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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ
ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

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3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

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POSITIVE EFFECT OF BETAIN-ARGININE SUPPLEMENT ON IMPROVED HYPERHOMOCYSTEINEMIA TREATMENT IN MARRIED COUPLES WITH REPRODUCTIVE DISORDERS

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Polymorphic variants of folate exchange and thus conditioned hyperhomocysteinemia (HHcy), recognized as a hereditary metabolic disorder, is a relevant factor of reproductive disorders.

For instance, the United States has shown that the fortification has given the possibility to remove genetic testing of the *MTHFR* gene variants from the clinical guidelines for the diagnostic of inherited thrombophilia and not to be carried out for patients with spontaneous abortions due to the folate status change on the population level. However, identified gene variants and moderate HHcy, as noted by clinical guidelines, in any cases, require medical genetic counseling to properly assess their impact on existing clinical symptoms. Genetic counseling should take into consideration the reason for the referral to a genetic test [12]. Some authors believe that after fortification the risk of folate-mediated diseases on the population level decreases considerably and it is impossible to determine the genetic constituent. But, genetic testing with gene-factor associations analysis would help find persons, which are at risk of developing clinical symptoms related to *MTHFR* gene variants, in order to conduct them personalized prevention measures with the consideration of the whole group B vitamins spectrum and metabolically related compounds [22].

Current precaution against folic acid (FA) “*Folic acid fortification and supplementation – good for some but not so good for others*” is the name of one of the first publications of Kim Y.I. about negative clinical effects of folic acid consumption [15], currently described [10]. Thus, the detection and personalized treatment of HHcy patients, personalized prescription optimal dose of FA in combination with other vitamins and nutrients to improve folate status and achieve stable decrease of homocysteine (Hcy) level is a conceptually new – precision medicine [3]. Timely and efficient HHcy treatment or prevention are especially necessary for patients of reproductive age to prevent undesired clinical consequences of folate-deficient conditions [4, 13].

Aim of the study was to investigate the main risk factors in the developing of HHcy in married couples with reproductive disorders and to evaluate the efficiency of short-term application of betaine-arginine supplement in treatment of identified patients.

Material and methods. The studies were conducted in a total of 206 couples with reproductive disorders. 33.49% of these had natural idiopathic sterility and 66.51% had previous reproductive losses in their family history. The inclusion criteria were determined during the study planning. A couple was not included into the study if any spouse had karyotype anomalies, obesity, somatic and oncologic pathology, acute and chronic infectious diseases. Additional exclusion criteria for men were azoospermia and presence of Y-chromosome deletions. All the patients gave their informed consent to the participation in the study, provided the results of clinical, laboratory and instrumental tests, conducted prior to their being referred to medical-genetic consultation, and filled in the questionnaire, which covered their medical data and information about their lifestyle. The approval of the bioethics committee was obtained for the study. The tests for all the folate exchange indices were conducted for all the study

participants: Hcy in blood plasma, FA and vitamin B12 in blood serum and polymorphism of folate exchange genes *MTHFR* (C677T, rs1801133; A1298C, rs1801131), *MTRR* (A66G, rs1801394), *MTR1* (A2756G, rs1805087), *RFC1* (G80A, rs1051266) using previously described methods [23, 24]. 116 (out of 118 detected) patients with HHcy were divided into Group 1 and Group 2. The patients in both groups were prescribed vitamins, containing 800 µg FA (in combination with 4 µg vitamin B12 average). Group 1 included 58 patients, prescribed a sachet of betaine-arginine dietary supplement - Betargin® (contains 1 g betaine, 1 g arginine and citrate ions) twice a day in addition to vitamins preparations. Group 2, also comprised of 58 patients, was prescribed vitamins preparations and not prescribed betaine-arginine containing supplement - Betargin®. Folate exchange indices (Hcy in blood plasma, FA and vitamin B12 in blood serum levels) were defined twice: before treatment and two weeks after vitamins administration.

The methods of single-factor statistical analysis were used to assess the impact of gene variants and other factors on the development of HHcy in the couples. The analysis of basic clinical characteristics and the assessment of quantitative laboratory indices involved the estimation of the mean value (M)±standard deviation (SD). The investigated indices were checked for the normality of distribution using Kolmogorov-Smirnov test. In case of normal distribution, the probability of differences in quantitative results for different groups of investigated patients was determined using Student's t-test; in case of distribution, which differed from the normal one, Mann-Whitney U-test was applied or the normalization of indices was done. Quality criteria, incidence of cases and genotype frequencies were analyzed using criteria χ^2 and odds ratio (OR) within 95% of the confidence interval (CI). The differences were deemed reliable for all the types of analysis at the level of significance (p) under 0.05. The risk factors were also analyzed using the multivariate method – binary logistic regression. The calculations were done using Microsoft Excel Pro Plus 2016 and SPSS v.27 programs.

Results and discussion. The excessive Hcy level, as was proven, has unfavorable effect on the pregnancy course and associated with the birth of children with certain pathologies, impaired development, smaller weight for the gestational age. Detected differences in some results shown the presence of gene-factor interactions, when additional consumption of FA eliminated the incidence of *MTHFR* gene related pathologies on the population level. [4, 5, 12]. Regardless of this fact, the attention of researchers to HHcy has not decreased [22, 24]. 10th revision of ICD-10 (October, 2017) defined hereditary HHcy related to folate gene variants as an autosomal recessive inherited metabolic disorder (code E72.1), but it still does not have clear reference values for the Hcy level, while WHO published reference values for blood serum FA and erythrocytes FA clearly [30]. Based on existing recommendations and some studies, we considered the Hcy level in blood plasma, equal and over 12 µmol/l to be excessive in our study [19,26].

The level of Hcy in plasma, exceeding 12 µmol/l, is deemed

to be cytotoxic. The increased level of Hcy is detected among healthy population but prevails among patients with cardiovascular diseases and reproductive disorders, especially in the countries without any fortification of food products. Additional risk factors (excessive consumption of coffee, meat, unbalanced diet, smoking, alcohol consumption, etc.) increase the total HHcy risk additively and synergistically, especially in case of existing variants in folate exchange genes, thus, must be recommended plasma Hcy level under 10 $\mu\text{mol/l}$. The studies found that the levels of Hcy correlated with the indices of FA and vitamin B12 in blood serum. The sufficient level of FA in the organism of a woman prior to the pregnancy and on early stages was proven to promote the prevention of thrombophilic disorders in women and normal development of the embryo [4,26,28]. WHO defined the threshold levels of FA in blood serum: under 3 ng/ml – defi-

ciency; 3-5.9 ng/ml – probable deficiency; 6-20 ng/ml – normal level. These threshold indices, indicated by WHO, highlight the need to control the level of folic acid in blood serum, which is first and foremost necessary for women of reproductive age, starting with the stage of planning the conception. It is believed that the optimal level of FA in blood serum prevents HHcy [30].

Our study detected HHcy in 118 (28.64%) cases (in 42 women and 76 men) among the couples with reproductive disorders, examined by us, when FA and B12 blood serum level among most was optimal (Table 1). The number of couples with the detected HHcy was 28.64% from the total number. In 18.93% of the couples, either the husband or the wife had HHcy, and in 9.71% – both husband and wife had HHcy which was conditioned by their specific diet (predominant excessive consumption of meat). Table 1 presents the results of comparison between the basic clinical and genetic charac-

Table 1. The comparison of the basic clinical and genetic characteristics in investigated groups

Characteristics		Patients with HHcy ($\geq 12 \mu\text{mol/l}$), n=118	Patients without HHcy (less 12 $\mu\text{mol/l}$), n=294	Statistical differences
Age, years		33.97 \pm 5.01	33.25 \pm 5.13	p>0.05
BMI		24.59 \pm 5.00	23.57 \pm 3.35	p>0.05
male/female, n (%)		76 (64.41%)/ 42 (35.59%)	130 (44.22%)/ 164 (55.78%)	OR=2.28 (1.47-3.55), $\chi^2=13.73$, p=0.0002
Homocysteine, $\mu\text{mol/l}$		16.95 \pm 11.96	8.88 \pm 1.81	p<0.05
Folic acid, ng/ml		7.98 \pm 5.20	11.60 \pm 5.74	p<0.05
Vitamin B12, pg/ml		294.11 \pm 107.40	476.58 \pm 139.16	p<0.05
MTRR A66G, gene variants n (%)	66AA	29 (24.6%)	51 (17.3%)	OR=1.55 (0.93-2.60), $\chi^2=2.81$, p=0.09
	66AG	49 (41.5%)	148 (50.3%)	
	66GG	40 (33.9%)	95 (32.3%)	OR=1.07 (0.68-1.69), $\chi^2=0.1$, p=0.76
	66A	0.45	0.43	OR=0.89 (0.66-1.21), $\chi^2=0.55$, p=0.46
	66G	0.55	0.57	
MTHFR C677T, gene variants n (%)	677CC	19 (16.1%)	161 (54.8%)	OR=0.16 (0.09-0.27), $\chi^2=51.16$, p<0.0001
	677CT	63 (53.4%)	121 (41.2%)	OR=1.64 (1.07-2.52), $\chi^2=5.10$, p=0.0239
	677TT	36 (30.5%)	12 (4.1%)	OR=10.32 (5.13-20.74), $\chi^2=57.13$, p<0.0001
	677C	0.43	0.75	OR=4.08 (2.97-5.62), $\chi^2=79.5$, p<0.0001
	677T	0.57	0.25	
MTHFR A1298C, gene variants n (%)	1298AA	76 (64.4%)	122 (41.5%)	OR=2.55 (1.64-3.97), $\chi^2=17.71$, p<0.0001
	1298AC	38 (32.2%)	136(46.3%)	OR=0.55 (0.35-0.86), $\chi^2=6.82$, p=0.009
	1298CC	4 (3.4%)	36 (12.2%)	OR=0.25 (0.09-0.72), $\chi^2=7.53$, p=0.006
	1298A	0.81	0.65	OR=0.44 (0.31-0.64), $\chi^2=19.92$, p<0.0001
	1298C	0.19	0.35	
MTR1 A2756G, gene variants n (%)	2756AA	43 (36.4%)	194 (66.0%)	OR=0.3 (0.19-0.46), $\chi^2=30.08$, p<0.0001
	2756AG	64 (54.2%)	83 (28.2%)	OR=3.01 (1.94-4.69), $\chi^2=24.81$, p<0.0001
	2756GG	11 (9.3%)	17 (5.8%)	OR=1.68 (0.76-3.69), $\chi^2=1.67$, p=0.20
	2756A	0.64	0.80	OR=2.31 (1.65-3.22), $\chi^2=24.82$, p<0.0001
	2756G	0.36	0.20	
RFC1 G80A, gene variants n (%)	80GG	20 (16.9%)	95 (32.3%)	OR=0.43 (0.25-0.73), $\chi^2=9.88$, p=0.0017
	80GA	62 (52.5%)	132 (44.9%)	OR=1.36 (0.89-2.09), $\chi^2=1.97$, p=0.09
	80AA	36 (30.5%)	67 (22.8%)	OR=1.49 (0.92-2.40), $\chi^2=2.68$, p=0.10
	80G	0.43	0.55	OR=1.59 (1.17-2.15), $\chi^2=8.98$, p=0.0027
	80A	0.57	0.45	

teristics of the examined couples depending on the detected HHcy using the methods of single-factor analysis.

Significant genetic determinant of HHcy was variants of *MTHFR*, *MTR1*, *RFC1* gene. The protective impact on HHcy development was determined for *RFC1* gene variant (80GG), but other *MTHFR*, *MTR1* gene variants increased the risk. HHcy was found significant frequently among men from the couples with reproductive disorders compared to women. Other significant factors of HHcy risk were the level of FA and B12 in serum blood at the beginning of the study, but their mean value in both groups (Table 1) located within known described threshold levels [2,6,30]. FA serum blood level was reliably lower among male patients (not shown in the Table 1) with HHcy (6.94±3.67 ng/ml) compared to females with HHcy (9.87±6.86 ng/ml).

Historically, the deficiency of vitamin B12 was determined and studied in clinical conditions, when the symptoms, caused by malignant anemia, malabsorption or severe vegan diet, were studied [1]. However, it has been determined that vitamin B12 deficiency is widely common among many groups of population and is considered to be the healthcare system problem. According to the data of different studies, the incidence of vitamin B12 deficiency is about 40 % [11]. The total concentration of vitamin B12 in blood serum or plasma is used as a biomarker of the first line of deficiency. According to WHO recommendations, the threshold value is 203 pg/ml [6]. But, there are other threshold values in the scientific literature – from 100 to 350 pg/ml, and the researchers indicate that vitamin B12 deficiency may occur even in case of its normal concentrations [2]. Our analysis found that the mean index of vitamin B12 in blood serum was within the threshold values in both investigated groups but considerably lower in patients with HHcy compared without (Table 1).

Some authors proved that the increase within the threshold values of folate status indices, namely, the levels of FA and vitamin B12 in blood serum, in the couples during IVF planning increased the live birth rate. These studies were conducted by A.J. Gaskins et al. for the population of women, residing in the country with fortification practice [8]. A similar effect was noted for men in the work of J. Hoek et al., who demonstrated the

relevance of the folate status of men, and determined that both low and high pre-conception levels of folates in erythrocytes of men were associated with the delayed embryonic growth in spontaneous pregnancy [13]. The paternal status of folic acid is an impact factor for embryo programming and endometrium sensitivity [17]. The study of J. Hoek et al. demonstrated that the increased levels of FA were as harmful as the decreased ones, and considering possible epigenetic events, they may be a relevant unpredictable risk factor for the health of the progeny. In this study, such risk effect was determined only for spontaneous pregnancy, not the ones via IVF [13]. Therefore, it is an urgent task to search for the balanced personalized approach to improving folate status indices and HHcy prevention with the consideration of genetic specificities of patients. It also requires the population-wise specificities of FA consumption and current welfare of people of reproductive age. As seen from the results of our study, HHcy in the patients under our investigation was conditioned by variants of folate exchange genes and was more remarkable for men from the couples with idiopathic sterility or spontaneous abortions. It is also known that the HHcy level is usually higher in men than women, which increases on the level of population with age [4,26].

The method of binary logistic regression was used to assess the impact of variants of the investigated genes of folate exchange on the risk of HHcy development in our patients. A reliable genetic model of risk was built with the consideration of variants C677T of *MTHFR* gene and A2756G of *MTR1* gene and had the highest predictive value – 77.2 % (Table 2).

The next analysis included gene variants, basic clinical indices, diet specificities, personal consumption of folic acid and other vitamins, determined the highest predictive value – 85.7% for the significant model of risk (Table 3), which covered variants of genes, gender, level of vitamin B12 in serum blood and additional consumption of vitamin B12 before beginning this study. Significant determinants of HHcy development were male gender, *MTHFR*, *MTR1* gene variants, low vitamin B12 level and its consumption. Therefore, it is important for the patients in our investigation to have optimal intake of vitamin B12 and its increasing level in blood serum during and after HHcy treatment.

Table 2. Genetic model of HHcy risk

Genes variants	Regression coefficient	P	Exp (OR) (95% CI for exp (OR))
<i>MTHFR</i> C677T (TT)	3,319	0,0001	27,627 (11,902-64,128)
<i>MTHFR</i> C677T (CT)	1,943	0,0001	6,980 (3,267-14,914)
<i>MTR1</i> A2756G (AG)	0,926	0,053	2,525 (0,989-6,451)
<i>MTR1</i> A2756G (GG)	-0,383	0,422	0,682 (0,268-1,735)
Constant	-1,535	0,005	0,215

Table 3. HHcy risk model (including clinical and genetics characteristics)

Characteristics	Regression coefficient	p	Exp (OR) (95% CI for exp (OR))
<i>MTHFR</i> C677T (TT)	3,015	0,0001	20,382 (7,3109-56,8437)
<i>MTHFR</i> C677T (CT)	1,667	0,0001	5,297 (2,075-13,518)
<i>MTR1</i> A2756G (AG)	0,83	0,145	2,293 (0,751-6,998)
<i>MTR1</i> A2756G (GG)	-0,425	0,457	0,654 (0,213-2,004)
Gender (male)	1,042	0,001	2,834 (1,498-5,365)
Vitamin B12 level	0,010	0,0001	1,010 (1,007-1,013)
Vitamin B12 ingestion	2,213	0,038	9,144 (1,128-74,092)
Constant	-5,573	0,0001	0,004

Remethylation of Hcy and its disposal occur via methyl groups, formed during metabolic transformation involving betaine or 5-methyltetrahydrofolate [20, 27]. Betaine, a choline derivative, was proved to be extremely useful in the treatment of mild HHcy. It is especially true for patients with variants of *MTHFR* gene with low functionality when the occurring deficiency of remethylation via decreasing the activity of the enzyme produces the increase in Hcy level and the decrease in the level of methionine, whose transformations are required for the synthesis of nucleotides, proteins, neurotransmitters, etc. In some clinical cases of HHcy, related to variants of *MTHFR* gene, betaine was found to be the only supplement, able to improve the Hcy level of patients; as for our patients, the leading factor of HHcy development were variants 677TT and 677CT of *MTHFR* gene [16]. It was determined for healthy people that the level of Hcy decreased reliably better in case of FA administration compared to betaine, but the stabilizing effect on Hcy level was found for betaine [27].

There have long been hypotheses that betaine-dependent remethylation is a leading way to decrease the excessive Hcy level regardless of the reason of its occurrence [14]. Some studies proved that regardless of the genetic basis and the factor of HHcy development, there is an observed decrease in betaine level in blood plasma and tissues (liver, brain, heart, etc., but not in kidneys). It was demonstrated while examining the patients and conducting experimental work with animals. The decrease in betaine was rather considerable, on average 60% below the normal value. The decrease in betaine concentration in patients with remethylation deficiencies (for instance, variants of *MTHFR* gene, deficiency of *MTR1*) is hardly a surprise as for these patients BHMT remains the only enzyme, capable of remethylating homocysteine to methionine. Moreover, for all the reasons of HHcy occurrence there may be observed increased consumption of betaine via accumulation of Hcy – substrate for enzyme BHMT. While monitoring patients with acquired HHcy, treated without betaine, it was found that the concentrations of Hcy and betaine changed towards normalization, starting with the 6th day of treatment with vitamin B12. Therefore, the application of betaine will decrease the load on Hcy remethylation via the reaction with methionine synthase, whose activity is controlled by *MTR1* gene, which in our investigation is a component of genetic and clinical-genetic models of risk and requires vitamin B12 as a reaction cofactor [27].

Considering the described interaction between remethylation pathways and the decrease in betaine concentration in blood and

tissues in case of long-term HHcy, it is relevant to consider its efficiency in treating this condition with reproductive disorders. Previous studies, using animal models, proved that deficient *MTHFR* was accompanied with the decrease in betaine concentration in liver, thus, its application in our patients with HHcy is completely justified as the variant of *MTHFR* gene was a leading genetic risk factor for them, and both folic acid and vitamin B12 are deposited in the liver [25]. The attraction of betaine-arginine supplement for patients with HHcy and reproductive disorders is additionally enhanced due to the determined correlation between the level of betaine and homocysteine, which was observed during pregnancy and reported in the study of Silvia Fernàndez-Roig et al. [7]. According to this investigation, a low folate status enhanced the decrease in betaine and its correlative relationship with Hcy level during pregnancy. In addition to a similar correlative effect, another study determined long-term stabilization of Hcy level when betaine was taken, in cases of low folate status and the action of provocative factors [27].

L-arginine, presented in the composition of Betargin®, is a source of nitrogen oxide, regulating NO-synthetase via the feedback mechanism [21]. The physiological function of nitrogen oxide lies in relaxing smooth muscles of blood vessel walls, inhibiting the aggregation of platelets and their adhesion and regulating cardiovascular and genitourinary system as well as the main components of cell immunity. The formation of nitrogen oxide by immunocompetent cells ensures the protection of the organism from bacterial infections and oncologic diseases due to the participation in the regulation of apoptotic processes [18]. Nitrogen oxide impacts the activity of many enzymes and proteins, including the one of antioxidant protection, especially in conditions of disease and stress due to excessive burden, during adaptation processes and correction of metabolic shifts. First of all, the deficiency of nitrogen oxide promotes the development of endothelial dysfunction, which accompanies the development of cardiovascular diseases and reproductive disorders, thus, when L-arginine is used, the state of the vascular wall improves and the vasodilation and fibrinolytic effects develop. Similar clinical effects of L-arginine are required to decrease the toxic effect of increased Hcy on the vascular wall [29].

Group 1 and Group 2 patients with HHcy were treated for 2 weeks. Group 1 patients received betaine-arginine supplement in addition to folic acid and vitamin B12. We found no differences in homocysteine, folic acid, vitamin B12 levels of patients Group 1 and Group 2 before treatment (Fig. 1-3).

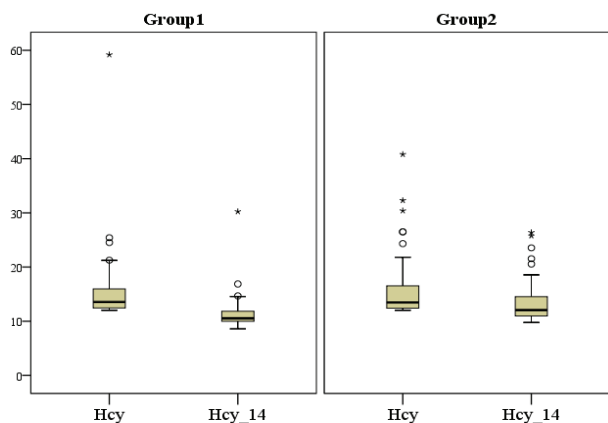


Fig. 1. Hcy (µmol/l) in patients: before (Hcy) and after treatment (Hcy_14)

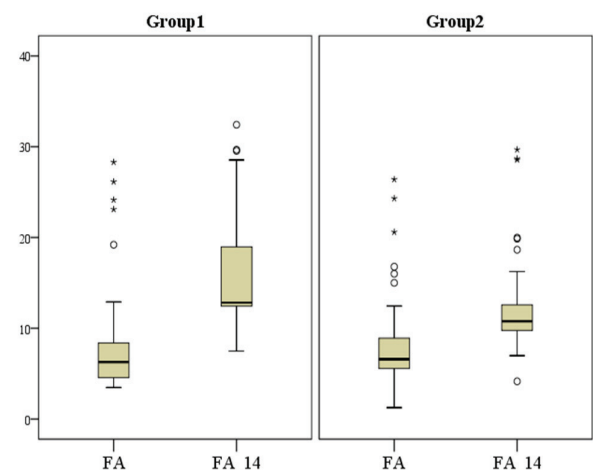


Fig. 2. FA (ng/ml) in patients: before (FA) and after treatment (FA_14)

Hcy mean values among patients Group 1 and Group 2 were $15.34 \pm 6.62 \mu\text{mol/l}$ and $15.93 \pm 5.73 \mu\text{mol/l}$ respectively, before treatment (Fig. 1), significantly decreased after treatment in both groups: $11.28 \pm 3.00 \mu\text{mol/l}$ and $13.52 \pm 3.82 \mu\text{mol/l}$, respectively. Hcy mean values was significantly lower after treatment among patients of Group 1 compared to patients of Group 2 (Fig. 1).

FA mean values among patients of Group 1 ($8.07 \pm 5.59 \text{ ng/ml}$) and patients of Group 2 ($7.86 \pm 4.75 \text{ ng/ml}$) did not differ significantly at the beginning of treatment and increased significantly after the ingestion of vitamins (Fig. 2) in both groups. But patients of Group 1 ($15.43 \pm 5.35 \text{ ng/ml}$) had significantly higher level then in Group 2 ($12.21 \pm 4.82 \text{ ng/ml}$) after treatment.

Our analysis of B12 vitamin mean values identified the same significant rise as for FA mean values after 2 weeks of vitamins admission (Fig. 3). B12 vitamin mean values significantly increased after treatment in comparison before treatment. Also no reliable difference was in B12 vitamin mean values before vitamins consumption: Group 1 ($300.95 \pm 125.69 \text{ pg/ml}$) and Group 2 ($288.37 \pm 87.34 \text{ pg/ml}$) (Fig. 3), then a significantly increased indices was observed in Group 1 ($542.40 \pm 137.84 \text{ pg/ml}$) compared to Group 2 ($432.31 \pm 85.31 \text{ pg/ml}$) after treatment.

The patients of Group 1 with betaine-arginine supplementation had significantly lower Hcy mean values compared to patients of Group 2. The number of patients with Hcy level over $12 \mu\text{mol/l}$ significantly decreased in 47 patients from 58 (81,03%) in Group 1 against 29 patients from 58 (50%) in Group 2 ($\chi^2=12.36, p=0.0004$).

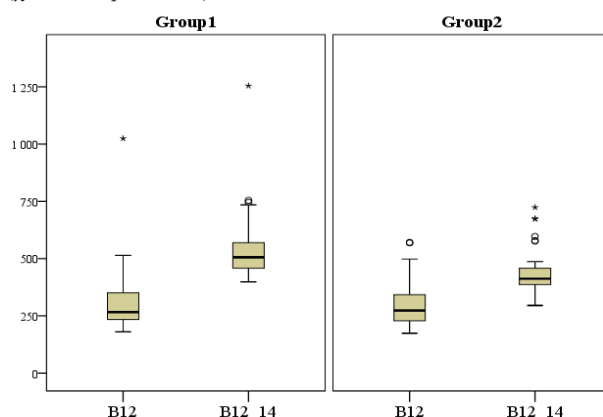


Fig. 3. Vitamin B12 (pg/ml) in patients: before (B12) and after treatment (B12_14)

Thus, the most efficient treatment was in patients group where prescribed betaine-arginine supplement in addition to FA and vitamin B12. The mentioned clinical effect indicated that the application of a betaine-arginine supplement improved the folate status of patients with reproductive disorders considerably, which is relevant in increasing the live birth rate in the family in the future.

Conclusions. The highest predictive value of hyperhomocysteinemia development in patients with reproductive disorder was identified for the risk model included *MTHFR*, *MTR1* gene variants, male gender, low level of vitamin B12 in blood serum and its low additional consumption. The prescription for hyperhomocysteinemia treatment in patients with reproductive disorder folic acid, vitamin B12 and betargin during two weeks significantly improved all indices (homocysteine in plasma blood, folic acid and vitamin B12 in blood serum)

compared to patients without betargin consumption. Betaine-arginine supplementation provided significantly the best reduction of homocysteine level (less than $12 \mu\text{mol/l}$ in patient). The application of betaine-arginine supplement in the couples with reproductive disorders is a promising way of restoring all folate status indices quickly if variants of *MTHFR*, *MTR1* genes in patients are present. Further studies are required to determine the duration of betaine-arginine intake to achieve the target homocysteine level and to estimate the durability of the achieved effect.

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SUMMARY

POSITIVE EFFECT OF BETAINE-ARGININE SUPPLEMENT ON IMPROVED HYPERHOMOCYSTEINEMIA TREATMENT IN MARRIED COUPLES WITH REPRODUCTIVE DISORDERS

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Treatment of hereditary hyperhomocysteinemia and the achievement of optimal folate status is necessary for persons of reproductive age in order to increase live birth rate. Patients are usually advised to take folic acid, a key nutrient in homocysteine remethylation. The results of study showed risk factors for hyperhomocysteinemia development in investigated married couples: male gender, *MTHFR*, *MTR1* genes variants, lower vitamin B12 blood serum and no additional intake of vitamin B12. Since *MTHFR*, *MTR1* genes variants affect to decrease the efficiency of homocysteine metabolic transformations, to contribute also to endothelial dysfunction in one of patients group we used betargin combined with folic acids and vitamin B12 administration. Patients group with combined administration including betargin within 2 weeks, in comparison with the group without its supplement, had significantly decreased level of homocysteine in plasma, less than 12 $\mu\text{mol/l}$ (81.03% and 50% of cases, respectively). Folic acid and vitamin B12 mean values in blood serum was significantly increased in patients after two week vitamins administration including betargin. Further research is needed to establish the duration of betaine-arginine intake until the target homocysteine level will be reached, as well as to estimate the durability of clinical effect achieved after consumption.

Keywords: married couples, hyperhomocysteinemia, reproductive disorder, treatment, betargin.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ БЕТАИН-АРГИНИН СОДЕРЖАЩЕЙ ДОБАВКИ В ЛЕЧЕНИИ ГИПЕРГОМОЦИСТЕИНЕМИИ В СУПРУЖЕСКИХ ПАРАХ С РЕПРОДУКТИВНЫМИ НАРУШЕНИЯМИ

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Лечение наследственной гипергомоцистеинемии и достижение оптимального фолатного статуса необходимо лицам репродуктивного возраста с целью увеличения рождаемости. Пациентам обычно рекомендуют принимать фолиевую кислоту - ключевой нутриент для реметилирования гомоци-

стена. Результаты исследования выявили факторы риска развития гипергомоцистеинемии в обследованных супружеских парах: мужской пол, варианты генов *MTHFR*, *MTR1*, пониженное содержание витамина В12 в сыворотке крови и отсутствие дополнительного употребления витамина В12. Поскольку варианты генов *MTHFR*, *MTR1* влияют на снижение эффективности метаболических преобразований гомоцистеина и на эндотелиальную дисфункцию, в одной из групп пациентов использовали бетаргин в сочетании с фолиевой кислотой и витамином В12. В группе пациентов с лечением, включавшим бетаргин

в течение 2 недель, был значительно снижен уровень гомоцистеина в плазме крови, менее 12 мкмоль/л (81,03% случаев) в сравнении с группой без него (50% случаев). Уровни фолиевой кислоты и витамина В12 в сыворотке крови были значительно повышены у пациентов после двухнедельного приема витаминов, включая бетаргин. Необходимы дальнейшие исследования для определения продолжительности приема бетаин-аргинин содержащей добавки до достижения целевого уровня гомоцистеина, а также для оценки продолжительности клинического эффекта, достигаемого после приема.

რეზიუმე

ბეტაინ-არგინინის შემცველი დანამატის ეფექტურობა ჰიპერჰომოცისტეინემიის მკურნალობაზე რეპროდუქციული დარღვევების მქონე ცოლქმრულ წყვილებში

^{1,2}ზ.როსოხა, ^{1,2}ლ.ფიშუკი, ^{2,3}ლ.შეიკო, ^{1,6}მ.მედვედევა, ^{2,3}ნ.გოროვენკო

¹მოდერული დიაგნოსტიკის რეფერენს-ცენტრი; ²გენეტიკური და რეგენერაციული მედიცინის სახელმწიფო ინსტიტუტი, მეცნიერებათა აკადემია; ³პ.შუპიკის სახ. დიპლომის შემდგომი განათლების ეროვნული სამედიცინო აკადემია, კიევი, უკრაინა

მემკვიდრეობითი ჰიპერჰომოცისტეინემიის მკურნალობა და ოპტიმალური სტატუსის მიღწევა აუცილებელია შობადობის ამადლებისათვის რეპროდუქციული ასაკის პირებში. პაციენტებს, როგორც წესი, ურჩევენ ფოლიუმის მჟავას - საკვანძო ნუტრიენტს ჰომოცისტეინის რემეთილირებისათვის. კვლევის შედეგებით გამოვლინდა ჰიპერჰომოცისტეინემიის განვითარების რისკის ფაქტორები: მამრობითი სქესი, გენების ვარიანტები *MTHFR*, *MTR1*, ვიტამინ B₁₂-ის დაბალი შემცველობა სისხლის შრატში და ვიტამინ B₁₂-ის დამატებითი მიღების არარსებობა. რადგანაც გენების ვარიანტები *MTHFR*, *MTR1* მოქმედებს ჰომოცისტეინემიის მეტაბოლური გარდაქმნების ეფექტურობასა და ენდოთელურ დისფუნქციაზე, პაციენტების ერთ-ერთ ჯგუფში გამოყენებოდა ბეტარგინი ფოლიუმის

მჟავასთან და ვიტამინ B₁₂-თან ერთად. პაციენტების ჯგუფში, ვისთანაც მკურნალობა მოიცავდა ბეტარგინს ორი კვირის განმავლობაში, სისხლის პლაზმაში ჰომოცისტეინის დონე მნიშვნელოვნად ნაკლები იყო - 12 მკმოლ/ლ-ზე ნაკლები (შემთხვევათა 81,03% და 50%, შესაბამისად), ბეტარგინის გარეშე ჯგუფთან შედარებით. ფოლიუმის მჟავას და ვიტამინ B₁₂-ის დონე სისხლის შრატში მნიშვნელოვნად მომატებული იყო პაციენტებში ვიტამინების ორკვირიანი მიღების შემდეგ, ბეტარგინის ჩათვლით. აუცილებელია შემდგომი კვლევების ჩატარება ბეტაინ-არგინინის შემცველი დანამატის მიღების ხანგრძლივობის განსაზღვრისათვის ჰომოცისტეინის სამიზნე დონის მიღწევის მიზნით, ასევე, მიღების შემდეგ მიღწეული კლინიკური ეფექტის ხანგრძლივობის შეფასებისათვის.

MODERN METHODS IN OTORHINOLARYNGOLOGY: POWERED-SHAVER ADENOIDECTOMY

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Adenoids are nasopharynx lymphoid tissues, which participate in the formation of Waldeyer's ring and they were described by Meier for the first time in 1868 [8]. Nowadays, adenoidectomy represents the most common procedure in childhood years, which is performed by resection of adenoids only, or in line with tonsillectomy and/or insertion of ventilation tubes in tympanic membranes [2]. Widespread conventional adenoidectomy was described the first time in 1885 [7]. While precise resection of adenoids along with maximum protection of the adjacent tissues of nasopharynx, complications are avoided, such as: bleeding, incomplete resection of adenoids, stenosis of Eustachian tube

and in very rare cases, stenosis of nasopharynx. Incompleteness of conventional method with regard to complete and safe resection of adenoids leads to development of alternative methods, among them, adenoidectomy with shaver [3,6]. This become possible via development of endoscopic surgical instruments [1]. In our study, description of adenoidectomy with shaver is provided in line with its advantages and disadvantages.

Material and methods. 50 patients were enrolled in the prospective study, all of them underwent adenoidectomy with shaver within the period from January 2019 to June 2020 inclusive. Age range was 2-26 years old (average age-14 years old),