypothyroidism, as in the case of hyperthyroidism, erectile dysfunction is widespread, and thyroid hormone replacement therapy restored normal erectile function [37]. Therefore, the authors of clinical trials *recommend screening for thyroid dysfunction* in *men* who present with *erectile dysfunction*.

Thyroid hormone deficiency during *early* stages of *testicular development affects* testicular maturation and reproduction later in life [42]. Thus, severe and prolonged hypothyroidism that occurs at an early age leads to a moderate failure of the secretion of gonadotropins by the pituitary gland, which, in turn, can affect the morphology and function of the testicles [26].

Sperm abnormalities associated with hypothyroidism are partially similar to those reported in hyperthyroidism [19]. In rats whose thyroid gland was blocked by antithyroid drugs, there was a significant decrease in the *epididymal sperm* count, which was accompanied by a significant increase in the percentage of damaged spermatozoa [9]. There was also a significant decrease in the weight of the seminal vesicles and the ventral prostate lobes the compared with euthyroid controls. Hypothyroidism also decreased total and daily sperm production and increased the transit time of sperm through the epididymis, while progressive sperm motility decreased [30]. This decrease in sperm viability may be the result of an imbalance between increased oxidative stress caused by lipid peroxidation and decreased antioxidant systems such as catalase and superoxide dismutase. According to a number of authors, thyroid hormones regulate the antioxidant defense of the testes, and any change in their level can affect the physiology of the testes due to oxidative stress. Thus, a decrease in the level of thyroid hormones can disrupt testicular function, especially spermatogenesis, by reducing the level of reduced glutathione in the testes, which plays an important role in the proliferation and differentiation of spermatogenic cells, protecting them from the harmful effects of reactive oxygen species [9].

In humans, teratozoospermia is the most common semen disorder in hypothyroid patients [23]. A decrease in the

proportion of progressive sperm cells has also been reported [34, 39]. Similar to hyperthyroidism, *semen* alterations during *hypothyroidism are reversible and mostly disappear* upon *achieving euthyroidism*.

Conclusion. The *recent* studies have significantly advanced our understanding of the mechanisms that regulate the action of thyroid hormones at the tissue and cellular levels. Research increasingly shows that the action of thyroid hormones depends not only on serum hormone concentrations, but also on the local set of transporters, deiodinases and receptors. The presence of thyroid hormone receptors in various types of testicular cells has been demonstrated in both animals and humans. Accordingly, hyperthyroidism and hypothyroidism have a marked effect on testicular function and, to a greater extent, on fertility. Hyperthyroidism and hypothyroidism are associated with changes that affect endocrine and reproductive function. Specifically, patients with hyperthyroidism have higher serum SHBG levels and lower free testosterone concentrations, higher levels of astheno-, oligo-, and teratozoospermia, and a higher prevalence of sexual dysfunctions such as premature ejaculation. In patients with hypothyroidism there are often observed teratozoospermia and a decrease in the proportion of sperm with progressive movement; hormonal changes are associated with a decrease in the levels of SHBG, total and free testosterone. Thyroid hormones also help maintain the redox status of testicular tissue by regulating the balance between reactive oxygen species and antioxidant defenses. Most patients with impaired thyroid function experience some sexual dysfunction that can be corrected by normalizing iodothyronine levels.

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GENES-MARKERS OF PEPTIC ULCER DISEASE

The review presents the analysis of the literature on genetic studies devoted to candidate genes for peptic ulcer disease. All the materials of these publications can be combined into two large groups: studies devoted to investigation of peptic ulcer inducer genes and studies devoted to protective genes. The main groups of ulcer inducer genes (*ABO, HLA, PSCA, IL-1B, IL1RN, IL-6, IL-8, IL-10, TNFα, TGF-b1, B1,2,3, CYP2C19, MMP-2, MMP-3, MMP-9, Toll,TLR4TLR9, MIF, MPO*) and protectors (*IL-1, IL-1RN, TNF, LTA, IL-1b, MMP-3*) were identified, but most of the results obtained to date are inconsistent, poorly reproduced in ethnically diverse populations, which makes it relevant to study this problem among different groups living in the Russian Federation.

Keywords: Peptic ulcer in women, peptic ulcer of the stomach and duodenum, genes, genes-markers of peptic ulcer disease, literature review.

Introduction. According to the world statistics, the prevalence of gastroduodenal ulcer is 5-15% of the world population [25]. Moreover, ulcer disease with localization in the duodenum is 4-13 times more common than gastric ulcers. Currently, there is an increase in the number of ulcer disease among women. The ratio of men and women in the incidence of duodenal ulcer is 1,9 : 1 in the USA, 2,2 : 1 in Europe and 3,6 : 1 in China. However, complicated forms ulcer diseases in women are observed 2-4 times less frequently than in men. Conspicuous is the fact that the highest incidence of Ulcer Disease in men is in their 20s with a gradual decrease by the age of 40 [8]. In women, the incidence rate is, on the contrary, higher with increasing age of the pathology [2].

It is commonly known that ulcerative defect of the mucous membrane of the stomach and duodenum occurs due to the predominance of aggression factors over protection factors. Nevertheless, later, during years of research, scientists discovered a bacterium unknown at that time, which was named H. pylori [2]. The microorganism was first isolated in 1982 by B. Marshall and R. Warren. They showed by their own example that this bacterium plays a fundamental role in the formation of gastric mucosa ulcers. Despite the fact that the cause of ulcers was "established" and experimentally proved, however, the question of differences in the frequency of ulcers in this or that category of people was still open. In addition to the infectious theory, inflammatory, gastric, peptic, vascular, spastic, mechanical, neurotrophic and cortico-visceral theories were considered as the ultimate cause of ulceration. However, none of these theories could explain the true nature of the ulcer. The question of Crouvellier (1835), "why does an ulcer arise in one place, while the rest of the mucosa remains intact," is still relevant today.

The possibility of determining disposition towards many multifactorial diseases has become a reality due to the development of molecular genetics. The results of treatment of these diseases can be determined by a specific set of polymorphic gene variants. The study of the genetic basis of these diseases allows not only to predict the course of the disease, but also prevents the occurrence of complications. Some genetic markers, such as blood group O (*ABO* gene, rs505922) [22], asecretory status, hyperpepsinogenemia (I/D)[19] and HLA antigens, polymorphic loci of the *PSCA* gene (prostate stem cell antigen, rs2294008) [19] have been described as associated with ulcer disease, although so far the results have been contradictory.

Due to the increasing incidence of ulcer disease and the frequent development of complications, the study of genes involved in the formation of ulcer disease is an extremely important task, the solu-

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