Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 90 - 97
Received 16 February 2021; Accepted 08 March 2021.

Features of Amino Acid Composition of Blood in Post-Infarction Patients with Impaired Carbohydrate Exchange and Its Interconnection with Cardiovascular Risk Factors

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Abstract

Amino acids (AA) are important predictors of ischemic changes in the myocardium and insulin resistance. The purpose of this study is to learn serum AA in patients withpostinfarction cardiosclerosis (PICS) in combination with diabetes mellitus type 2 (DM) and without impaired carbohydrate metabolism, as well as the relationship of AA with indicators of carbohydrate and lipid metabolism as cardiovascular risk (CVR) factors, which may allow using AA as predictors of cardiovascularcomplications. 31 patients with PICS and concomitant DM were selected for the study, which formed the main group (MG). The comparison group (CG) included 27 patients with PICS without DM. Patients with PICS and DM showed a statistically significant increase in the total concentration of AA compared with the CG – by 24.91% ($p<0.05$) andin the concentration of branched-chain amino acids (BCA) -isoleucine -by 28,39%, leucine-by 41.11% ($p<0.001$), valine – by 34.1% ($p<0.05$); lysine concentration – by 11.8% ($p<0.05$), aspartate – by 17.3% ($p <0.001$), glutamate – by 11.4% ($p<0.05$). In patients of the MG there was a significant decrease in the concentration of taurine, arginine, methionine, glycine: by 11.3% ($p<0.05$), 18,1% ($p<0.05$), 7.7% ($p<0.001$), 10.12% ($p<0.001$), respectively, compared with patients with PICS without impaired carbohydrate metabolism. According to the results of this analysis, the average strength of the inverse correlations of AA with the parameters of lipid metabolism: between taurine and very low-density cholesterol (VLDL) ($r= -0.54$; $p<0.05$), total cholesterol ($r=-0.52$; $p>0.05$);between methionine and VLDL ($r =-0.62$; $p<0.05$) and ApoB/ApoA1 ($r = -0.59$; $p<0.05$).The average strength of the correlation of AA with carbohydrate metabolism was also established: inverse – Tau with HbA1c ($r = -0.55$; $p <0.05$), HOMA index ($r=-0.45$; $p<0.05$), insulin ($r=-0.41$; $p<0.05$);methionine with HOMA index ($r=-0.62$; $p<0.05$), and insulin ($r=-0.55$; $p<0.05$).Direct correlations of medium strength were found for ARL and Ala ($r=0.56$ and $r=0.55$; $p <0.05$). The presence of correlations between CVR indicators and the content of individual blood AAs suggests the possibility of using AAs as prognostic markers of fatal cardiovascular events and requires further research.

Keywords: amino acids, cardiovascular risk factors, diabetes mellitus type 2, posinfarction cardiosclerosis

Introduction

According to the statistical forecast, cardiovascular mortality over the next decade will be about 25 million cases per year, mainly due to coronary heart disease (CHD) [1].Patients with previous myocardial infarction (MI)belong to a very high-risk group of patients [2,3]. The association between type 2 diabetes mellitus (DM) and cardiovascular diseases (CVD) was established in the Framingham study[4]. According to the equivalence of

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Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 90 - 97
Received 16 February 2021; Accepted 08 March 2021.

cardiovascular risk stratification (CVR), even with satisfactory metabolic control, diabetes mellitus is equated to a post-MI. The combination of these diseases mutually aggravates their course[5].

In order to improve the diagnosis and treatment of this combined pathology, more and more indicators are used that affect the metabolism of the ischemic myocardium.Amino acids (AA) are important predictors of ischemic changes in the myocardium AAare regulators of enzyme activity and substrates for a number of biochemical reactions [6,7].

AA exchange in CHD has been studied since the beginning of the fifties of the XX century.In further studies, an association of AA with insulin resistance was found.The presence of an AA imbalance becomes obvious with a combination of DM and CHD.However, these studies were predominantly experimental in nature, were carried out on animals, or individual AA and their ratio were studied.The relationship between blood AA and blood lipids as factors of CVR has not been studied either[8,9,10].

Also, previous studies have shown a positive effect of prescribing individual AA (for example, taurine) on autonomic regulation of cardiac activity, normalization of heart rate variability in patients with diabetes and postinfarction cardiosclerosis (PICS), correlation of individual amino acids and their ratios with arrhythmic complications and CVR in patientswith PICS[11,12]. The question of a comprehensive assessment of blood AA in patients with diabetes mellitus and PICS as a predictor of CVR remained unstudied.

Purpose: to learn serum AA in patients with PICS in combination with diabetes mellitus and without impaired carbohydrate metabolism, as well as the relationship of AA with indicators of carbohydrate and lipid metabolism as CVR factors, which may allow using AA as predictors of cardiovascularcomplications.

Materials and methods

The study was performed at the Department of Internal Medicine No.4BogomoletsNational Medical Universityon the basis of the Kyiv City Clinical Hospital No.12.From December 2018 to March 2020, patients were examined.As a result of the screening, 31 patients with PICS and concomitant DM were selected for the study, which formed the main group: 17(54.83%) men and 14(45.16%) women, the median age of patients—57.1 years (MI (interquartile range) — 54.4–58.5 years.The average duration of DM in this group was 5.62 years (MI 5.45–6.12) years, the age of PICS — 5.8 (MI 5.09–7.04) years.The comparison group included 27 patients with PICS without carbohydrate metabolism, comparable in age and sex with patients in the main group: 11 women and 16 men, median age — 55.6 years (MI — 54–57.5 years), the age of PICS— 5.4 (MI 4.5-6.48) years.Between the main group and the comparison group there were no significant differences in age, sex, duration of myocardial infarction, the presence of concomitant heart failure, hypertension, types of myocardial infarction in different localizations. Normative valuesof instrumental and laboratory indicators were obtained during the examination of the control group—24 practically healthy individuals, comparable with patients of the main group and the comparison group by age and sex.

The study of patients was voluntary.All patients were informed about the nature of the examinationsand personally signed an informed consent to the study.The research protocol was approved by the Commission on Bioethical Expertise and Research Ethics (expert opinion No. 111 of May 3, 2018).

Criteria for inclusion in the study were: signed voluntary informed consent to participate in the study; men and women aged 24 to 70 years; the presence of PICS and DM. Criteria that excluded patients from the study were: the presence of chronic heart failure stage IIB-III; acute coronary syndrome in the last 12 months; congenital and acquired heart defects; malignant and benign neoplasms; severe liver damage (excess of AST and / or ALT 3 or

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more times relative to the upper limit of normal) and/or kidney (serum creatinine level> 180 μmol/l), creatinine clearance less than 30 ml/min.10; the presence of autoimmune pathology; individuals who have undergone courses of immunomodulatory and immunosuppressive therapy (including glucocorticosteroids) less than 6 months before inclusion in the study;lesions of the endocrine system (except type 2 diabetes).

Examination of all patients included a detailed collection of medical history and life history, assessment of complaints, laboratory (immunological and biochemical) and instrumental research methods.

The amino acid composition of patients' blood was determined by ion exchange liquid column chromatography.Indicators of lipid metabolism were determined by immunoturbodimetric, enzymatic-colorimetric (total cholesterol, low and very low-density lipoprotein cholesterol) methods).Carbohydrate metabolism parameters were determined by enzymatic (venous blood glucose), immunoturbodimetric (glycosylated hemoglobin) and immunochemical with electrochemiluminescent detection (insulin) methods.

Statistical analysis of the data was performed using statistical packages SPSS version 22, EZR version 1.38 (Saitama Medical Center, Jichi Medical University).The Shapiro-Wilk test was used to check the normality of the distribution.When comparing the two groups, the indicators of which did not correspond to the normal distribution of traits, the nonparametric Wilcoxon-Mann-Whitney test was used to evaluate the results.The nonparametric Kruskal-Wallis test was used when comparing several groups with a distribution of features other than normal.To determine the correlation between indicators whose distribution differed from normal, we used the Spearman correlation coefficient (bilateral alternative hypothesis).

Results and discussion

According to the analysis of the amino acid composition of the blood, statistically significant ($p < 0.05$) changes in 18 of the 21 studied parameters were detected.(Table 1).

Table 1.Amino acid valuesin patients with postinfarction cardiosclerosis (PICS) and type 2 diabetes mellitus (DM), with postinfarction cardiosclerosis without carbohydrate metabolism disorders and persons of the control group. (mg/100 ml), Me (IQR)..

Indicator	Patients with PICS and DM (n=31)	Patients with PICS (n=27)	Control group (n=24)
Lysine	2.718*# (2.56-2.89)	2.317** (2.19-2.43)	1.453 (1.33-1.56)
Histidine	0.914* (0.86-1.12)	1.113 (1.02-1.15)	0.987 (0.71-1.14)
Arginine	0.19*# (0.12-0.31)	0.28** (0.21-0.32)	1.14 (0.75-1.19)
Ornithine	0.768 (0.63-0.89)	0.764 (0.67-0.92)	0.812 (0.78-1.12)
Taurine	0.186**## (0.145-0.290)	0.229** (0.212-0.262)	0.351 (0.311-0.397)
Threonine	1.345 (1.13-1.43)	1.453 (1.27-1.567)	1.419 (1.34-1.516)
Glutamicacid	1.917 (1.61-2.12)	1.576 (1.32-1.71)	1.121 (0.86-1.15)
Glycine	1.311*# (1.21-1.45)	1.716* (1.32-1.84)	3.212 (2.56-3.42)
Alanine	6.27**#	5.91**	2.741

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	(5.34-7.01)	(4.32-6.12)	(2.34-2.98)
Cystine	0.987 (0.75-1.14)	1.121 (0.37-1.19)	1.124 (0.85-1.17)
Valine	2.715 (2.34-2.86)	2.341 (2.21-2.67)	1.876 (1.32-1.92)
Methionine	0.213**# (0.14-0.31)	0.224** (0.13-0.26)	0.431 (0.31-0.51)
Isoleucine	0.898**# (0.74-0.92)	0.675** (0.61-0.72)	0.487 (0.41-0.53)
Leucine	2.412** (2.12-2.65)	1.453** (1.14-1.49)	0.918 (0.71-1.12)
Tyrosine	1.616 (1.32-1.87)	1.423 (1.31-1.51)	1.321 (1.24-1.45)
Phenylalanine	1.213** (1.12-1.46)	0.912* (0.76-1.09)	0.871 (0.81-0.92)

Notes:
1. The difference between the indicators is significant compared to those in the control group: * – $p < 0.05$;** – $p < 0.001$.
2. The difference is significant compared with those in patients with PICS without impaired carbohydrate metabolism: # – $p < 0.05$;## – $p < 0.001$.

Patients with PICS and DM showed a statistically significant increase in the total concentration of AA compared with the control group – by 74.85% ($p<0.05$), with the PICS group without impaired carbohydrate metabolism – by 24.91% ($p<0.05$).

Hyperaminocidemia in DM is explained by a slowdown in the catabolism of AA in hyperinsulinemia.The energy of adenosine triphosphate acid (ATA), which is formed during the catabolism of glucose, is spent on protein synthesis.At the level of formation and utilization of ATA there is a relationship between glucose metabolism and AA, which is that in hyperinsulinemia there is a decrease in the rate of protein synthesis due to insufficient energy supply of the anabolic process.In this case, there is a decrease in the amount of inclusion of AA in proteins and their accumulation in the blood – hyperaminocidemia develops [13,14,15].

Patients with PICS and DM also showed a statistically significant increase in the concentration of branched-chain amino acids (BCA), mostly leucine, compared with controls: isoleucine -by 28.39%, leucine-by 41.11% ($p<0.001$), valine – by 34.1% ($p<0.05$).

BCA are considered metabolic markers of high sensitivity in the prediction of insulin resistance and cardiovascular complications of diabetes. These AA play an important role in the synthesis of specific neurotransmitters, glycogen synthesis, regulation of energy and plastic metabolism, synthesis of specific neurotransmitters.Increased levels of these amino acids in patients with IR are explained by the activation of gluconeogenesis in the liver [16, 17].

Patients with PICS and DM also showed a statistically significant ($p<0.05$) increase in lysine concentration – by 34.8% ($p<0.05$), aspartate – by 35.3% ($p <0.001$), glutamate – by25.1% ($p<0.05$) compared with patients in the control group, and 11,3% ($p<0.05$), 17.3% ($p<0.05$), 11.4% ($p<0.001$), respectively, compared with individuals with PICS without impaired carbohydrate metabolism.

Increased concentrations of lysine, aspartate, glutamate in the blood of patients with PICS and type DM indicate the presence of additional factors that lead to hyperinsulinemia, as these amino acids potentiate the stimulating effect of glucose on insulin secretion [18, 19].

In patients of the main group there was a significant decrease in the concentration of taurine, arginine, methionine , glycine: by 35,1% ($p<0.05$), 61.1% ($p<0.05$), 29.7%

($p<0.001$), 40.1% ($p<0.01$), respectively, compared with individuals and by 11.3% ($p<0.05$), 18.1% ($p<0.05$), 7.3% ($p<0.05$), 10.12% ($p<0.01$), respectively, compared with patients with PICS without impaired carbohydrate metabolism.Changes in the levels of concentrations of individual AK can be explained by the pathogenesis of type 2 diabetes and associated insulin resistance and hyperinsulinemia.An insulin molecule formed by two polypeptide chains containing 51 amino acid residues: the A-chain consists of 21 AA residues, the B-chain is formed by 30 AA residues.The polypeptide chains are connected by two disulfide bridges through cysteineresidues, the third disulfide bond is located in the A-chain.

Insulin has a relatively high content of lysine, aspartate, glutamate, phenylalanine, tyrosine, leucine, isoleucine, valine, alanine, does not contain taurine, metionine, tryptophan, has only 1 AA arginine residue [20,21].

The Framingham Offspring study showed that the levels of sulfur-containing AA, BCA and gluconeogenic AA are associated with the development of insulin resistance and cardiovascular disease [22, 23].

Alanine can be synthesized from pyruvate using the glucose-alanine ring.Elevated alanine aminotransferase, a key enzyme in the glucose-alanine cycle in which alanine is formed, has been associated with a high risk of developing DM.It has been suggested that alanine may also contribute to the development of diabetes due to hyperinsulinemia because it induces insulin secretion by pancreatic beta cells [24, 25].

The results of another randomized study suggest that alanine was significantly elevated in Japanese with visceral obesity.In addition, a formula was developed that included alanine to identify patients with high visceral fat levels using multidimensional logistic regression analysis.This formula has been closely associated with visceral fat deposition, regardless of body mass index [26,27].

Another biomarker of insulin resistance is the content of taurine in the serum.The level of taurine excretion in the urine was inversely proportional to the risk of developing DM and cardiovascular disease according to the results of an extensive epidemiological study.Tau has been shown to alter gene expression in obesity, lipid metabolism and DM.In addition, it is assumed that genetic susceptibility interacts with metabolic status, determining the risk of disease.

In an experimental study, Takashi et al., it was shown that the reduced content of taurine in the blood causes a decrease in glucose utilization, regardless of the decrease in insulin levels and body weight, which means a deterioration in tissue energy metabolism [28].

The decrease in the content of taurine in the blood of patients with diabetes can be explained by the accumulation of sorbitol in the tissues during the activation of the polyol pathway of glucose oxidation in conditions of hyperglycemia.The above is a compensatory response aimed at maintaining intracellular osmolarity.Also important is the increased activity of the key enzyme sorbitol aldose reductase, which leads to impaired formation of glutathione, which is one of the most important antioxidants and reduces the number of free radicals that are excessively formed during oxidative stress [29, 30, 31, 32].

Among the tasks we set was the assessment of the possibility of the relationship between the indicators of AK, the parameters of carbohydrate and lipid metabolism as factors of CVR (Table 2).

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 90 - 97
Received 16 February 2021; Accepted 08 March 2021.

Table 2. Correlations between valuesof individual amino acids and other clinical and laboratory parameters in patients with postinfarction cardiosclerosis with diabetes

Index	Totalcholesterol	Verylowdensitylipoproteins	Apolipoproteine B/ Apolipoproteine A1	HbA1C	Index HOMA	Insuline
Taurine	R=-0.54p<0.05	R= -0.43 p<0.05	R= -0.46 p<0.05	R= -0.55 p<0.05	R= -0.45 p<0.05	R= -0.41 p<0.05
Methionine	R= -0.42 p>0.05	R= -0.57 p<0.05	R= -0.59 p<0.05	R= -0.43 p>0.05	R= -0.62 p<0.05	R= -0.55 p<0.05
BCA	R= 0.31 p<0.05	R= -0.23 p>0.05	R= 0.23 p>0.05	R= 0.25 p>0.05	R= 0.56 P<0.05	R= 0.32 p>0.05
Alanine	R= 0.38 p<0.05	R= -0.26 p>0.05	R= 0.27 p>0.05	R= 0.25 p>0.05	R= 0.58 P<0.05	R= 0.39 p>0.05

According to the results of this analysis, the average strength of the inverse correlations of AA with the parameters of lipid metabolism: between taurine and very low-density cholesterol (VLDL) (r= -0.54; p<0.05), total cholesterol (r=-0.52; p>0.05);between methionine and VLDL (r =-0.62; p<0.05) and ApoB/ApoA1 (r = -0.59; p<0.05).

The average strength of the correlation of AA with carbohydrate metabolism was also established: inverse – Tau with HbA1c (r = -0.55; p <0.05), HOMA index (r=-0.45; p<0.05), insulin (r=-0.41; p<0.05);methionine with HOMA index (r=-0.62; p<0.05), and insulin (r=-0.55; p<0.05).Direct correlations of medium strength were found for ARL and Ala (r=0.56 and r=0.55; p <0.05).

The obtained data are consistent with the data described above on the possible mechanisms of changes in the level of individual AA in coronary heart disease and diabetes, but do not indicate a causal relationship of CVR with these changes, which requires further research.

Conclusions

In postinfarction patients, a change in AA blood composition was revealed in comparison with conventionally healthy individuals.The most pronounced AA imbalance was found in patients with concomitant diabetes mellitus, which indicates that the presence of diabetes aggravates violations of the AA blood composition.Thus, in patients with ischemic heart disease and diabetes, a significant increase in the total concentration of AA, BCA, glutamate, lysine, aspartate, a significant decrease in the content of taurine, methionine and glycine was found in comparison with patients without a violation of carbohydrate metabolism.The presence of correlations between CVR indicators and the content of individual blood AAs was found, which suggests the possibility of using AAs as prognostic markers of fatal cardiovascular events and requires further research.In postinfarction patients, a change in AA blood composition was revealed in comparison with conventionally healthy individuals.The most pronounced AA imbalance was found in patients with concomitant diabetes mellitus, which indicates that the presence of diabetes aggravates violations of the

AA blood composition.Thus, in patients with ischemic heart disease and diabetes, a significant increase in the total concentration of AA, BCA, glutamate, lysine, aspartate, a significant decrease in the content of taurine, methionine and glycine was found in comparison with patients without a violation of carbohydrate metabolism.The presence of correlations between CVR indicators and the content of individual blood AAs was found, which suggests the possibility of using AAs as prognostic markers of fatal cardiovascular events and requires further research.

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