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COMPLEX APPLICATION OF CERTAIN MICRONATRIENTS IN MEN WITH ANDROGEN DEFICIENCY AND PATHOSPRIMES

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Abstact

A complex approach was made for the deactivation of deuterine micronutrients, which include antioxidant and metabolic metabolism, in individuals with androgen deficiency and idiopathic pathospermia. It has been shown that is using the complex preparation «FEROLL» for 60 days leads to increase the parameters of the spermogram to normal values on the background of normal androgen levels of blood in these patients.

Keywords: androgen deficiency, micronutrient, pathospermia, testosterone.

Introduction. Literature dates suggests that in 15 % of married couples living a regular sex life with not protected for one year pregnancy does not occur and in about half of cases the cause of infertility is a violation of spermatogenesis (6 % of the total number of married couples) [1, 2].

A number of authors now consider the etiology of male infertility in some cases to be multifactorial. The main reasons for infertility in men are the following: hormonal, negative

effects of chemical substances, high temperatures, radiation, heavy metals, estrogens, pesticides, lifestyle factors (smoking, alcohol, emotional and physical stress, excessive accurate body weight, irregular and unbalanced nutrition); deficiencies of micronutrients with antioxidant properties (vitamins A, E, C, B_{12} and microelements: zinc (Zn), selenium (Se)); varicocele, sexually transmitted infections (STIs), accompanied by leukocytospermia; inflammatory diseases of the urogenital tract (prostatitis, vesiculitis, epididymitis), autoimmune and systemic diseases; age [3, 4, 5, 6].

According to the recommendations of the European Association of Endocrinologists, a diagnosis of androgen deficiency are established in the case of specific symptoms and signs that are accompanied by a decrease in blood testosterone levels (T) (Bhasin S. et al., 2010). One of the symptoms is infertility, namely pathospermia.

The reasons leading to the formation of micronutrient deficiencies are usually divided into primary (the deficient is a consequence of insufficient food intake) and secondary, which include genetic factors (polymorphism and mutations of genes), features of nutritional interactions (micronutrient-micronutrient: zinc-copper, iron-magnesium, cadmium-zinc, zinc-vitamin A), physiological stress (diseases associated with the characteristics of the metabolism of micronutrients: diabetes, hypertension), using some drugs, as well as the effect of the chemical substances and toxicants [7, 8].

The pathophysiology of male infertility are explained by a cascade of molecular and bio-chemical processes that are accompanied by the destruction of proteins, lipid peroxidation, the destruction of the biological membrane of sperm cells and the destruction of their DNA. These changes are manifested in most cases by changes in the morphology, mobility and concentration of spermatozoa. The imbalance between oxidative processes and peroxidation processes in sperm leads to metabolic and functional disorders of the cells of the germinal epithelium, which may be the primary cause of some forms of infertility, accompanied by an increase in the levels of active oxygen species (AOS) in sperm. This condition is called oxidative stress (OS), which is noted in 25-40 % of infertile men [9]. The accumulation of AOS is accompanied by a decrease in the antioxidant properties of sperm, which leads to toxic effects on the qualitative and functional parameters of sperm, in particular, a negative effect on sperm motility [9, 10, 11].

In maintaining spermatogenesis processes, the balanced state of the pro- and antioxidant systems is essential, which ensures metabolic processes in the sperm. The antioxidant system of seminal fluid is represented by extracellular, membrane and intracellular antioxidants. For intracellular (essential) include superoxide dismutase, catalase

and glutathione peroxidase (GLP). Extracellular includes vitamin C, urates, ubiquinone, sulfhydryl groups (proteins, glutathione), bilirubin, and vitamin E (tocopherols). The membrane includes tocopherols, carotenoids, transferrin, ceruloplasmin, haptoglobin, hemopexin [12].

The most important antioxidants that play a key role in the protection of spermatozoa from the OS are represented by the general antioxidant capacity and include the following components: superoxide dismutase, catalase, GLP, Se and selenoproteins (such as phospholipid hydroxyperoxide GLP, glutathione reductase), vitamins A, C and E, glutathione, spermine, thiols, urates, albumin, taurine, gipotaurin, Zn and L-carnitine [13]. Some authors also assign the role of the thioredoxin reductase system, the functioning of which depends on the content of Se, which regulates its activity [11].

The role of nitric oxide (NO) in ensuring reproductive function in men is confirmed by the analysis of literary sources, which showed its irreplaceable physiological role and, at the same time, the pathological effect, in case of its excess, on sperm motility and DNA destruction [14]. At physiological conditions, the synthesis of NO occurs from L-arginine (conditionally essential amino acid) under the action of neuronal, endothelial and macrophage NO-synthases (depending on location) with the final formation of the second product, L-citrulline.

Constitutive NO is represented in two isoforms (like endothelial and brain), is produced directly by spermatozoa, takes part in the inactivation of free oxidation products and inhibits the production of superoxide anion [13]. Thus, experimental data have shown the irreplaceable role of NO in ensuring fertility in rats [15]. In addition, L-arginine is a biochemical precursor necessary for the synthesis of putrescine, spermidine, and spermine [16, 17].

Se is an essential micronutrient. In the form of selenocysteine, it is an integral part of the catalytic center of the main enzyme of the antioxidant system GLP, which ensures the inactivation of AOS. Experimental data showed that in rats there is a defect in flagella in spermatids and mature spermatozoa when using a diet with a low content of Se. It was found that Se deficiency leads to specific ultrastructural changes in the spermatozoa of the tail part of the epididymus, in the flagellar and middle parts of them, as well as in violation of the post-test processes of their maturation [18, 19].

Se provides male fertility [20]. In one research found that Se concentration in semen positively correlates with sperm motility, as well as testosterone concentration (T), which is known to be involved in ensuring spermatogenesis [21]. A diet with a low content of Se leads

to a decrease in all indicators of spermograms in healthy men [22], and a low content of Se in serum is observed in men with azo- and oligozoospermia compared to men with normozoospermia [23, 24].

According to the existing European recommendations on the use of vitamins and minerals, an adult's need for Se is 65 μg/day, and the optimal concentration in serum is 115-120 μg/l. If its concentration in the blood drops below 50 μg/l, the selenium-deficient state develops because of the activation of lipid peroxidation processes, which is caused by a decrease in the activity of HLP [25], which increases the likelihood of the development of pathospermia in men. These data are relevant in connection with the problem of low Se content in wheat flour of northern and northwestern regions of Ukraine [26].

The role of Zn is the participate in the physiological and biochemical mechanisms of spermatogenesis, namely the oxygen supply of spermatozoa, nuclear compaction of chromatin and its stabilization, acrosomal reaction, acrosin activity, as well as steroidogenesis, synthesis of T and its conversion into dihydrotestosterone [27]. Zn is also involved in different periods of spermatogenesis. During the initiation of spermatogenesis, it is involved in the activity of ribonuclease, directly during spermatogenesis, participates in the maturation of spermatozoa, and at the final stages in increasing their motility [28].

L-carnitine is a vitamin-like natural compound. It is secreted by the cells of the basal-lateral and luminous membrane of the canalic epithelium of the epithelium of the testicle, followed by its accumulation in the epididymal fluid. There is a direct dependence of sperm motility on its concentration. It provides for the participation of fatty acid transport in spermatozoa mitochondria (for use as an energy source) and beta-oxidation during the post-test spermatozoa maturation in the epididymis. L-carnitine has an antioxidant activity, which is manifested in resistance to the action of peroxidases, an obstacle to the effects of OS on spermatozoa. It also participates in the normalization of the acrosomal reaction, the increase of its inducibility and affects the functional characteristics of spermatozoa [29].

Coenzyme Q10 (ubiquinone) is an endogenous antioxidant. It has energy-potentiating property. It plays a key role in the transport of electrons in the mitochondrial respiratory chain. It is a stabilizing and protective factor of membranes and cell lipoproteins from the OC in the male reproductive system, and is also the bioenergy component of mitochondria for promoting energy in the middle part of the sperm. Its semen levels significantly correlate with quantitative indices and sperm motility [30]

Glutathione plays an important role in the formation of phospholipid hydroxyperoxide GLP, an enzyme that is present in spermatids and plays a role in the formation of the structure of the middle part of mature spermatozoa [31].

Folic acid plays a key role in DNA synthesis. Folate - micronutrient, which is indispensable for the processes of proliferation [32].

Vitamin E is a nonspecific stimulator of the pituitary-gonad axis, a synergist of androgens, and also the main antioxidant of the sperm membrane, preventing peroxidation processes. It is necessary for the normalization of pro-and anti-antioxidant balance of seminal fluid. The AGES study showed that the presence of vitamin E in the diet was significantly correlated with the active motility of spermatozoa, and its level in seminal fluid was significantly correlated with an increase in the number of mobile forms [33, 34].

In 50 % of cases, the reason for the spermatogenesis disorders are a violation of the synthesis of T_{gen}, i.e. a decrease in its level below 12.0 nmol/l and/or a decrease in T_{free} below 0.31 nmol/l. This condition is defined as pathospermia and diagnosed in case of a decrease in the number of motile and/or active motile forms of spermatozoa, such as asthenozoospermia (AstZS), a decrease in the concentration of sperm cells as OZS, the absence of sperm cells, as AZS [35].

At the same time, the corresponding therapeutic practice has not been established, and in such cases, as a rule, empirical therapy is applied for a 3-6 months taking into account the full 74-day spermatogenic cycle [36, 37, 38, 39]. One of the aspects of therapy, in particular, OS in infertile men, along with the exclusion of the effects of toxicants, smoking, alcohol, prescription of antibiotics for STIs and surgical treatment of varicocele, is the appointment of a diet [4]. In cases of an established fact of irregular and unbalanced nutrition, as well as the presence of other causes, potentially causing OS and accompanied by an increased need for the supply of certain nutrients, we can talk about the expediency of its appointment to prevent the deficiency of some micronutrients and replenish their increased need for men with pathospermia.

One of the options for maintaining the balance of microelements, in particular, having antioxidant properties, is the addition to the diet of a combination of various micronutrients: vitamin E, L-carnitine, L-Arginine, Zn, Se, coenzyme Q_{10}, glutathion and folic acid, which prevent damage to reproductive organs with high sensitivity to the damaging effects of environmental, behavioral, genetic factors and aging processes [38, 39, 40, 41, 42, 43].

All of the above micronutrients are included in the composition of the registered domestic dietary supplement to the diet of the population «FEROLL» (LLC «ELITE-

PHARM», Ukraine). In addition, this drug contains licorice root extract (*Glycyrrhiza glabra*), licorice – a perennial herb of the legume family. It consists of minor components that have an antioxidant effect. Highly active glycosides, glycyrrhizin (glycyrritic acid is chemically similar to steroid hormones, has a strong anti-inflammatory effect), and flavonoids, exhibiting a pronounced antispastic effect, mannitol that enhancing diuresis, sitosterin, mannitol, bitter, protein and pectin substances, ascorbic acid, mineral salts, traces of essential oils. The pharmacological activity of this component is manifested in anti-inflammatory and hormonal effects, inhibition of the growth of viruses, streptococci and staphylococci, stimulation of the formation of interferon, and reduction of estradiol levels [44, 45]. Its positive effect on sperm motility in men with AstZS has been shown in an in vitro study [46]. The composition of 1 capsule of the drug «FEROLL» (500 mg) includes: L-carnitine L-tartrate - 110 mg, licorice root extract (*Glycyrrhiza glabra*) - 100 mg, L-arginine - 62.5 mg, vitamin E - 15 mg, L-glutathione - 20 mg, zinc asparaginate (citrate) - 10 mg (zinc - 2.8 mg), coenzyme Q_{10} - 3.75 mg, folic acid - 0.1 mg, sodium selenite - 0.015 mg (selenium - 6.8 mcg. The recommended daily dose of the drug is four capsules per day. The drug is taken in two capsules 2 times a day in the morning and in the evening.

The correspondence of the dosages to the daily needs for micronutrients and their characteristics are given in Table 1.

Table 1

Correspondence of the daily dosage of the components of the drug «FEROLL» that needs of men in micronutrients

Micronutrient	Content in «FEROLL», mg	Daily dosage, mg	Characteristic of dosage
L-carnitine	440	300	Therapeutic dose
L- arginine	250	5000-6000	Preventive dose
Zinc	11,2	10-15	Daily dose
Selenium	0,027	0,065	Preventive dose
Vitamin E	60	15	Therapeutic dose
Glutathione	80	No dates	Empiric dose
Folic acid	0,4	0,2	Therapeutic dose
Coenzyme Q_{10}	15	30	Preventive dose
Licorice root extract	400	-	Empiric dose

Thus, «FEROLL» is a balanced composition of some micronutrients that has antioxidant and metabolic effects and can be recommended for men with pathospermia.

The aim of the article is to study the effect of the drug «FEROLL» at 60 days using on the dynamics of the parameters of spermograms in men with androgen deficiency and pathospermia.

Materials and methods. Under our supervision there were 48 men aged 21–40 years who for a year or more could not conceive a child in marriage with regular sexual life without protection. On the part of their wife's dates of the disturbance of their reproductive function was absent. In accordance with the existing recommendations, 26 men were diagnosed with AstzS, 15 – OZS and 7 - AZS [35].

All men studied the history of anamnesis, namely, negative factors that potentially contribute to the formation of OS were taken into account. The body mass index (BMI) was calculated using the well-known formula: BMI = body weight, kg / weight, m^2.

Andrological status was studied by well-known methods [47]. To study the state of the prostate gland and the organs of the scrotum, ultrasound diagnostics were used.

Before and after the end of the intake of the drug «FEROLL», the parameters of the spermogram were studied in accordance with the WHO criteria (2010) [35], as well as the levels of T in the blood by the ELISA method.

It should also be noted that none of the men took known drugs that have a suppressive effect on spermatogenesis [48].

For all the time of taking the drug, no side effects have been established.

Statistical processing of the results obtained for the dynamics of parameters of spermograms and T levels was performed using Student's t-test.

Results and their discussion. The study of the andrological status in men allowed them to exclude hypogonadism, varicocele, traumatic and inflammatory diseases of the urogenital system. The results of ultrasound diagnostics confirmed this data.

The results of the study of BMI showed compliance with the standards of the vast majority of men (18.5 - 25.0 kg/m^2). An increase of more than 25.0 was noted in 5 men, which allowed them to establish excess body weight.

After 60 days from the start of taking the complex drug, normalization of all parameters of the spermogram was observed in 42 men (87,5%). The dynamics of the therapeutic effect are presented in table 2.

Table 2

Dynamic of therapeutical effect under the condition of complex drug in men with androgen deficiency and pathospermia, n

Pathospermia	Before therapy, n	После терапии, n
AstzS	26	3
OZS	15	2
AZS	7	1

Thus, a significant therapeutic effect was observed in all groups.

Analysis of T levels in the blood showed that all patients had an androgen deficiency (Table 3).

Table 3

Levels of total and free testosterone before and after treatment with a complex preparation for 60 days

Pathospermia	Total testosterone, nmol/l		Free testosterone, pmol/l		P
	Before therapy	After therapy	Before therapy	After therapy	
AstzS	10,3±,08	15,5±1,0	22,4±1,4	34,6±1,7	< 0,05
OZS	9,2±0,7	14,7±1,0	18,7±1,2	35,6±1,7	< 0,05
AZS	9,7±0,9	14,9±1,0	19,0±1,2	37,8±1,6	< 0,05

Thus, 60 days after the treatment, there was a significant increase in serum levels of T_{total} and T_{free}, which indicated a positive therapeutic effect at the treatment.

It should be noted that at the end of the introduction of the drug in all groups there was a significant decrease in the number of pathological forms of spermatozoa, as well as an increase in the total number of spermatozoa and their mobile forms (table 4).

Table 4

Динамика параметров спермограмм у мужчин с андрогенодефицитом и паспермиями под влиянием приема комплексного препарата в течение 60 дней

Pathospermia	Astenozoospermia		Oligoozoospermia		Azozoospermia	
Parameter	Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
The volume of ejaculate, ml	3,4±0,2	3,9±0,2	3,0±0,2	3,4±0,3	3,7±0,4	3,8±0,4
The number of spermatozoids, mln/ml	31,0±2,1	42,8±3,0*	8,7±1,3	19,9±2,1*	0	16,8±1,4*
Moving forms of spermatozoids, %	33,2 ± 1,6	54,7±4,5*	26,2±1,7	48,8±3,0*	0	44,7±3,0*
Active forms of spermatozoids, %	17,3 ± 1,5	34,9±1,9*	23,2 ± 1,0	35,9±2,7*	0	33,8±2,8*
Pathological forms of spermatozoids	56,5 ± 2,8	38,7±2,9*	60,8 ± 3,6	34,8±2,1*	0	40,7±3,0*

Notes: * - $p<0,05$.

Thus, the drug «FEROLLL» may be recommended for men with AND and patospermia.

Conclusions:

1. The use of the complex drug «FEROLL» for 60 days leads to a significant increase in the levels of total and free testosterone in the blood of men with pathospermia.

2. The drug «FEROLL» is a balanced composition of micronutrients necessary to maintain hormonal, antioxidant and metabolic processes to ensure spermatogenesis in men.

3. Acceptance of the drug «FEROLL» within 60 days in most cases leads to the normalization of the parameters of sperm in men with patospermia.

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