

ORIGINAL ARTICLE

DYNAMICS OF FUNCTIONAL CONDITION SEEDMANS AND LIVER IN MEN WITH INFERTILITY UNDER THE INFLUENCE OF ARGININ THERAPY WITH THE COMPLEX OF L-CARNITIN AND BETAINE

DOI: 10.36740/WLek202004114

Volodymyr O. Bondarenko¹, Andriy S. Minukhin², Evgeniy I. Skornyakov¹, Nadiia M. Kononenko², Maryna O. Ostapets²

¹INSTITUTE OF PROBLEMS OF ENDOCRINE PATHOLOGY NAMED AFTER V. YA. DANILEVSKY NAMS OF UKRAINE, KHARKIV, UKRAINE

²NATIONAL UNIVERSITY OF PHARMACY, KHARKIV, UKRAINE

ABSTRACT

The aim of this work was to study the hormonal status androgen-dependent indicators of the ejaculate, spermogram parameters and liver transaminases in the blood of the infertile males for the treatment of arginine, carnitine and betaine.

Materials and methods: The parameters of spermograms, the levels of testosterone, estradiol, alanine aminotransferase and aspartate aminotransferase in the blood, and concentration of fructose in the ejaculate of 31 men with idiopathic pathospermia before and after using the L-Betargin, which contains 1 gram of arginine, 300 mg of L-carnitine and 1 gram of betaine.

Results: It is shown that after treatment there is an increase of sperm concentration and their motility, increase the level of fructose in the ejaculate. It is established that the positive effect on spermatogenesis, L-Betargin associated with activation of endocrine function of the testes, improving the androgen-estrogen balance and functional state of the liver in men with infertility.

Conclusions: The use of L-Betargin for a month in men with idiopathic pathospermia leads to an increase in the concentration of sperm and increase their motility, while normalizing all parameters of the spermogram.

KEY WORDS: idiopathic pathospermia, L-Betargin, spermogram, liver transaminases, testosterone

Wiad Lek. 2020;73(4):700-704

INTRODUCTION

Currently, due to the difficult demographic situation in Ukraine, where mortality is prevalent over birth, the prevention and treatment of reproductive health disorders become especially social significant [1]. At the same time, the pathology of the reproductive system in men is the reason of no children was born in marriage in nearly half of the cases [2].

According to the literature dates, the genital organs, hypogonadism, endocrine and somatic diseases, varicocele are the factors that leading to the male interfamily [3, 4]. Also, there is idiopathic pathospermia, when there are no obvious causes of impaired spermatogenic function of the testicles in men [5, 6].

One of the main pathogenic mechanisms that lead to a disorder of spermatogenesis, in virtually all forms of infertility, is hyperproduction of active forms of oxygen (AFO) in the semen – oxidative stress (OS) [2, 7]. Accumulation of AFO in sperm leads to damage of the sperm membrane, reducing their motility [2]. This condition involves the use of antioxidants in the treatment of male infertility that protects sperm from the negative effects of the OS [8]. These include vitamins, trace elements, and also L-carnitine and arginine [5, 7, 9].

L-carnitine has a pronounced antioxidant activity that prevents AFO from affecting spermatozoa. In addition, it provides transport of fatty acids in the mitochondria of sperms for use as energy in the process of β -oxidation during posttesticular maturation of sperm in the adnexa of the testicles [7, 10].

Of particular interest to many researchers is the use of arginine in the treatment of male infertility. In addition to antioxidant action, arginine indirectly participates in hormonal regulation of spermatogenesis, stimulating the secretion of insulin, somatotrophic hormone and prolactin [11]. But the main role of arginine in the body is to be a substrate for the synthesis of nitric oxide (NO) that affects the modulation of vascular peritoneum and thus acts on spermatogenesis [1, 12]. Experimental data suggests that arginine stimulates the growth and maturation of the germ cells by improving blood supply to the testicles and suppressing oxidative apoptosis [13].

Men with infertility have a positive correlation between the concentrations of arginine in the sperm and blood and the level of testosterone (T) in the blood [14]. In addition, there is a decrease in the content of arginine in the seed fluid with idiopathic pathospermia [14]. All this demonstrates the importance of arginine in providing normal spermatogenesis in men.

The literature data indicates that the appointment of arginine in doses of 3-4 grams per day for one to three months for men with infertility led to an increase in the concentration of sperm in ejaculate and to increase their motility [1, 15, 16]. At the same time, a probable increase in the concentration of androgen-dependent indicators of ejaculate – fructose and citric acid, a decrease in the levels of estradiol (E_2), androgen-binding globulin, an increase in the values of the index of free androgen and T/E_2 – a coefficient indicating an increase in androgenization of male organism [1, 16]. This was observed against the background of normalization of levels of liver transaminases [16]. A similar improvement of the liver functional state is due to the fact that arginine contributes to the transformation of ammonia into urea that binds toxic ions of ammonium, which are formed by catabolism of proteins in the liver [17]. It also helps to prescribe betaine for the improvement of the liver functional state. It prevents the accumulation of lipids in the liver [17]. In addition, betaine effects on increasing of the betaine-dependent pathway of homocysteine (GC) remethylation and reduces its level in the blood [18]. Increasing of the GC level is noted among the patients with infertility that leads to a disorder of the NO activity, stimulation of the OS and cellular apoptosis, and as a consequence, damage to spermatogenesis [19, 20]. The common use of arginine and betaine for the men with erectile dysfunction led to a possible decrease in the levels of GC, cholesterol and hepatic transaminases with the growth of the relative androgenization index, the T/E_2 ratio [21].

At the same time, the literature does not contain the information on how the parameters of the men spermograms with infertility change under the influence of therapy that

include arginine, carnitine and betaine, and the dynamics of the sex hormones levels and liver transaminases.

THE AIM

To study the hormonal status, androgen-dependent indicators of ejaculate, parameters of spermograms and hepatic transaminases in blood in infertile men in the treatment of arginine, carnitine and betaine.

MATERIALS AND METHODS

31 men aged 24-40 ($33,2 \pm 0,7$) years old with the infertile marriage for more than a year was examined. Based on the analysis of anamnesis data, clinical and instrumental examination in patients, the presence of hypogonadism, varicocele, inflammatory diseases of the genital organs was excluded. It gave us the reason to establish the idiopathic infertility in the patients.

L-Betargin was prescribed for all the examined by one liquid pack three times a day during the month. One liquid pack of L-Betargin contains 1 gram of arginine, 300 mg of L-carnitine and 1 gram of betaine. The parameters of spermograms were analyzed according to WHO criteria among infertility man before and after the therapy [23], the concentration of fructose in ejaculate [22, 23] determined the levels of T and E_2 in blood by the immune enzyme method. In addition, both before and after treatment, blood levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by the Rietman-Frenkel method, which characterize the functional state of the liver and are essential for T-exchange [17, 23].

Table I. The dynamic of spermogram indicators and fructose concentration in ejaculate after therapy

Indicator	Pathospermium		Control group, n=12
	Before therapy, n=31	After therapy, n=31	
Volume of ejaculate, ml	$3,5 \pm 0,3$	$3,7 \pm 0,2$	$4,7 \pm 0,6$
Amount of spermium, millions/ml	$32,5 \pm 3,0^*$	$45,8 \pm 2,6^{***}$	$78,5 \pm 7,1$
Total sperm motility,%	$32,7 \pm 1,5^*$	$52,3 \pm 2,3^{**}$	$55,4 \pm 1,4$
Motility sperm class A+B, %	$16,8 \pm 0,8^*$	$34,5 \pm 2,1^{**}$	$39,2 \pm 1,3$
Morphological anomaly forms of spermium, %	$70,5 \pm 1,7^*$	$62,3 \pm 2,4$	$65,5 \pm 1,5$
Concentration of fructose, mmol/l	$11,2 \pm 0,3^*$	$13,6 \pm 0,4^{**}$	$15,2 \pm 0,8$

Notes. * – the probable difference ($p < 0,05$) with the control group;

** – the probable difference ($p < 0,05$) with indicators before therapy.

Table II. The parameters of spermogram before and after therapy in men with infertility, %

Indicator	Before therapy, n = 31		After therapy, n = 31		Statistical indicator	
	n	%	n	%	χ^2	P
Concentration of spermium, millions/ml	22	71,0	30	96,8	5,84	$< 0,05$
Total sperm motility,%	6	19,4	26	83,9	23,31	$< 0,001$
Motility sperm class A+B, %	1	3,2	21	66,7	25,43	$< 0,001$
All parameters of spermogram	-	-	21	67,7	28,80	$< 0,001$

Table III. The dynamics of hormones level and hepatic transaminases by the effect of therapy in surveyed patients

Indicator	Pathospermium		Control group, n = 12
	Before therapy, n = 31	After therapy, n = 31	
T, nmol/L	14,2±0,6*	16,4±0,5**	17,2±1,2
E ₂ , nmol/L	0,22±0,01*	0,18±0,01**/**	0,15±0,01
T/E ₂ , RU	73,4±7,1*	96,3±7,2**	124,4±12,1
ALT, U/L	42,3±2,7*	33,7±1,7**	30,9±2,3
AST, U/L	44,1±3,1*	32,9±1,5**	31,7±2,0

Notes. * – the probable difference ($p < 0,05$) with the control group;
** – the probable difference ($p < 0,05$) with indicators before therapy.

Table IV. Frequency of compliance with the norm of hormonal parameters and levels of liver transaminases before and after therapy in men with infertility, %

Indicator	Before therapy, n = 31		After therapy, n = 31		Statistical indicator	
	n	%	n	%	χ^2	P
T, nmol/L	16	51,6	29	93,5	11,67	< 0,001
E ₂ , nmol/L	14	45,2	26	83,9	8,53	< 0,01
T/E ₂ , RU	7	22,6	15	48,4	4,42	< 0,05
ALT, U/L	15	48,4	26	83,9	7,20	< 0,01
AST, U/L	14	45,2	27	87,1	10,34	< 0,001

Similarly, 12 healthy men (control) were examined and normospermia (NZS) was established.

Statistical processing of the data was carried out using the standard application package Statistica 6.0. The reliability of average differences values was determined using the Student's t-criterion. The significance of the differences between the groups was estimated by χ^2 . The data is presented as an average and an average error ($X \pm \pm Sx$).

RESULT AND DISCUSSION

71 % of patients had asthenozoospermia (AstZS) before therapy, when there was a disorder of sperm motility. 20 % of patients had an oligozoospermia (OZS) or decreased sperm concentration in ml of ejaculate, and only 9 % of the patients were diagnosed with oligoasthenozoospermia (OAsZS) – a disorder of the concentration and motility of sperm.

The recommended treatment scheme effects the increase of the sperm concentration, as well as the percentage of motility sperm class of A+B. Significant changes were not noted in the number of morphologically anomaly forms of spermium, but their percentage corresponded to the indicators in the control group after the treatment (Table I).

It should be noted that the sperm motility rates did not differ from their average values after the treatment in the control group. These positive changes in the parameters of spermatogenesis were observed against the background of a significant increase in the average values of androgen-dependent and energy-supplying sperm of the ejaculate-fructose index. In addition, this therapy contributed to the normalization of the concentration and motility of sperm (Table II).

It should be noted that the sperm motility rates did not differ from their average values after the treatment in the control group. These positive changes in the parameters of spermatogenesis were observed against the background of a significant increase in the average values of androgen-dependent and energy-supplying sperm of the ejaculate-fructose index. In addition, this therapy contributed to the normalization of the concentration and motility of sperm (Table II).

At the same time, complete normalization (or NSA) of all parameters of the spermogram was established among 67,7 % of the patients.

The analysis of the hormones level and hepatic transaminases found a significant increase in the average values of T blood level when it reached the rates of healthy men (Table III).

At the same time there was a significant decrease in the average values of the E₂ level in the blood that led to the normalization of the ratio T/E₂ – an indicator of relative androgenization of the male body. The increase in androgen-estrogenic ratios and the positive dynamics of secretion of sex hormones can be attributed to improved liver function. This is evidenced by a significant decrease in the level of ALT and AST in the blood (Table III).

Normalization of the liver function, where the exchange of T, is a factor contributing to the improvement of the processes of androgenization in men with hypotestosteronemia formation [16, 23]. It should be emphasized that our patients did not have a marked increase in liver transaminases. This indicated the presence of latent liver dysfunction. Moreover, the increase in the level of ALT and AST in the blood was similar to changes in concentrations in blood serum T and E₂ (Table IV).

In parallel, normalization of the level of liver transaminases normalized the level of sex hormones. Positive influence on the function of the liver we have been established with a long, for three months, the appointment of 4 grams of arginine per day for men with infertility [16]. Using 3 grams of arginine citrate and 3 grams of betaine for only one month in men with excess body weight and latent liver dysfunction helped normalize liver transaminases within a month of therapy [21]. However, this therapy, despite the fact that the level of E₂ decreased cholesterol and GC in the blood did not affect the mean values of T in the blood.

At the same time, the complex of arginine, betaine and L-carnitine in the composition of L-Betargin probably more significantly affects the in vitro function of the testicles, not only by improving their blood supply, but by also reducing the OS in the tissues of the testicles. All this contributed to the improvement of the processes of spermatogenesis in men with idiopathic pathospermia. It can be assumed that this therapy should be prescribed in the complex treatment of other forms of infertility, when it is necessary to improve the functional state of the liver, to compensate the androgen-estrogen balance and reduce the level of the OS, in particular with pathospermia due to inflammation of the prostate-vesicular complex, varicocele and obesity.

CONCLUSIONS

1. The use of L-Betargin for a month in men with idiopathic pathospermia leads to an increase in the concentration of sperm and increase their motility, while normalizing all parameters of the spermogram.
2. The men with idiopathic infertility have the positive influence on the spermatogenesis of L-Betargin that is associated with the activation of the sucrose function of the testicles, the improvement of the androgen-estrogen balance and the functional state of the liver.

REFERENCES

1. Gorpichenko I.I., Gurzhenko Yu.N. Ispolzovanie preparata Tivortin pri lechenii ekskretorno-toksicheskogo besplodiya u muzhchin. [Using of the drug Tivortine for treatment of excretory-toxic males' infertility]. Health of Man. 2014; 4: 127-130. (In Russian).
2. Lesovoy V.N., Arkatov A.V., Panasovskiy N.L. Apiprost v lechenii ekskretorno-toksicheskoy formy muzhskogo besplodiya. [Apiprost for the treatment of toxic form of male infertility]. Health of Man. 2011; 3: 141-142. (In Russian).
3. Lisoviy V.N., Arkatov A.V., Knigavko O.V. Choloviche bezpliddya: etiopatogenez, diagnostika, likuvannya. [Male infertility: etiopathogenesis, diagnostic, treatment]. H.: Rarities of Ukraine, 2011: 128 s. (In Ukrainian).
4. Gorpichenko I. I., Gurzhenko Yu. N., Imshinetska L. P. Proekt nadannya klinichnogo protokolu nadannya medichnoyi dopomogi hvorim z cholovichim faktorom bezpliddya podruzhnoyi pari. [Project of provision of a clinical protocol providing medical care to patients with male infertility marriages couples]. Health of Man. 2014; 4: 137-149. (In Ukrainian).
5. Isidori A.M., Pozza C., Qianfrilli D. Medical treatment to improve sperm quality. Reproductive Bio Medicine Online. 2006; 12(1): 23-32.
6. Mshalaya G.Zh., Kalinchenko S.Yu., Tyuzikov I.A. et al. Muzhskoe besplodie. [Males' infertility]. M.: Practical Medicine, 2014: 80 s. (In Russian).
7. Minuhin A.S., Bondarenko V.A. Kompleksnoe primeneniye nekotorykh mikronutrientov u muzhchin s idiopatcheskimi astenozoospermiyami. [Complex using of some micronutrients in man with idiopathic astenozoospermia]. Health of Man. 2014; 4: 131-136. (In Russian).
8. Zini A., Al – Hathal N. Antioxidant Therapy in male infertility: Fact or fiction. Asian Journal of Andrology. 2011; 13: 374-382.
9. Morgante G., Scolaro V., Tosti C. et al. Treatment with carnitine, acethylcarnitine, L-arginine and ginseng improves sperm motility and sexual health in men with asthenozoospermia. Minerva Urol. Nephrol. 2010; 62(3): 213-218.
10. Vinogradov I.R., Blohin A.V., Afanaseva L.M. et al. Opyit primeneniya L-karnitina v lechenii sekretornogo besplodiya u muzhchin (Obzor literatury). [Experience of using L-carnitine in the treatment of secretory infertility in men (Literature review)]. Andrology and genital surgery. 2009; 2: 19-22. (In Russian).
11. Holdcraft R.T., W.Braun B.E. Hormonal regulation of spermatogenesis. Inf. J. of Androl. 2004; 27: 335-342.
12. Battaglia C., Guilini S., Regnali G. et al. Seminal plasma nitrit/nitrat and intratesticulares Doppler Slow fertile and infertile Subjects. Human Reprod. 2000; 15(12): 2554-2558.
13. Romanyuk A.M., Saulyak S.V., Moskalenko R.A. et al. Vpliv soley vazhkih metaliv na spermatogennu funktsiyu i yih korektsiya preparatom tivortin. [Having injected the salts of the heavy metal on the spermatogenic function and their correction with the drug tivortin]. Likars'ka sprava. 2012; 1-2: 123-128. (In Ukrainian).
14. Bondarenko V.A., Karpenko N.A., Velichko N.F. et al. Znachenie opredeleniya soderzhaniya arginina i stabilnykh metabolitov tsikla oksida azota v spermalnoy plazme u besplodnykh muzhchin. [The value of determining the content of arginine and stable metabolites of the nitric oxide cycle in sperm plasma in infertile men]. Health of Man. 2014; 1: 142-144. (In Russian).
15. Sindair S. Male infertility: Nutricional Environmental Consideration. Alternative Medicine Review. 2000; 5(1): 28-38.
16. Bondarenko V.O., Skorniyakov E.I., Alekseeva I.I. et al. Dinamika funktsionalnogo stanu sim'yanikov ta pechinki u neplidnih cholovikov pid vplivom terapiyi L-argininom. [The dynamics of the functional condition of the testis and liver in infertility man by influence the L-arginine therapy]. The problems of endocrine pathology. 2013; 2: 56-61. (In Ukrainian).
17. Harchenko N.V., Anohina G.A., Harchenko V.V. Pechinkovi ta pozapechinkovi efekti likuvalnogo kompleksu z L-argininom ta betayinom u hvorih iz metabolichnim sindromom. [Hepatic and extrahepatic effects of complex with L-arginine and betaine in patients with metabolic syndrome]. Modern gastroenterology. 2015; 3: 32-38. (In Ukrainian).
18. Atkinson W., Slow S., Elmsile J. et al. Dietary and supplementary betaine: effect of betaine and homocysteine concentrations in males. Nutr. Metab. Cardiovasc. Dis. 2009; 19(11): 767-773.
19. Ge Y.F., Wang C.H., Oung L.X. et al. Determination of plasma homocysteine in oligospermia and/or astenospermia patients. Zhonhua Nan Ke Xue. 2008; 14(12): 1112-1114.
20. Bondarenko V.A., Minuhin A.S., Skorniyakov E.I. Urovni gomotsisteina i holesterina v krovi i androgen-estrogennyiy balans u muzhchin s idiopatcheskimi patospermiyami. [Levels of homocysteine and cholesterol in the blood and androgen-estradiol balance in man with idiopathic pathospermia]. Problems of endocrine pathology. 2015; 4: 7-13. (In Russian).

21. Bondarenko V.A., Minuhin A.S., Lutsenko A.G. et al. Opyit primeneniya L-arginina v komplekse s betainom pri lechenii erektilnoy disfunktsii. [The Experience of using L-arginine in complex with betaine for treatment of erectile dysfunction]. Norwegian Journal of development of the International Science. 2017; 7: 35-40. (In Russian).
22. Cooper T.G., Noonan E., von Eskardstein S. et al. World Health Organization reference values for human semen characteristics. Human Reprod. Update. 2010; 16(3): 231-245.
23. Kalinchenko S.Yu., Tyuzikov I.A. Prakticheskaya andrologiya. [Practical andrology]. M.: Practical Medicine, 2009: 399 s.

ORCID and contributionship:

Volodymyr O. Bondarenko – 0000-0002-9254-3875^{C,F}

Andriy S. Minukhin – 0000-0003-2524-7512^D

Evgeniy I. Skorniyakov – 0000-0003-3733-7304^E

Nadiia M. Kononenko – 0000-0002-3850-6942^{A,B}

Maryna O. Ostapets – 0000-0002-6900-5833^B

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Nadiia M. Kononenko

Department of Pathological Physiology

National University of Pharmacy

Kulikovska str., 12, 61002, Kharkiv, Ukraine

tel: +380662517404

e-mail: kononenkonn76@gmail.com

Received: 08.07.2019

Accepted: 21.02.2020

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article