Original Article

Amino Acid Ratios In Postinfarction Patients With Type 2 Diabetes Mellitus

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Abstract

The aim of the study: to determine serum amino acids as markers and predictors of arrhythmic complications in post-infarction patients with insulin resistance.

Materials and methods: 117 patients were examined, who, according to the presence of type 2 diabetes, were divided into two groups: the main group - 85 patients with coronary heart disease with postinfarction cardiosclerosis (PICS) on the background of type 2 diabetes (DM 2) and a comparison group of 32 patients with PICS without carbohydrate metabolism disorders. The median age of the patients was 64.2 years (interquartile range – 60–66.5 years). 21 amino acids (AA) and separate ratios between amino acids competing for entry through the cell membrane were studied. According to Holter ECG monitoring (HMEKG), arrhythmic disorders and heart rate variability (HR and HRV) were determined.

Results: A statistically significant decrease in the Tau/Ala index of patients with pathology compared to patients from the control group was determined ($p<0.001$). At the same time, a more pronounced and reliable decrease was observed in postinfarction patients with insulin resistance. The index was found to be highly specific with a high positive predictive value (PPV).

Conclusions: 1. Postinfarction patients with insulin resistance are characterized by a decrease in the Tau/Ala index, which can be one of the potential mechanisms of arrhythmias and insulin resistance. 2. It is advisable to use the Tau/Ala index as a predictor of life-threatening arrhythmias in order to target the targeted therapy of postinfarction patients with insulin resistance. The value of Tau/Ala (<0.038) is advisable to use for the purpose of prescribing therapy and for monitoring the results of treatment of postinfarction patients with insulin resistance.

Keywords: coronary heart disease, diabetes mellitus type 2, amino acids, taurine, alanine

Introduction

Cardiovascular diseases (CVD) and their complications are the cause of approximately 80% of deaths in patients with diabetes mellitus (DM). Insulin resistance and hyperinsulinemia are recognized as independent risk factors for CVD [1, 2].

Data from numerous epidemiological studies indicate the existence of a relationship between the level of glycosylated hemoglobin, the risk of developing CVD and mortality due to their complications. When the level of glycosylated hemoglobin increases by 1%, the risk of developing CVD increases by 10% [3]. In the structure of cardiovascular pathology in patients with type 2 diabetes (DM 2), CVD occupies a leading place.

The risk of myocardial infarction (MI) in patients with type 2 diabetes mellitus is equal to the risk of patients with a history of MI and no diabetes mellitus [4]. It is clear that the risk is particularly significant when a history of MI is combined with established diabetes mellitus.

However, the presence of a high level of traditional risk factors does not mean the need to eliminate the need to determine the so-called non-traditional factors. This is a proven fact [5]. The rate of sudden coronary death (SCD) in patients with DM 2 is 2–3 times higher compared to the general population and accounts for about 40% of the total mortality of patients with DM 2 [6]. This indicator has a tendency to increase, regardless of the impact on recognized traditional risk factors. Therefore, the task of influencing new indicators, which must be taken into account together with the generally recognized ones, when stratifying the risk and determining the treatment tactics of coronary artery disease against the background of DM2 is particularly relevant [7].

The myocardium is known as a metabolic structure because it uses a variety of substrates: fatty acids, glucose, ketone bodies, pyruvate, lactate, amino acids, and its own proteins in descending order of the benefits of their consumption. The above-mentioned substrates are necessary for maintaining ion homeostasis, electrical activity capacity, metabolism, normal operation of transmembrane pumps and transporters, contractility. Electrical and metabolic activity of the myocardium changes under conditions of ischemia. With a lack of oxygen, the mechanisms of the use of the above-mentioned substrates by the myocardium

also undergo changes. The effect of ischemia on the electrical activity of the myocardium is deeply studied, but the changes in the metabolic advantages of the heart in these conditions are insufficiently described and have a number of questions.

Despite the presence of a significant amount of data on the cardioprotective properties of those AA, their role in the metabolism of myocardium in CHD is insufficiently studied [8].

Research data on the relationship between AA and insulin resistance is also mixed. An increased content of branched-chain AA and aromatic AA, a decrease in the glycine/serine ratio are associated with an increased risk of diabetes [9]. At the same time, the effectiveness of additional taurine intake in DM2 is proven [10]. The results of a number of studies showed an increase in the sensitivity of tissues to insulin with the additional use of methionine.

Opposite changes of AA in certain clinical forms are explained by the existence of specific transport systems, competitive with respect to a number of AMC. Competitive inhibition is the cause of disruption of the normal supply of AA tissues, which is the basis of pathological conditions and is the point of application of medicinal products [11].

Thus, with the help of numerical studies, a significant role of AA in the formation of both insulin resistance and ischemic changes was revealed, however, the data are still ambiguous. Objective criteria for the additional use of AA for diagnostic and therapeutic purposes have not been developed, and the problems of their selection remain unresolved. The development of this direction will make it possible to develop additional possibilities in the prediction and treatment of CHD in combination with DM 2. Thus, the presence of many unresolved issues that require further study determined the necessity, purpose and task of conducting this study.

Aim of the study

The purpose of the study is to determine the features of the AA composition of blood and to improve the prognosis of complications in coronary heart disease with PICS and concomitant DM 2.

To achieve this goal, we set ourselves the following tasks:

1) find out the amino acid composition of blood serum in patients with PICS and DM 2 and compare it with patients without impaired carbohydrate metabolism;

2) to study the relationship between individual AA and their correlations with cardiovascular risk indicators and results of HMEKG;

3) to determine the diagnostic value of individual AA and their ratios, the expediency of application for the purpose of screening, targeted therapy and control of treatment in patients with PICS and DM 2.

Materials And Methods

The single-center cross-sectional study is a fragment of the complex research work of the Department of Internal Medicine No. 4 of the Bogomolets National Medical University "Disturbances of hemodynamics, coronary blood circulation and ectopic activity of the myocardium in patients with ischemic heart disease with accompanying diabetes, methods of drug correction" (state registration number 0117U006000).

We analyzed the examination data of 116 patients who, according to the presence DM 2, were divided into two groups: the main group - 84 patients with PICS on the background of DM 2 (48 (57.14%) men and 36 (42.85%) women) and a comparison group of 32 with PICS without violations of carbohydrate metabolism (14 (43.75%) men and 18 (56.25%) women). The median age of patients was 65.2 years (interquartile range – 60–67.5 years) (Table 1).

Table 1: General clinical characteristics of the examined patients

Index	*Patients with PICS and DM2 (n=84)*	*Patients with PICS (n=32)*	*P*
Age, years	*64 (60-69)*	*64 ,5 (62-67)*	*<0,05*
Sex: female/male, n, %	*48(57,14)/36(42,85)*	*14 (43,75)/ 18 (56,25)*	*<0,05*
Duration of MI, years	*4,45(4,02-4,56)*	*4,57 (4,03-5,14)*	*<0,05*
Duration of DM 2, years	*6,98 (6,01-7,12)*	---------	*<0,05*

Patients with PICS and concomitant DM 2, who gave appropriate informed consent, were included in the study.

Exclusion criteria from the study: chronic heart failure stage III according to the Strazheska-Vasilenka classification, acute coronary syndrome within the last 12 months, congenital and acquired heart defects, autoimmune diseases, malignant oncological diseases, severe renal, hepatic, respiratory failure, others endocrine diseases, an implanted pacemaker, II-III stage AV blockade, atrial fibrillation.

AA of the patients' blood was determined by chromatography (MicrotechnaT339 analyzer). 20 AMAs and 12 ratios between them were determined, in which AA were united by a competitive mechanism of transport into the cell.

Normative values of AA were obtained during examination of 22 conditionally healthy persons, comparable in age and gender (10 men and 12 women, median age - 64.1 years (interquartile range - 58–65.5 years), who made up the control group (CG).

24-hour Holter ECG monitoring (HECG) was performed on the Cardiosens system.

The following indicators of HECG were evaluated:

1. Maximum, minimum and average heart rate per day;

2. Dynamics of the ST segment:

a) duration of depression of the ST segment greater than or equal to 1 mm in minutes (ST sum);

b) the frequency of episodes of depression of the ST segment greater than or equal to 1 mm - the number of episodes - (ST ep.);

c) ST segment depression depth in mm;

d) duration of the maximum ST segment with a depth of depression greater than or equal to 1 mm in minutes (ST max);

3. The total number of supraventricular and ventricular rhythm disturbances of various gradations per day.

To characterize the degree of severity of ventricular arrhythmias (L1-5), we followed the classification according to Lown, Wolf (1971).

Arrhythmias of high gradations (L3-5, K3-4) were evaluated as prognostically unfavorable, and arrhythmias of small gradations (L1-2, K1-2) were prognostically indifferent.

In the process of analyzing HM ECG data, temporal and spectral indicators of heart rate variability were determined.

The following indicators were determined:

SDNN is the standard (root mean square) deviation of the R-index interval, which depends on the activity of both parts of the nervous system, both sympathetic and parasympathetic. This indicator can be used to estimate heart rate variability as a whole, since it is an interval indicator.

HF is an indicator of parasympathetic modulation. LF is an indicator of perception by pacemaker effects of the sinus node on the sympathetic division of the nervous system.

In the studied EMIAT, the combination of low HRV with a decrease in left ventricular ejection fraction below 40% was correlated with the risk of death in patients who suffered MI [12].

The obtained data gave grounds to the European Society of Cardiology in 2001 to recommend HRV testing for risk stratification of sudden cardiac death in patients who have undergone MI (class I, level of evidence A) [13]. It should be noted that among all indicators of Holter ECG monitoring, only HRV parameters had such a high level of evidence.

Statistical data analysis was carried out with the help of statistical packages SPSS, MedStat, EZR. Diagnostic value was determined using Receiver Operating Characteristic (ROC) analysis. Sensitivity, specificity, positive and negative prognostic value, diagnostic accuracy, and the ratio of the likelihood of positive and negative results were calculated. Based on this, the possibility of using indices at different stages of the study was determined: for screening purposes or for the purpose of determining target therapy and control of treatment.

Results And Discussion

As a result of the conducted research, we established that patients of the main group had a statistically significant decrease in the concentration of Tau ($p<0.001$) compared to practically healthy individuals of CG. At the same time, the level of Tau compared to patients from the comparison group was also lower ($p<0.05$) (Table 2).

When comparing the results, a statistically significant decrease in the concentration of Tau in the blood was also found in comparison with the CG patients in the comparison group ($p<0.001$).

Thus, the obtained results demonstrate a decrease in Tau concentration in both groups of examined patients compared to patients

with CG. At the same time, a more significant decrease in Tau concentration is observed in patients with PICS and DM 2.

The data we obtained do not contradict the results of most of the works of other authors. The results of numerous studies show that taurine content in patients with DM 2 is significantly reduced [14].

This fact is explained by the accumulation of sorbitol in tissues during the activation of the polyol oxidation pathway glucose absorption in conditions of hyperglycemia. On the one hand, this leads to a decrease in the synthesis of taurine in cells, and on the other hand, to a decrease in the activity of glutathione reductase, and, therefore, to a decrease in the recovery of oxidized glutathione. As a result, oxidative stress occurs [15].

The antioxidant properties of taurine are realized by reducing the content of sorbitol in conditions of hyperglycemia. The connection between a decrease in the level of taurine during pregnancy and the possibility of developing DM 2 in the offspring in the future has been described [16].

One of the main pathogenetic factors in the development of DM 2 is insulin resistance, which progresses with the development of carbohydrate metabolism disorders

associated with oxidative stress.

During glucose self-oxidation under conditions of hyperglycemia, excessive formation of diacylglycerol occurs, the main stimulator of protein kinase C (PCC) activity. Activation of the PKS leads to disruption of signal transmission through insulin receptors of cells.

The multicenter large-scale epidemiological study CARDIAC (1982–2005, Japan) revealed an inverse correlation between taurine consumption and population mortality from CHD. When analyzing the data obtained, it was determined that 59% of CHD mortality is caused by taurine deficiency. It is known that ischemia and heart failure are accompanied by the release of catecholamines into the blood, which in turn leads to an overload of calcium ions and further degeneration of the heart muscle [17].

Taurine helps normalize the intracellular content of potassium ions and stabilize the membrane potential (MP).

Taurine has an inhibitory effect on the central nervous system (CNS), sometimes stronger than gamma-aminobutyric acid (GABA). In addition, it inhibits the release of norepinephrine from the presynaptic endings of adrenergic fibers [18].

As a result of our study, it was also established that patients of the main group had a statistically significant increase in Ala concentration in comparison with practically healthy individuals of CG ($p<0.001$). At the same time, the level of Ala compared to patients from the comparison group was also higher ($p<0.05$) (Table 2).

Table 2: Tau/Ala, Ala, Tau indicators in patients with PICS and type 2 diabetes, with PICS without impaired carbohydrate metabolism, and subjects of the control group

Index	Patients with PICS and DM2 (n=84)	Patient with PICS (n=32)	Control group (n=22)
Tay, mg/100 ml	0,187 (0,147-0,290)*	0,229 (0,212-0,262)	0,351(0,311-0,397)
Tau/Ala	0,032 (0,021-0,042)**	0,039 (0,023-0,046)	0,950 (0,832-0,983)
Ala, mg/100 ml	8,741 (8,412-9,812)	8,161 (8,012-9,015)	5,431 (4,976-5,673)

* – $p<0.001$ – compared to control group patients;

** – $p<0.05$ – compared with patients from the comparison group.

When comparing the results, a statistically significant increase in the concentration of Al in the blood was also found in comparison with CG patients in persons from the comparison group ($p<0.001$).

Thus, the obtained results demonstrate an increase in Al concentration in both groups of examined patients compared to patients with CG. At the same time, an increase in Al concentration is observed in patients with PICS and DM 2.

An increase in the content of Ala, which is a competitor of Tau for penetration through the CMC membrane, is associated with increased SSR according to the results of previous studies [4, 19].

Competitive inhibition for entry into the cell is described as the cause of disruption of the normal supply of AMK tissues, which is the basis of pathological conditions and is the point of application of the action of drugs. [16; 22]. Specific transport systems are described as competitive with respect to a number of certain AAs: the B²ATI system – for BCA, and Met, the ß-system for

Tau and Ala [20,21,22,23].

As a result of the conducted research, we found that in patients of the main group, compared with practically healthy individuals, there is a statistically significant decrease in the Tau/Ala ratio ($p<0.001$). At the same time, this indicator was also lower compared to patients from the comparison group ($p<0.05$) (Table 2).

When comparing the results, a statistically significant decrease in the Tau/Ala ratio was also found in comparison group patients compared to CG patients ($p<0.001$).

Thus, the obtained results testify to a decrease in the Tau/Ala ratio of the examined patients compared to patients with CG. At the same time, a more significant decrease is observed in patients with PICS and T2DM.

We found statistically significant correlational relationships between the determined AA parameters and the results of the HM ECG characterizing HRV (Table 3).

Table 3: Correlation relationships between Tau/Ala, Ala, Tau and ACP and HRV indicators

Index	VE	SVE	SDNN, ms	HF, ms2	LFms2
Taurine	r=-0,41; p=0,01	r=-0,43; p=0,02	r=0,47; p=0,01	r=0,25; p=0,02	r=-0,33; p=0,01
Taurine/Alanin e	r=-0,62; p=0,01	r=-0,64; p=0,01	r=0,51; p=0,02	r=0,67; p=0,01	r=--0,44; p=0,01
Аланine	r=-0,23; p=0,01	r=0,29; p=0,01	r=-0,42; p=0,01	r=-0,35; p=0,01	r=0,31; p=0,01

Between Tau and SHE, Tau and NSHE, Tau and SDNN, Tau and LF, the strength of the connection was moderate, between Tau and HF it was weak. Ala demonstrated a weak relationship with all parameters of ACP and HRV, except for SDNN, where a relationship of moderate strength was found. It was found that between Tau/Ala and SHE, NSHE, SDNN, NF, the strength of the connection was significant, between Tau/Ala and LF of moderate strength.

It was found that the Tau/Ala index has high specificity (Sp) and positive predictive value (PPV) and low sensitivity (Se) and negative predictive value (NPV). Tau showed low Sp and PPV with high Se and NPV.

Conclusions

1. For patients with PICS on the background of DM 2, a decrease in the content of Tau and Tau/Ala is characteristic, which may be one of the pathogenetic mechanisms of arrhytmias and changes in HRV and carbohydrate metabolism disorders.

2. In patients with CHD with PICS without impaired carbohydrate metabolism, the content of Tau and Tau/Ala is reduced, but higher compared to patients with PICS and DM 2, which may indicate a more active participation of Tau and Ala in the processes of carbohydrate metabolism.

3. It is advisable to use Tau/Ala as prognostic markers of arrhytmias and HRV disorders and for the purpose of targeting targeted therapy for patients with coronary heart disease with PICS on the background of DM

4. Since none of the determined indicators demonstrated high specificity and sensitivity for arrhytmias and HRV at the same time, the indicators should be used in accordance with the stage of the study: Tau (<0.212 mg/100 ml) is most acceptable for screening purposes, Tau/ Ala(<0.038) is more appropriate to use for the purpose of targeted therapy and as a treatment control.

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