Modern Aspects of Studying the Features of Morphofunctional Characteristics of Testes Under Various Factor Influences

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ABSTRACT

Male infertility is a widespread disease among married couples. In almost 50% of cases, infertility is associated with a man, mainly due to a violation of spermatogenesis. Recently, the causes of male infertility have been increasing due to the progressive development of the environment and global changes. Psychological stress, general injuries, exposure to temperature and various chemicals, mobile phone, malnutrition, aging, hormonal imbalance play a crucial role in infertility in men. This review examines the features of the morphofunctional characteristics of the testes under the action of various factors affecting male fertility.

Keywords: Testes, Fertility, Stress, Convoluted Seminal Tubules, Hypogonadism

Introduction: Several studies have studied the relationship between sperm quality, changes in the structure of the testes, violation of their regulation and the presence of stress factors, increased or decreased testicular temperature, exposure to various irradiations and chemicals, the impact of traumatic brain injury. The decline in male fertility, especially associated with old age, improper lifestyle and environmental factors, plays an important role in fertility, and its consequences for the future population make this an important public health problem. Thus, lifestyle changes through a structured program of educational, environmental, nutritional/physical exercises and psychological support combined with the use of antioxidants can prevent infertility and, therefore, can help couples improve their quality of life and increase the likelihood of spontaneous conception or optimize their chances of conception [1].

Reproductive health can be positively or negatively affected by numerous factors, such as the age of paternity, exercise, obesity, nutrients, caffeine, scrotum temperature, clothing, mobile phones [4,5], which, thus, can affect the quality of life of sperm parameters and DNA damage caused by reactive oxygen species (ROS) [6]. In addition, the altered balance between the antioxidant system [7] and oxidative stress can determine poor fertilization/embryonic development, miscarriage, birth defects [8,9,10].

The role of stress on the testicles of rats: During one experiment, the animals of the experimental group were exposed daily to two stressors alternating in random order: rotation in the cage for 50 minutes at a speed of 60 rpm, forced swimming in cold water (4 minutes at a temperature of 11-12°C), placement in a dark refrigerator with a temperature of 4-5 °C for 60 minutes, bright lighting at night, no light during the day, isolation in individual cells at night, immobilization in individual plastic containers with free air access for 60 minutes, deprivation of water and food for a 12-hour period. The duration of the experiment was 10 days. Microscopic examination of histological preparations of testes of rats exposed to chronic stress revealed pronounced morphological changes in interstitial tissue and convoluted seminal tubules (CST) of the organ. So, in animals, vessels, including those related

to microcirculatory, were in a state of moderate, and sometimes pronounced fullness.
In most animals, significant areas with sharply reduced CSTs in diameter were identified in the testicular tissue. Compression of the CST was accompanied by the appearance of optically empty spaces in the testicular tissue between the walls of the CST and the connective tissue partitions of the organ. Areas with a sharp decrease in the diameter of the CST were determined both in the central part and along the periphery of the organ section, pronounced destructive phenomena from the spermatogenic epithelium were noted up to the phenomena of testicular necrosis. Destructive changes in the spermatogenic epithelium consisted in violations of integrative connections between Sertoli cells and developing germ cells, which led to their separation with the appearance of more or less pronounced voids between the cells of the spermatogenic epithelium [2,3,4]. Acute stress can also disrupt the function of the testicles. Testicular tissue of stressed rats shows higher levels of cortisol, demonstrating apoptosis of both germ cells and Leydig cells [14,1]. Sperm parameters can potentially be associated with stress, the presence of which can reduce the release of luteinizing hormone and testosterone, which, in turn, reduces spermatogenesis and sperm quality [12,13].
The effect on the testes of *an increase in temperature* can worsen fertility due to changes in the parameters of spermatozoa (quantity, mobility and morphology) and violation of the integrity of the membranes of spermatozoa [7]. The temperature of the scrotal sac reflects the temperature of the testicles, and its thermoregulation is a fundamental protective mechanism [8]. Higher temperatures contribute to an increase in the formation of ROS, followed by damage to the plasma membrane of spermatozoa and deterministic DNA fragmentation of both nuclear and mitochondrial genomes, which leads to cell damage and apoptosis [9]. Animal studies confirm the concept that an increase in testicular temperature by 1-1.5°C leads to a decrease in testicular size, a decrease in sperm production, abnormal forms [10] and a decrease in mobility [11,12,19]. Heat stress can affect the testicles, especially cells with a high rate of mitosis, such as mature spermatocytes and spermatids of spermatozoa [14,15]. According to studies conducted on mice, hyperthermia affects sperm cells, determining DNA damage and apoptosis by internal or external means [16,17,18]. The consequence of this is a poor ability to fertilize in vivo and in vitro.
During *cold exposure*, the following changes were noted in the testes of experimental rats: morphologically, the seminal tubules were characterized by a rectilinear shape, narrowing of their diameter due to a decrease in the width of the epitheliospermatogenic layer in them. Swelling of the inter-tubular stroma was also observed. The Leydig cells located in the interstitial tissue were mostly rounded or process-shaped and were located either singly or in clusters near the vessels. Spermatogenic cells were mainly represented by spermatogonia and spermatocytes of the first order. This may indicate a violation of the generative and excretory activity of the testes [20,21,22].
The negative effect of *titanium dioxide nanoparticles* on the morphological parameters of rat testicles affects key characteristics for this structure, such as the proliferative activity of cells and their ability to differentiate, specific structural changes were also detected, indicating an adverse effect of the studied nanoparticles on the reproductive system of male rats, a sharp decrease in the number of mature spermatids was noted, as a result of which the epitheliospermatogenic layer it was represented by only three generations of germ cells: spermatogonia, spermatocytes of the first and second orders. The total effect of the detected changes in the testicles of rats is a violation of the processes of spermatogenesis. The obtained results of the conducted studies may indicate not only the direct effect of titanium nanoparticles, but also be a consequence of their effect on the humoral systems of the body [23,24].
When *lipopolysaccharide* was administered against the background of hyperandrogenemia, the diameter of the tubules was statistically

significantly higher compared to the control and the values of the comparison group. Thus, the signs of alteration of the seminal tubules when exposed to endotoskin on the background of hyperandrogenemia were more pronounced. The level of testosterone in the blood serum decreased by 3 times. The areas of the nuclei of Leydig cells were smaller, which corresponds to the levels of testosterone in the blood serum. The index of spermatogenesis was lower than in the control, which indicates suppression of spermatogenesis. The level of testosterone in the blood serum decreases by 10 times. [26,27,28].

The effect *of prolonged light stress exposure* (light desynchronosis) affects both the reproductive and endocrine parts of the testes of white male rats. interstitial tissue edema is visually noted, morphometric analysis shows a significant increase in the area (4.3%) and diameter (1.5%) of the cross-section of the convoluted seminal tubules (CST), which is accompanied by a decrease in such indicators as the thickness of the epitheliospermatogenic layer (12.3%) and the number of spermatids (2.6%) and spermatogonia (5.3%), and there is also a decrease in the number of Leydig cells (7.1%). Under stress of various etiologies in rats, there is a violation in the hypothalamic-pituitary system, which leads to an imbalance in the synthesis of releasing factors and, as a result, the production of gonadotropins (FSH and LH) of the anterior pituitary gland is inhibited. This leads first to the stimulation of testosterone synthesis, which manifests itself in the number of spermatids, i.e. stimulation of spermatogenesis, and then to a decrease in its secretion, which is characterized by a decrease in the quantitative composition of spermatogonia, spermatids, i.e. there is an inhibition of spermatogenesis [29].

The testicular system of males is highly sensitive to the action of *xenobiotics*. The accumulation of various toxic substances in the testes is possible, leading to a violation of spermatogenesis, a change in the qualitative and quantitative parameters of spermatozoa. In rats, when intoxicated with the herbicide 2,4-DA, changes are observed in the protein membrane of the testis: collagen fibers are loosely located due to cracks of various sizes, some of the fibers are in a state of destruction, and some of the fibers have a tortuous course, blood vessels are hyperemic. On the periphery of the testis, near the albumen, the convoluted tubules are located quite freely. Destructive and necrotic phenomena are detected in the peripherally located tubules, their emptying as a result of necrosis of many cells. Sometimes there is a detachment of the spermatogenic epithelium on the inner part of the tubules. As a result, there is a decrease in the number of cells in the spermatogenic epithelium, voids are formed, many cells lose their connection with sustentocytes, syncytia disappear. In the centrally located convoluted tubules, there is an increase in the size of the nuclei of cells at the stages of growth and reproduction. Many nuclei are in a state of karyopycnosis. In some convoluted tubules, the cells are hypertrophied and have an oxyphilic color. The use of complex analysis using light-optical and ultrastructural methods made it possible to observe the relationship of spermatogenic epithelium and sustentocytes in the testicles of rats. During the formation of sperms, a change in shape, the distribution of chromatin in the nucleus, and the formation of an acrosome were observed. When a flagellum is formed, microtubules and many mitochondria are structured. When animals were intoxicated with xenobiotics, similar deep destructive changes were found in the stroma, endocrine apparatus, vascular system and spermatogenic epithelium. [30,31].

In the testes of rats exposed to a single *gamma radiation*, changes in the microstructure of the gonads were manifested. The spermatogenic epithelium of the convoluted seminal tubules of rats is a highly sensitive tissue to single ionizing irradiation of animals at doses of 0.5 and 1.0 Gr, which manifests itself in pronounced morphological disorders of its structure already 3 days after irradiation. In the experimental group of rats exposed to radiation at 90 days of age, the diameter of the convoluted seminal tubules is 4% smaller compared to the control, and their cross-sectional area is 6% smaller. In addition, the height of the spermatogenic epithelium is less by 7%, the diameter of the lumen of the seminal tubule is 9%, the weight of the testes is 4%, the length of the testes is 4%, the thickness of the testes is 3% and the volume of the testes is 6%. The number of Leydig cells decreases by 8%, and their size by 3%. [32,33].

The effect *of immunosuppressors*: after the use of cyclophosphamide, the morphometric parameters of the epithelium significantly differed from the values of the control data. So, the height and width of the cells decreased. The volume of epithelial cells also significantly decreased statistically. Also, one of the pharmacodynamic effects of the drug in an immunosuppressive dosage is the disorganization of the biosynthetic and mitochondrial apparatus of the cell, which leads to violations of its energy and metabolic metabolism and functions performed. Similar results were obtained by V. I. Zvyagina et al. [34,35] in the study of structural and functional changes of the mitochondrial enzyme complex under conditions of inhibition of its activity in the cells of the appendage of the testis. The early reaction of organs from the male reproductive system in response to the immunosuppressive effect of the complex of inhaled pollutants was also established by the studies of V. G. Koveshnikov et al. [36]. In addition to the direct effect of the immunosuppressor on the morphostructure of the organ under study, it is also possible indirectly – by disrupting the hormone-dependent regulation of the interaction of structural and functional elements of the appendage. Thus, the depressing effect of a single application of a high dose of cyclophosphamide on the androgen-receptor apparatus of the supporting cells and glandulocytes of the testicles of rats of the reproductive period was proved by K. N. Lapin et al. [36,37].

The effect of traumatic brain injury on the testes: Gonadotrophic hormones (follicle-stimulating hormone and lutenizing hormone) are reduced acutely, but their deficiency does not appear to produce clinically important sequelae. Someone with TBI can have one or more problems, depending on the injury. Problems that often occur soon after TBI include [38,39].:

- Adrenal insufficiency: when the adrenal glands don't make enough hormones; results in fatigue, weight loss, low blood pressure, vomiting, and dehydration. Adrenal insufficiency can be life-threatening if not treated [40,41].
- Diabetes insipidus: when the pituitary doesn't make enough ADH; results in frequent urination and extreme thirst [42,43].
- Hyponatremia: when certain hormone problems upset the balance of salt and water in the body; can result in headache, fatigue, vomiting, confusion, and convulsions.

Problems that may occur later and their symptoms include:

- Hypothyroidism (not enough thyroid hormone): fatigue, constipation, weight gain, irregular menstrual periods, cold intolerance
- Hypogonadism (not enough sex hormones): in women, a stop in menstruation and loss of body hair; in men, sexual dysfunction, breast enlargement, loss of body hair, and muscle loss [44, 45].

Hypopituitarism can be a subclinical condition, identified only by hormonal tests, or its clinical manifestations can be acute and severe, pointing toward the need for immediate treatment. However, the deficit of gonadotropins will lead to partial hypopituitarism due to hypogonadotropic hypogonadism presenting chronic morbidity. Hypogonadism in men is associated with decrease in life quality, fatigue, mood impairment, insomnia, osteoporosis, loss of libido, impaired sexual function, loss of facial, pubic and body hair. In other hand, hypogonadism in women is associated with loss of libido, dyspareunia, oligoamenorrhea, infertility and decreased quality of life. The time factor is particularly important in post-TBI hypogonadism. The development or disappearance of post-TBI sequels does not have a specific time to occur. Temporary and mild hypogonadism can disappear

after several months, since the damaged tissues can recover spontaneously. According to current evidences and considering the huge amount of potential post-TBI patients to be tested for hypogonadism (and hypopituitarism) all over the world, it seems to be reasonable that follow-up be done at least one year after the TBI event and not before this period of time [46,47]. Considering the high incidence of TBI, post-TBI hypogonadism arises as a critical problem for Public Health, due to the unproductive condition of non-treated patients, as well as to comorbidities brought about by metabolic alterations. Hormonal replacement therapy may reduce morbidity, optimize rehabilitation and improve the quality of life of the patients. Follow-up programs for post-traumatic hypopituitarism should constitute a part of the clinical routine care for patients with cranial trauma[48]. These programs require multidisciplinary cooperation among endocrinologists, neurosurgeons, psychologists and other Health professionals in order to help cranial trauma victims to resume their normal life.

Conclusions: Modifiable factors play a crucial role, lifestyle factors play in the development of male infertility, thereby arousing growing interest in this area. There are associations between psychological attitudes and infertility, but it is currently difficult to establish a causal relationship. Although stress (physical, emotional, biological, etc.) can reduce the potential of male fertility, there is no consensus on how to objectively measure it. The influence of chemical and physical factors has been studied by preclinical and clinical studies, so they apparently worsened the parameters of sperm. As well as an increase in the number of severe injuries affected male fertility. All cited observational studies concerning these factors may indicate an association, but not a causal relationship. Properly planned randomized controlled trials are needed to confirm these correlations.

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