

Men's Reproductive Health: Oxidative Stress and the Effectiveness of Antioxidant Therapy

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Abstract

This review article surveys and summarizes the literature data concerning the problems of deterioration of the main indicators of men's reproductive health and the effectiveness of therapy with drugs with antioxidant properties.

The analysis of domestic and foreign literature confirms that oxidative stress accompanies and/or is one of the pathogenetic links in the development of many types of reproductive pathology in men. The health status of the male population is influenced by the following factors: lifestyle, existing diseases, the state of the environment, and the genotype of the population. The interaction of several weak, but unidirectional, factors creates a high risk of developing male reproductive pathology. The polyetiological nature of fertility disorders in men causes certain difficulties in creating adequate methods of treating this pathology and causes multicomponent biocomplexes to appear on the pharmaceutical market that contain active substances that can affect the quality of the ejaculate. (**International Journal of Biomedicine. 2021;11(3):333-336.**)

Key Words: men • reproductive health • oxidative stress • infertility • antioxidant therapy

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Today, there is an important trend in the demographic policy of the State to preserve the reproductive health of the population. In recent years, there has been a decline in the absolute population because its reproduction has been reduced, and each subsequent generation is smaller than the previous one.⁽¹⁻⁵⁾

Over the past few years, a progressive decline in fertility among adult men has been noted both in Russia and abroad, and therefore the standards of the spermogram have been revised in the direction of reducing the quantitative and qualitative indicators of the ejaculate.

It is known that different indicators of the ejaculate, such as the number, motility, and morphology of sperm, are sensitive to the action of free radicals. Spermatozoa were the

first type of cells in which the formation of free radicals was described.^(2,5,6)

Reactive oxygen species (ROS) normally form the spermatozoa themselves, and ROS play an important physiological role in the mechanism of the acrosomal reaction, that is, they are necessary in the process of the sperm penetrating the egg. Along with the formation of ROS, they are continuously deactivated by a special system of antioxidants contained in the seminal plasma, which provides a balance between the oxidant and antioxidant systems in the vas deferens. Violation of this balance inevitably leads to a deterioration in fertility and as a result to a violation of the reproductive potential.^(4,7-9)

Spermatozoa are more sensitive to oxidative stress than any other cells, due to the small volume of the cytoplasm, low concentration of antioxidants, and a large amount of polyunsaturated fatty acids, which are easily subjected to peroxidation.⁽⁶⁻⁸⁾ In addition, the structural features of spermatozoa are such that antioxidant enzymes are not able to protect the cell membrane at the levels of the tail and

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acrosome.^(4,8,9) In response to the widespread hypothesis that free radicals play a leading role among most processes of the body, it was assumed that the intake of antioxidants can reduce or prevent the development of oxidative stress and slow down the process of cell destruction. This will stop the progression of many diseases and prolong the active years of a person's life, and in the case of infertility – improve the characteristics of spermatozoa and the quality of the ejaculate as a whole.^(10,11) It has been shown that there are vitamins, minerals, amino acids, and other organic compounds that can reduce oxidative stress by enhancing metabolic processes, activating nuclear-cytoplasmic transport, and reducing the activity of inflammation and weakening autoimmune reactions; and that taking drugs containing these compounds in infertile men leads to an improvement in sperm parameters, restoration of the sperm function and an increase in the frequency of pregnancy.⁽¹²⁾

We analyzed the possibility of using antioxidant supplements to prevent and treat infertility, using publications included in the Cochrane Library, EMBASE, MEDLINE, PubMed, and eLibrary databases. The most effective and important classes of dietary supplements are natural dietary antioxidants and dietary supplements in preparations because the formation of free radicals under oxidative stress plays a confirmed role in the violation of sperm function.

The groups of antioxidants are classified as endogenous and exogenous. Endogenous are divided into enzymatic, such as catalase, superoxide dismutase, glutathione peroxidase, and non-enzymatic, such as glutathione, vitamin E, vitamin A, vitamin C, coenzyme Q10, and L-carnitine. Exogenous antioxidants (vitamins E and C, carotenoids) enter the body with food.^(5,11) Oral administration of antioxidants significantly reduces the index of DNA fragmentation, including under conditions of oxidative stress.⁽¹³⁾

A decrease in the concentration of malondialdehyde in semen, a product formed under the action of ROS during the degradation of polyunsaturated fats and a marker of oxidative stress, was noted by S.A. Suleiman et al. (1996), while establishing a concomitant increase in sperm motility in men with asthenozoospermia and a higher frequency of natural conception, compared to the control group. Multicomponent biologically active complexes containing L-carnitine, vitamin E, folic acid, and zinc in increased dosages have been widely used to correct oxidative stress in infertile men. According to the results of the use of the complex, patients showed an increase in the volume of ejaculate by 10% and in the concentration of spermatozoa by 15.6%, and a decrease in the dilution time by 32%, against the background of a significant decrease in the levels of ROS and fragmentation of the DNA of spermatozoa.⁽¹⁴⁾

Micronutrients can help reduce inflammation, weaken autoimmune processes, improve intermediate metabolism, activate nuclear-cytoplasmic transport, and restore the integrity of sperm membranes. The most significant work is the Cochrane review, which analyzed the cases of 2,867 couples who participated in 34 studies. There was a statistically significant increase in the frequency of pregnancy and childbirth in subfertile couples. Micronutrient supplements

may also be useful for patients who resort to assisted reproductive technologies.⁽¹³⁻¹⁵⁾

The review studied and evaluated the effectiveness of the basic sperm supplement containing glutathione, L-carnitine, L-arginine, coenzyme Q10, α -tocopherol, folic acid, zinc and selenium in patients planning to resort to IVF. The tests were taken initially and after 12 months, before the use of assisted reproductive technologies. Semen samples were obtained from 147 patients. The results of the analysis showed a sharp increase in the indicators of motility and the total number of spermatozoa in patients with oligoastenoteratozoospermia.^(7,13,16)

A study by Neymark et al.⁽¹⁷⁾ showed the effectiveness of a dietary supplement composed of a complex of trace elements and vitamins: selenium, zinc, vitamin E, vitamin C, and beta-carotene. Zinc has a high bioavailability due to the organic form of lactate, and the synergism of the components enhances the antioxidant effect of the drug as a whole. Three months after treatment, the following indicators of ejaculate were obtained in patients: an increase in the volume of ejaculate by 59%, an increase in the number of spermatozoa by 79%, an increase in the number of viable spermatozoa by 28%.⁽¹⁷⁾ The resulting positive effect is probably due to the antioxidant effect of zinc by the activation of glutathione peroxidase of spermatozoa, since sufficient activity of this enzyme ensures normal maturation and motility of spermatozoa.⁽¹⁸⁾ The replacement of zinc deficiency also leads to an increase in the overall activity of the antioxidant system and an increase in the number of pro-inflammatory cytokines.^(18,19)

Quite a lot of biologically active additives (dietary supplements) have been developed that affect certain parts of the male reproductive system or certain diseases.⁽¹⁷⁻¹⁹⁾ Taking into account the pathogenesis of disorders that occur in the pathology of the male reproductive system, as well as the peculiarities of the effect of biologically active substances on the body, a multicomponent natural complex containing plant extracts, B vitamins (B5, B6, B12), vitamin C, and L-arginine was created.⁽²⁰⁾ The presented complex is recommended to be used to stimulate the synthesis of testosterone in case of its insufficiency in various etiologies. Unlike synthetic hormonal drugs, it does not violate the physiological mechanisms of hormonal regulation, increasing the level of androgens only when they are deficient in the body. Oral intake of a dietary supplement can play a direct role in improving the parameters of sperm and restoring its function. Studies of targeted nutraceuticals, which include fat- and water-soluble antioxidants, amino acids, and metabolic cofactors, have shown a 10.2% improvement in the DNA fragmentation index. There was also a 70% increase in sperm count and an 85% increase in motility. The volume of ejaculate increased from 2.6 ml to 4.3 ml, an increase of 39.5%.⁽²⁰⁾

A new biocomplex, including retinol, α -tocopherol, glycyrrhizic acid, coenzyme Q10, arginine, carnitine, carnosine, zinc, and selenium, has recently appeared on the pharmacological market; this complex improves the quality of the ejaculate by affecting various parts of the pathogenesis of fertility disorders.⁽²¹⁾ The synergistic effect of the components of the biologically active complex is due to the use of Actielease nanotechnology in the production (separation

of active ingredients into microscopic nanoparticles), which provides an optimal concentration of components, high bioavailability and stability of the composition. The components of the drug contribute to the improvement of microcirculation, indirectly stimulate the release of testosterone, have a detoxifying, antihypoxic, reparative effect, normalize lipid and carbohydrate metabolism, have a powerful antioxidant effect, are able to inhibit apoptosis, and protect the cells of the reproductive system.^(17,22) After a course of therapy (30 days), patients showed a significant increase in all indicators, compared to the initial parameters (the volume of ejaculate increased by 78.2%, the number of spermatozoa in 1ml increased by 80.7%, the viability of spermatozoa by 1.35 times, the number of spermatozoa with normal morphology – by 1.57 times).⁽¹⁷⁾ There was a statistically significant decrease in sperm DNA damage (in absolute values-by 4%), while the positive dynamics of DNA fragmentation during treatment occurred in 67% of men. Also, during treatment, the severity of oxidative stress significantly decreased, which was confirmed by a decrease in ROS production by washed spermatozoa, on average by 2-5 times, compared to the baseline level.⁽²¹⁾

Modern multicomponent complexes for improving spermatogenesis and increasing male fertility include a combined drug containing (in addition to vitamin E, coenzyme Q10, carnitine, selenium, and zinc), docosahexaenoic acid, which not only has antioxidant properties, improving the composition of membranes, but also affects various parts of spermatogenesis disorders, preventing DNA fragmentation and increasing sperm motility and survival.⁽²³⁾ The criterion for the effectiveness of therapy is the improvement of the main indicators of the spermogram: the volume of ejaculate, the concentration of spermatozoa, the proportion of spermatozoa with translational movement, and the normal morphology of spermatozoa.

According to the research data of Korenkov et al.,⁽²³⁾ no cases of drug intolerance were recorded. The spouse of one of the patients in the main group became pregnant 11 weeks after the start of therapy. However, in the study of Bozhedomov et al.,⁽²⁴⁾ on the contrary, there was no significant effect of this drug on spermogram parameters, sperm DNA fragmentation, or the percentage of pregnancies that occurred.

Despite the rather diverse composition of the presented supplements, none of them contain such an important substance for male fertility as vitamin D.⁽²⁵⁾ Vitamin D deficiency is observed in people of all ages, including men of reproductive age, in many countries of the world, including Russia. There is evidence that vitamin D deficiency negatively affects sperm quality (reduced overall and progressive sperm motility, total motile sperm count) and hormone function, and the frequency of pregnancy and childbirth is significantly higher in couples with normal vitamin D levels.⁽²⁵⁾ Enzymes that metabolize vitamin D are simultaneously expressed in Sertoli cells, Leydig cells, sperm cells, and epithelial cells lining the male reproductive tract. The somatic or germ cells of the testis appear to be able to synthesize and activate vitamin D locally.

By means of genomic mechanisms, 1,25(OH)2D3 regulates the expression of androgen biosynthesis enzymes in Sertoli cells; by means of a non-genomic mechanism (in

particular, activation of the signaling cascades of protein kinases A and C, MEK kinase), 1,25(OH)2D3 stimulates the absorption of calcium and increases the activity of gamma-glutamyl transpeptidase. In the studies of Wadhwa et al.,⁽²⁶⁾ it was noted that vitamin D increases sperm motility because it directly affects sperm cells, including non-genomic-controlled modulation of intracellular calcium homeostasis and activation of molecular pathways involved in sperm motility, condensation, and acrosome reaction. Even at low doses (200 IU/day, 3 months), vitamin D in combination with calcium (600 mg/day) significantly improved the condition of patients with idiopathic oligoasthenozoospermia, improving, in particular, sperm motility.

Spermatogenesis is an energy-intensive process that requires a sufficient and balanced amount of vitamins and minerals in the body. The results of the analysis of domestic and foreign authors show that a positive trend in fertility disorders in men is given by phytotherapy, treatment with micronutrients, and therapy with antioxidant drugs containing retinol, α -tocopherol, vitamin D, glutathione, coenzyme Q10, L-arginine, L-carnitine, carnosine, selenium, zinc, B vitamins, docosahexaenoic acid, glycyrrhizic acid, and folic acid in various combinations.^(27,28)

However, there is not enough data to provide convincing recommendations based on the high reliability of the evidence regarding the dosage, frequency, and duration of each drug. Do not forget that antioxidants, despite their versatility, are not a panacea, but a very subtle regulatory tool. Studying the regulatory system as a whole, it is necessary to determine which cases can be treated with antioxidants alone and which require complex therapy, in which other biologically active substances are used in addition to antioxidants.^(27,29)

The presented analysis of publications devoted to the conservative treatment of male infertility and fertility disorders demonstrated that most of the drugs are effective, but at the same time, more study is required to improve pharmacological achievements in the fields of endocrinology and urology. This requirement determines the direction of further research.

Competing Interests

The authors declare that they have no competing interests.

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