

# MEDICAL SCIENCES

## ОЦІНКА ВІДПОВІДІ НА ЛІКУВАННЯ ТАУРИНОМ ТА МЕЛЬДОНІЄМ ЗА АМІНОКИСЛОТАМИ КРОВІ У ПОСТІНФАРКТНИХ ХВОРИХ З ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

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## RESPONSE EVALUATION ON THE TAURIN AND MELDONIUM TREATMENT OF BLOOD AMINO ACIDS IN POST-INFARCTION PATIENTS WITH TYPE 2 DIABETES

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### Анотація

Важливе значення у комбінованому лікуванні хворих з постінфарктним кардіосклерозом (ПІКС) з цукровим діабетом типу 2 (ЦД 2) надається метаболічній терапії (МТ), зокрема, препаратам з антиоксидантною активністю, до яких належать таурин (ТН) та мельдоній (МН). Аналіз амінокислот крові може бути важливим в контексті цільового призначення метаболічної терапії та визначення необхідності зміни препарату при його неефективності. Окрім впливу на фармакологічний ефект метаболічних препаратів, доведено роль амінокислот у патогенезі інсулінорезистентності, аритмій, ішемічних змін міокарда. Оцінка залежності відповіді на лікування від вихідного стану амінокислотного спектра плазми крові у хворих з ПІКС та ЦД 2. Пацієнти з ПІКС та ЦД 2 (n=68) основної групи отримували базову терапію (БТ) ПІКС та ЦД 2, та додатково МЕ по 1 капсулі 500 мг 2 рази на день і ТН по 1 капсулі 400 мг 3 рази на день протягом 3 тижнів. Пацієнти групи порівняння (n=30) приймали лише БТ. Пацієнти основної групи, підгрупи таурину та мельдонію, з позитивною відповіддю на лікування, отримали умовну назву "відповідачів". Хворі без динаміки або негативною відповіддю на лікування отримали умовну назву "невідповідачів". Критеріями відповіді на лікування вважали дані холтерівського моніторингу ЕКГ: зниження на 50% загальної кількості шлуночкових екстрасистол, на 90% частоти парних шлуночкових екстрасистол, зникнення "пробіжок" шлуночкової тахікардії, зменшення кількості епізодів безбольової ішемії міокарда до 3 і менше протягом доби, сумарної тривалості ішемії протягом доби нижче 40 хвилин. Багатофакторний логістичний регресійний аналіз із покроковим виведенням показників та проведенням ROC-аналізу показав, що вихідне відношення таурин/аланін виявилось амінокислотним маркером, який проявив кореляцію з результатами лікування хворих підгруп таурину, мельдонію та мельдонію+ таурин незалежно від наявності інших чинників, за якими достовірно відрізнялися відповідачі і невідповідачі цієї групи. У хворих, які відповідають значенню Таурин/Аланін( $\leq 0,043$ ), та тирозин+фенілаланін/метіонін у плазмі крові  $>34,41$ , доцільним є призначення комплексу таурин+мельдоній додатково до базової терапії.

### Abstract

Metabolic therapy (MT), in particular, antioxidant activity drugs, which include taurine (TN) and meldonium (MN) are of vital importance in the combined treatment of patients with postinfarction cardiosclerosis (PFCS) with type 2 diabetes (diabetes mellitus). Analysis of blood amino acids may be important in the context of the purpose of metabolic therapy and the need to change the drug in case of its ineffectiveness. In addition to influencing the pharmacological effect of metabolic drugs, the role of amino acids has been proved in the pathogenesis of insulin resistance, arrhythmias, and ischemic changes of the myocardium. The research objective was to evaluate the dependence of the response to treatment on baseline amino acid spectrum of blood plasma in patients with PFCS and type 2 diabetes mellitus. Patients with PFCS and type 2 diabetes mellitus (n = 68) of the main group received basic therapy (BT) of PFCS and type 2 diabetes mellitus, and additionally 1 capsule 500mg 2 times a day of MN and 1 capsule 400mg 3 times a day for 3 weeks of TN. Patients in the comparison group (n = 30) took only BT. The main group and the taurine and meldonium subgroup patients having positive response to treatment were given the conditional name of "responders". Patients without dynamics or with a negative response to treatment were referred to as "non-responders". The criteria for responding to treatment were Holter monitor data: 50% reduction in total ventricular extrasystoles, 90% reduction in paired ventricular extrasystole frequency, disappearance of ventricular tachycardia jogging, reduction of episodes of painless myocardial ischemia to 3 and less times a day, and total duration of ischemia per day is less than 40 minutes. Multi factor logistic regression analysis with step-by-step indexing and ROC analysis showed that the initial taurine/alanine ratio was an amino acid marker, which showed correlation with the results of treatment of patients with taurine, meldonium and meldonium + taurine regardless of the presence of other factors that significantly differentiated the defendants and non-responders of this group. In patients with Taurine/Alanine ( $\leq 0.043$ ) and plasma tyrosine + phenylalanine/methionine  $>34.41$ , it is appropriate to appoint the taurine + meldonium complex in addition to basic therapy.

**Ключові слова:** цукровий діабет 2-го типу, постінфарктний кардіосклероз, таурин, мельдоній.  
**Keywords:** 2<sup>nd</sup> type diabetes mellitus, postinfarction cardiosclerosis, taurine, meldonium.

### Introduction

Metabolic therapy (MT), in particular, antioxidant drugs to which taurine (TN) and meldonium (MN) belong, is important in the combined treatment of post infarction patients with type 2 diabetes [4,7,8,14,16,17,19,24]. The effectiveness of MT depends not only on the presence of concomitant diseases in the patient, sex and age, but also from the individual condition of the so-called endogenous mechanisms of cardioprotection [9,10]. It has been proved that the amino acid spectrum is both a substrate and a regulator of enzyme activity [1,2,12]. Analysis of blood amino acids is important in the context of the purpose of metabolic therapy and the need to change the drug in case of its ineffectiveness [13,15,20,21]. Besides the influencing on the pharmacological effect of metabolic drugs, the role of amino acids has been proven in the pathogenesis of insulin resistance, arrhythmias, ischemic myocardial changes [5,6,11,18,22].

Research objective: to evaluate the dependence of the response to treatment on the baseline of the amino acid spectrum of blood plasma in patients with PFCS and type 2 diabetes mellitus.

### Materials and methods

We examined 98 patients with PFCS and concomitant type 2 diabetes mellitus, which were randomly divided into two groups: main (MG), (n = 68): 36 women and 32 men, median age of patients — 65.5 years (interquartile interval - 61-68 years old), and comparison group (CG) (n = 30): 17 women and 13 men, median age — 64.7 years old (interquartile interval — 64–68 years old). Patients with PFCS and concomitant type 2 diabetes mellitus who provided informed consent were involved into the research. The monitor group (MG) was represented by 30 patients with a balanced age and sex with PFCS and concomitant type 2 diabetes mellitus.

Exclusion criteria: IIB-III stage chronic heart failure according to Strazheska and Vasylenko classification, acute coronary syndrome during the last 12 months, congenital and acquired heart diseases, complete bundle branch block, implanted cardiac pacemaker, II-III stage AV block, A-fib, autoimmune diseases, malignant oncological diseases, expressed renal, hepatic, respiratory failure, endocrine diseases (except for type 2 diabetes). General clinical characteristics of patients are shown in table 1.

Table 1.

General characteristic of the examined patients (*Me (IQR)*)

Characteristic	Examined patients, n= 98
Age	64 (60-69)
Gender: female/male, n,%	50 (51.0%) /48(48.97%)
Age of diabetes, years	7.69 (7.45-8.12)
Age of IM, years	6.09 (5.35-8.02)
Body mass index, kg/m <sup>2</sup>	31.72 (27.8-39.11)
Concomitant heart failure, n, %	98 (100.0 %)
Associated arterial hypertension, n (%)	98 (100.0 %)
HOMA-IR	6.02 (5.11-6.16)
Office systolic blood pressure, mmHg	144.2 (126.7-154.5)
Office diastolic blood pressure, mmHg	87.45 (86.7-88.37)
C-reactive protein, mg/l	3.74 (3.12-5.11)
Glycosylated hemoglobin, %	7.92 (6.16-8.3)
phenylalanine + tyrosine/methionine	49.11(25.4-32.1)
Taurine/Alanine	0.031 (0.021-0.040)

Amino acid composition of patients' blood was determined by the method of ion exchange liquid column chromatography on an automatic amino acid analyzer Microtechna T339.

Holter monitor was performed on the Cardiosens machine. Estimated: total number of supraventricular and ventricular extrasystoles (VE) per day and their distribution during the day, the presence of paroxysms of ventricular and supraventricular tachycardia. Ventricular ectopic activity was evaluated according to the classification of B. Lown, L. Wolff (1991).

All patients have gone through ECG studies in 12 assignments at a speed of 50 mm/s. According to the ECG, the heart rate (HR) and absolute QT interval (in ms), its dispersion ratio, and the adjusted QT interval were evaluated.

The patients in the main group received basic therapy (BT), which included an ACE inhibitor,  $\beta$ -blocker, statin, antiplatelet agent, oral antidiabetic therapy and an additionally 1 capsule of 500mg twice a day of ME and 1 capsule of 400mg 3 times a day during 3 weeks of TN. Comparison group patients received only BT PFCS and type 2 diabetes mellitus drugs. In order to study the complex and isolated effects of TN and ME on the frequency of psychophysiologic disorder, main group was divided into 3 subgroups according to basic therapy supplementary treatment. The 1 subgroup (SB 1) included 22 patients who received TN, the 2 subgroup (SB 2) involved 23 patients receiving ME, and 3 subgroup (SB 3) includes 23 patients who comprehensively received ME and TN besides basic therapy. Main group and the taurine and meldonium subgroup patients with a positive response to treatment were given the

conditional name of the responders. Patients without dynamics or negative response to treatment received the conditional name of non-responders. The criteria for responding to treatment were Holter ECG monitoring data: 50% reduction in total ventricular extrasystoles, 90% reduction in paired ventricular extrasystole frequency, disappearance of ventricular tachycardia jogging, reduction of episodes of painless myocardial ischemia to 3 and less times a day, and total duration of ischemia per day is less than 40 minutes (criteria of effectiveness of anti-rhythmic therapy according to Horowitz and data of VI National Cardiology Congress of Ukraine) [5].

Statistical analysis of the data was performed using SPSS, MedStat, EZR packages. Checking the normality of the parameter distribution was evaluated using the Shapiro-Fork W-test. Continuous values were compared using the Mann - Whitney U test, since their distribution was different from normal. Quantitative data are presented as Me (IQR), where Me is the median, IQR is the interquartile interval (first and third quartiles). Dunn index was used to make multiple comparisons.

We used the binary logistic regression method with odds ratio (OR) and 95% confidence interval (CI) to study the relationship between the development of positive response to treatment and predictors. Potential predictors are amino acids that could be identified as independent predictors of the development of a positive response to treatment were determined using step-by-

step logistic regression analysis of multifactorial models. Each model included a separate amino acid or ratio between amino acids that compete for entry through the cell membrane. When developing the models we considered demographic, clinical, anamnestic, instrumental, and lab risk factors. Receiver Operator Characteristic (ROC) analysis was used to determine the quality of each regression model and calculate its sensitivity and specificity, as well as to determine the area for the ROC curve (AUC).

There were no statistically significant differences between responders and non-responders within the same subgroup and when comparing different subgroups of patients by the frequency of recording of rhythm disturbances and conductivity at the beginning of the study.

### Results and discussions

Multivariate logistic regression analysis with step-by-step indexing and ROC analysis showed that the initial taurine/alanine ratio was an amino acid marker, which showed correlation with the results of treatment of patients with taurine, meldonium and meldonium+ other taurine regardless of the presence of other factors that significantly differentiated the defendants and non-responders of this group.

The value of the taurine/alanine ratio  $\leq 0.042$  (AUC = 0.818; 95% CI 0.033–0.045) in blood serum was characterized by a sensitivity of 81.8% and specificity of 88.0% in predicting a positive response in patients who received taurine (Fig. 1).

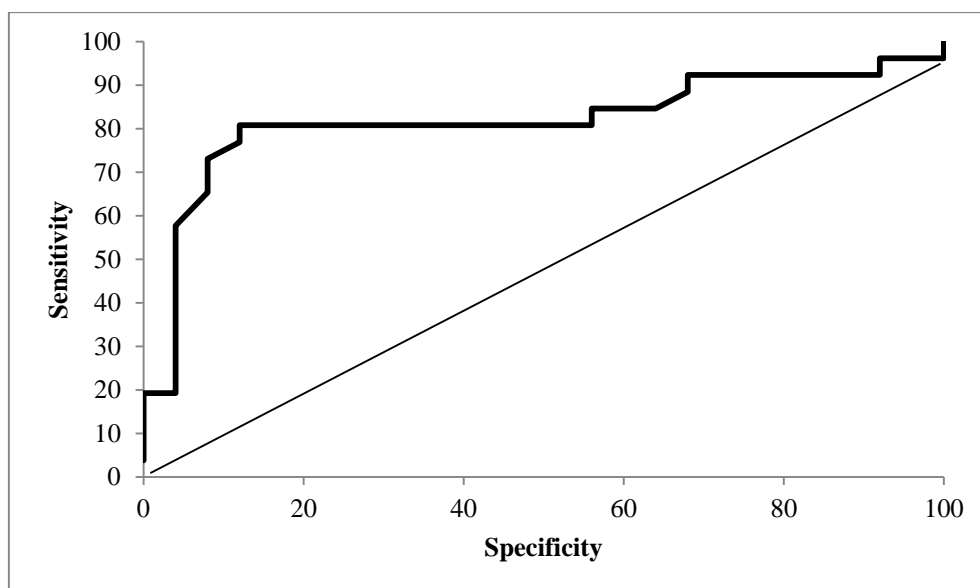


Figure 1. ROC curve of the positive response to taurine treatment from baseline taurine/alanine in the blood of patients with PFCS and type 2 diabetes mellitus.

In the meldonium subgroup, the positive response to treatment was significantly correlated with the value of the taurine/alanine blood ratio. The 0.043 taurine/alanine level was characterized by high sensitivity (80.77%) and specificity (88%) and high model quality (AUC = 0.845; CI 0.027-0.045) (Fig. 2).

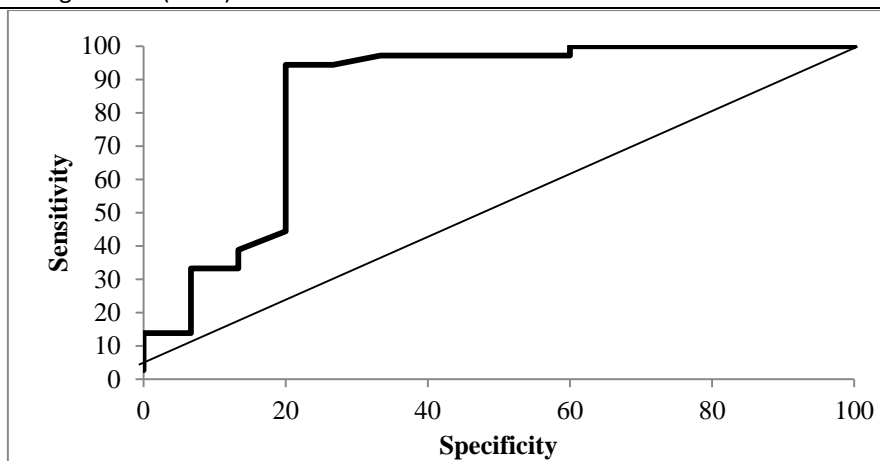


Figure 2. ROC curve of the positive response to treatment with meldonium from baseline taurine/alanine in the blood of patients with PFCS and type 2 diabetes mellitus.

The value of the taurine/alanine ratio  $\leq 0.048$  (AUC = 0.949; 95% CI 0.039–0.054) in blood serum was characterized by a sensitivity of 90.9% and a specificity of 96.55% in predicting a positive response in patients who received the taurine and meldonium complex (Fig. 3)

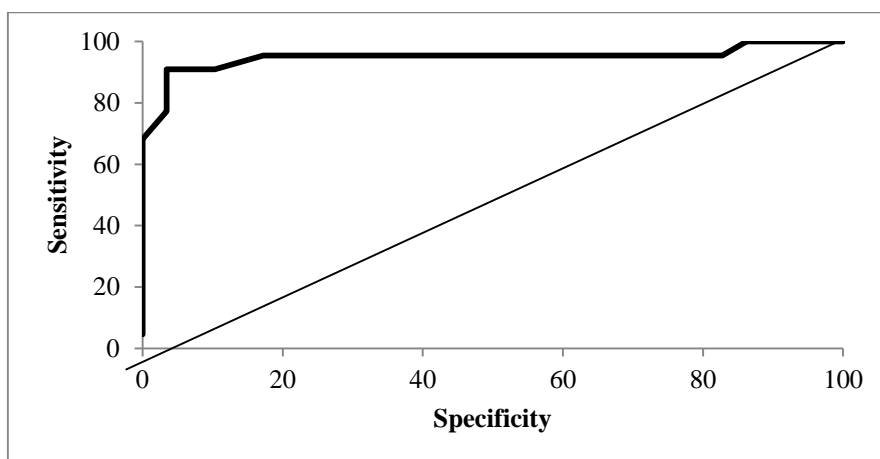


Figure 3. ROC curve of positive response of taurine and meldonium treatment to baseline taurine/alanine ratio in blood of patients with PFCS and type 2 diabetes mellitus.

In the taurine and meldonium subgroup, the positive response to treatment was significantly correlated with the value of the tyrosine + phenylalanine/methionine ratio (Table 5). Tyrosine + phenylalanine/methionine  $> 34.41$  was characterized by high specificity (92.59%) and moderate sensitivity (58.33%) and lower model quality compared to Taurine/Alanine (AUC = 0.745; CI 28.27-35, 45) (Fig. 4).

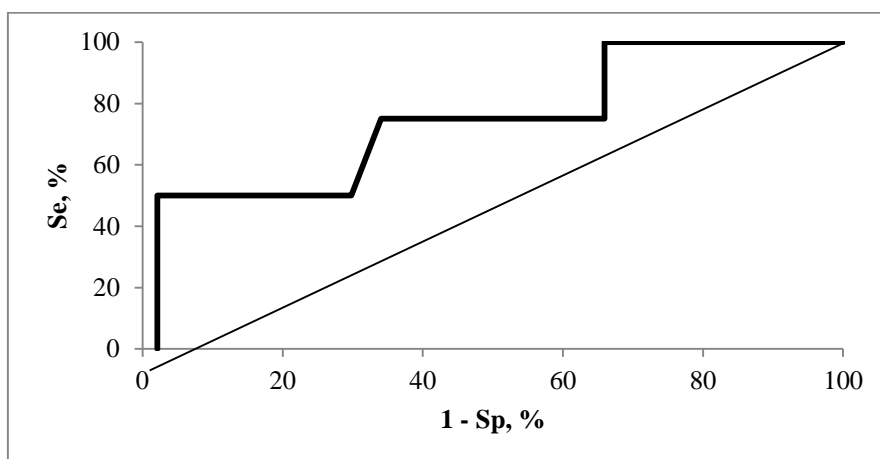


Figure 4. ROC curve of the positive response to taurine and meldonium treatment on baseline tyrosine + phenylalanine/methionine in blood of patients with PFCS and type 2 diabetes mellitus.

### Discussion of the results

The results are explained by the mechanisms of competitive inhibition of the entry of amino acids into the cell. To maintain the appropriate amino acid transportation a certain ratio of the concentration of K<sup>+</sup> and Na<sup>+</sup> is required; low and especially high ions concentrations inhibit the accumulation of amino acids and tissue sections, and thus they are inhibitors of amino acid transportation. Alanine competes to enter into the cell by the  $\beta$ -system. We described the mechanisms of competitive inhibition of these amino acids and the possibility of using the Taurine/Alanine ratio for therapeutic and therapeutic purposes.

Methionine and aromatic amino acids that penetrate into the cell are direct competitors for cell penetration. Taking into account that aromatic amino acids are not absorbed on condition of ischemia and methionine is used in ischemia as a donor to methyl groups, the decrease of this coefficient is an important indicator of the effect of metabolic therapy on myocardium [3, 23, 25].

### Conclusions

The effectiveness of cardio-protective therapy with meldonium and taurine depends on the ratio of individual blood amino acids involved in the processes of metabolic action and ischemic myocardial changes. The positive effect of meldonium and taurine is associated with a lower baseline plasma taurine/alanine ratio ( $\leq 0.043$ ). Patients who meet this criterion, it is advisable to prescribe a complex of taurine + meldonium besides the basic therapy. The administration of the taurine + meldonium supplement in addition to basic therapy is also appropriate for patients with baseline tyrosine + phenylalanine/methionine in blood plasma > 34.41.

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## РАЗВИТИЕ ЗДРАВООХРАНЕНИЯ И МЕДИЦИНСКОЙ НАУКИ В УФИМСКОЙ ГУБЕРНИИ НА ПЕРЕЛОМЕ ЭПОХ (КОНЕЦ XIX—НАЧАЛО XX ВВ.)

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## THE DEVELOPMENT OF HEALTH AND MEDICAL SCIENCES IN UFA PROVINCE AT THE TURN OF EPOCHS (END OF XIX—BEGINNING OF XX CENTURIES)

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### Аннотация

В статье рассмотрены основные аспекты истории развития медицины в Уфимской губернии на рубеже веков — в конце XIX—начале XX вв. Отражена история становления здравоохранения и системы медицинской помощи, крупные эпидемии, описаны лечебные и аптекарские учреждения, органы управления, учреждения осуществляющие подготовку медицинских кадров, в динамике приведена численность и кадровый состав работников.

### Abstract

The article describes the main aspects of the history of development of medicine in Ufa province at the turn of the century in the late nineteenth and early twentieth centuries, Reflected the history of the formation of health and medical care system, major epidemic, described medical and pharmaceutical companies, governments, institutions engaged in training of medical personnel in the dynamics of the given number and composition of workers

**Ключевые слова:** Уфимская губерния, здравоохранение, история медицины, Башкирская энциклопедия

**Keywords:** Ufa province, health, history of medicine, Bashkir encyclopedia