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PHARMACOGENETIC FEATURES OF THERAPY OF PATIENTS WITH ATHEROSCLEROSIS

Abstract

The complexity of therapy of lipid metabolism disorders is not only in comorbidity and polypragmasy, but also in predicting a genetically determined response to treatment. Our objective was to study the pharmacogenetics features of pharmacotherapy of patients with non-alcoholic fatty liver disease, with various forms of IHD, and patients taking statins.

We examined four study groups: I — 60 patients with 2 type diabetes and non-alcoholic fatty liver disease (*APOE* polymorphism); II — 187 patients with IHD (*eNOS, AGTR2, CYP2D6* polymorphisms); III — 111 people with essential hypertension and CHF (polymorphisms: *AGT*: 704 (Met235Thr), *AGT*:521 (Thr174Met), *AGTR1*: 1166, *AGTR2*: 1675, *CYP11B2*: -344, *GNB3*: 825, *ADD1*: 1378 (Gly460Trp), *NOS3*: -786); IV — 62 patients taking atorvastatin (*SLCO1B1*5* polymorphism).

Patients with E2, E4 alleles of the *APOE* gene, taking essential phospholipids, significantly improved parameters of total cholesterol, HDL, LDL, CA, AP; patients with E3 alleles had a positive dynamics of cholesterol, HDL, TG, LDL, VLDL, CA, and urea levels. Patients having "slow" variants of gene *CYP2D6*10*, *CYP2D6*4* had received metoprolol, had greater decrease in heart rate: 1.6 times for *CYP2D6*10*, and 1.7 — for *CYP2D6*4*. Earlier onset of IHD was noted in patients with TT variants of the eNOS gene comparing with the patients with GG and GT variants. Dosages of perindopril depend on *AGTR2* gene polymorphisms.

The prevalence of polymorphisms *AGTR2*: 1675, *CYP11B2*: -344, *NOS3*: -786, *AGT*: 704, *GNB3*: 825 increases with the increase of CHF stage. The parameters of intracardiac hemodynamics in patients with CHF are associated with *AGT*: 704, *NOS3*:-786, *GNB3*: 825, *ADD1*: 1378, *AGT*: 521 polymorphisms. Allele C of the *SLCO1B1*5* gene is associated with an additional risk of statin-induced myopathy. Thus, an individualized approach to the treatment of patients with diseases associated with lipid metabolism disorders is required to provide its safety and effectiveness.

Key words: *pharmacogenetics, IHD, CHF, polymorphism, APOE, eNOS, AGTR2, CYP2D6, AGT: 704 (Met235Thr), AGT: 521 (Thr174Met), AGTR1: 1166, AGTR2: 1675, CYP11B2: -344, GNB3: 825, ADD1: 1378 (Gly460Trp), NOS3: -786, SLCO1B1*5, metoprolol, atorvastatin*

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Introduction

Cardiovascular diseases have remained the main cause of deaths for the majority of European populations over the past 40–50 years [1]. Cardiovascular diseases (CVD) remain the leading cause of deaths in the Russian Federation. According to Rosstat data, in 2016 mortality from CVD was 615 per 100,000 of population, and absolute losses were about 900,000 people [2].

The etiological factor of this pathology is atherosclerosis, which is a systemic disease that generally affects several vascular territories and manifests as a dysfunctions of many vital organs [3]. Atherosclerosis is based on disorders of lipid metabolism, which play an important role in the development of various diseases such as non-alcoholic fatty liver disease, ischemic heart disease, strokes, atherosclerosis of the lower extremities, etc. [4, 5, 6, 7]. Difficulties in therapy of such diseases lie not only in comorbidity and polypharmacy [8, 9, 10], but also in predicting a genetically determined response to treatment [11].

Thus, the objective of our work was to study the pharmacokinetic features of pharmacotherapy in patients with nonalcoholic fatty liver disease and with various forms of ischemic heart disease, as well as in individuals taking statins.

Materials and Methods

This study involved 4 groups of patients comprising a total of 420 people with various forms of atherosclerosis and lipid metabolism disorders. All patients signed an informed consent to participate in the study.

The first study group consisted of 60 patients aged 18 years and older (8 (13.3%) males, 52 (86.7%) females with mean age of (58.2 ± 6.8) years), with an established diagnosis of type 2 diabetes and non-alcoholic fatty liver disease. The study group, in addition to a previous standard treatment of this pathology (Table 1), additionally received essential phospholipids — Glycyrrhizic acid + Phospholipides.

The *APOE* gene was studied. Patients with alleles of the *APOE* gene predisposed to lipid metabolism disorder (E2, E4) were combined into APOE 1 treatment subgroup consisting of 21 (35.0%) individuals. Patients with an isoform of the *APOE* gene not predisposed to lipid metabolism disorder (E3/E3) were combined into APOE 2 subgroup consisting of 39 (65.0%) individuals. The following patients were not included in the study: with type 1 diabetes mellitus or gestational diabetes; without ultrasonic liver changes typical for diffuse increased fat content; without liver dysfunction and hypercholesterolemia or dyslipidemia; with alcohol abuse; with the history of hepatitis regardless of its etiology; with any severe concomitant pathology; with the development of an adverse drug reaction; those taking drugs that can have a hepatotoxic effect.

The second group included 187 patients with various forms of IHD: myocardial infarction (n = 98), stable (n = 43) and unstable forms of angina (n = 46) (total of 108 males and 79 females with mean age of (62.9 ± 1.3) years). The following genetic associations were studied: *eNOS, AGTR2, CYP2D6* with the onset of IHD and peculiarities of pharmacotherapy. This study did not include patients: with diabetes, permanent forms of cardiac arrhythmias, thyroid diseases, cancers, mental illnesses, heart diseases.

The third group consisted of 111 individuals with hypertension and CHF (mean age of (63.5 ± 11.6) years). The following polymorphisms in their effects on the success of CHF

Table 1. *Characteristics of treatment in the group of essential phospholipids effectiveness study*

Treatment	Study group, n=60 (%)	Control group, n=67 (%)
I. Insulin therapy	20 (33,4)	21 (31,3)
II. Oral hypoglycemic drugs	34 (56,6)	39 (58,2)
III. Lifestyle change	6 (10,0)	7 (10,5)
IV. Hypotensive therapy	56 (93,3)	52 (77,6)
V. Hypocholesterolemic therapy	6 (10,0)	7 (10,4)

therapy and intracardiac hemodynamic parameters were studied: *AGT*: 704 (Met235Thr), *AGT*: 521 (Thr174Met), *AGTR1*: 1,166, *AGTR2*: 1675, *CYP11B2*: –344, *GNB3*: 825, *ADD1*: 1,378 (Gly460Trp), *NOS3*: –786. The study did not include patients with cancer and heart disease.

The fourth group included 62 patients (a total of 24 (38.7%) males and 38 females (62.3 %, mean age of (65.6 ± 1.7) years)) taking atorvastatin. The relationship between *SLCO1B1*5* gene polymorphisms and the severity of atorvastatin pleiotropic effects was determined. This study did not include patients: taking *CYP3A4* inhibitors or inducers with the exception of atorvastatin and amiodarone; with current exacerbation of rheumatological diseases or exacerbation in history over the past 6 months; with severe decompensated somatic diseases; with mental illness, disability, alcoholism or drug abuse in history; pregnant or lactating women; not willing to participate.

Statistical processing of the results was performed using Microsoft Excel and STATISTICA 10 software packages. To assess quantitative characteristics with normal distribution, Student's t-test was used, and to assess characteristics not related to normal distribution, the Mann-Whitney test was used. Differences were considered significant at $p < 0.05$ (p — achieved significance level). The Kruskall-Wallis test was used when analyzing the values for 3 groups. Regression analysis was used to determine the dependence of one characteristic on another; Spearman's correlation analysis was used to calculate the correlation between characteristics.

Results

APOE 1 and APOE 2 subgroups maintained differences in triglyceride levels between themselves ($p < 0.05$, Mann-Whitney test): before treatment (0.7 mmol/l) and at the end of treatment with essential phospholipids (0.6 mmol/l). The results are shown in table (Table 2).

It was found that EPL treatment leads to positive changes in lipid and carbohydrate metabolism: in comparison with the control group, HDL levels increased, and cholesterol, TG, LDL, CA, HbA1c, total and direct bilirubin, AST, and ALT levels decreased.

Table 2. *Mean values of biochemical parameters in patients with type 2 diabetes and non-alcoholic fatty liver disease: disposed (APOE 1) and undisposed (APOE 2) to atherosclerosis according to APOE alleles*

Parameter	APOE 1, n=21 (M ± m)		APOE 2, n=39 (M ± m)	
	Before treatment	After treatment	Before treatment	After treatment
Total cholesterol	6,1±0,2	5,0±0,2	5,9±0,2	5,1±0,2
Triglycerides	2,8±0,3	2,5±0,3	2,1±0,2	1,9±0,2
High density lipoprotein	0,9±0,04	1,2±0,03*	1,0±0,03	1,2±0,03*
Low density lipoprotein	3,5±0,2	2,8±0,2*	3,5±0,2	3,1±0,1*
Very low density lipoproteins	1,4 ±0,1	1,4±1,3	1,0±0,07	1,1±0,1
Coefficient of atherogenicity	5,2±0,5	3,8±0,2*	4,6±0,2	3,4±0,2*
HbA1c	8,0±0,4	6,9±0,3*	8,2±0,3	7,2±0,2*
Total bilirubin	17,6 ±1,8	14,8±1,2	18,7±12	16,5±0,9*
Direct bilirubin	4,8±0,6	3,4±0,3*	5,0±0,4	3,7±0,2*
AST	30,0±3,2	22,2±1,1*	36,0±4,1	28,2±1,9*
ALT	32,7±3,6	21,1±1,4	40,5±5,6	29,9±2,9*
AP (Alkaline phosphatase)	205,1±14,48	192±10,5	219,9±11,0	228,8±8,8
Urea	5,7±0,4	4,6±0,7	5,5±0,2	4,6±0,2*

Note: * — $p<0.05$ when comparing results before and after treatment (Wilcoxon test)

All target values of lipid metabolism parameters in each individual patient with diabetes could not be reached.

Differences in the efficacy of EPL therapy in patients with the studied diseases associated with *APOE* gene polymorphism were revealed:

- Patients with alleles of the *APOE* gene, predisposed to atherosclerosis (E2, E4), during EPL treatment have significantly improved overall cholesterol, HDL and LDL, CA, and ALP levels.
- Patients with only protective alleles (E3) in relation to the development of atherosclerosis had an improvement in cholesterol, HDL, TG, LDL, VLDL, CA, and urea levels.

In the second study group, association of the TT allele of the *eNOS* gene with early onset of IHD compared with GG and GT alleles (Table 3) was detected. Regression analysis revealed that the presence of polymorphic T allele was associated with earlier development of coronary artery disease ($b = -2.54$, $p < 0.05$).

Analysis of mean perindopril doses needed for sufficient hypotensive effect in patients with different alleles of the *AGTR2* gene revealed that in patients with homozygous GG allele, perindopril doses were 1.3 times lower than in homozygotes with polymorphic AA variant (GG — (4.6 ± 1.9) mg, AA — (6.2±2.0) mg, $p < 0.05$).

Pharmacogenetic study of CYP2D6*10 and CYP2D6*4 in patients taking metoprolol showed that in carriers of slow variants of the *CYP2D6*10* gene, *CYP2D6*4*, unlike carriers of normal alleles, greater decrease in HR was detected when taking comparable doses of metoprolol: 1.6 times for *CYP2D6*10*, 1.7 times for *CYP2D6*4* (Table 4).

Thus, the presence of slow GA and CT variants of the *CYP2D6*4* and *CYP2D6*10* genes, respectively, requires the administration of lower doses of metoprolol than for GG and CC carriers.

In the third study group it was found that the rate of gene polymorphisms varies depending on the CHF stage (Table 5). In particular, it can be traced for *AGTR2*: 1675, *CYP11B2*: –344 and *NOS3*: –786 gene polymorphisms. The incidence of *AGTR2*: 1,675 gene polymorphism is most significant at stage 2A (21.3%) compared to stage 1 of CHF (the Russian Classification System of CHF). The detected changes were associated with changes in the frequency of heterozygotes. When comparing the incidence of gene polymorphisms at stage 1 and 2B, the results showed a high frequency of *AGTR2*: 1,675 (37.5%) and *CYP11B2*: –344 (62.5%) gene polymorphisms at the severe stage of CHF. It can be assumed that these gene polymorphisms are responsible for a more

Table 3. *Age of IHD onset: stable and unstable angina, myocardial infarction depending on the polymorphism of the eNOS gene*

Polymorphic variant of the *eNOS* gene	Age of IHD onset	t value	p-value
GG	56,4±0,7*	2,25	0,03
GT	55,8±0,7**	2,46	0,02
TT	47,0±0,8*, **	-	-

Note: — * — when comparing GG with TT; ** — when comparing GT with TT. Statistical processing was carried out by Student's t-test

Table 4. *The difference in heart rate before and after administration of metoprolol depending on CYP2D6 * 10 and CYP2D6 * 4 variants*

Gen	Alleles	Difference in heart rate, n=113	Heart rate before metoprolol administration
*CYP2D6*10*	Homozygote — norm (CC)	10,7±0,5*	76,0±1,9
	Heterozygote (CT)	16,8±0,7*	78,1±0,9
*CYP2D6*4*	Homozygote — norm (GG)	10,6±0,5**	76,1±1,5
	Heterozygote (GA)	17,9±0,7**	78,4±0,9

Note: — *, ** $p<0.05$. Student's t-test

Table 5. *Frequency of occurrence of gene polymorphisms depending on the stage of CHF*

Gene polymorphisms	stage 1, n=40 (36,03%)	stage 2A, n=47 (42,3%)	stage 2B, n=24 (21,6%)
ADD1: 1378	8 (20%)	11 (23,4%)	7 (29,2%)
- mutation-homozygote	-	-	1 (4,2%)
- heterozygote	8 (20%)	11 (23,4%)	6 (25%)
AGT: 704	30 (75%)	39 (82,9%)	20 (83,3%)
- mutation-homozygote	11 (27,5%)	16 (34,5%)	6 (25%)
- heterozygote	19 (47,5%)	23 (48,9%)	14 (58,3%)
AGT: 521	11 (27,5%)	12 (25,5%)	9 (37,5%)
- mutation-homozygote	1 (2,5%)	2 (4,2%)	2 (8,3%)
- heterozygote	10 (25%)	10 (21,3%)	7 (29,2%)
AGTR1: 1166	13 (32,5%)	15 (31,9%)	8 (33,3%)
- mutation-homozygote	1 (2,5%)	1 (2,1%)	1 (4,2%)
- heterozygote	12 (30%)	14 (29,8%)	7 (29,2%)
AGTR2: 1675	15 (37,5%)	24 (51,1%)	11 (45,8%)
- mutation-homozygote	13 (32,5%)	14 (29,8%)	7 (29,2%)
- heterozygote	2 (5%)	10 (21,3%)*	9 (37,5%)**
CYP11B2: -344	27 (67,5%)	37 (78,7%)	19 (79,2%)
- mutation-homozygote	13 (32,5%)	12 (25,5%)	4 (16,7%)
- heterozygote	14 (35%)	25 (53,2%)	15 (62,5%)**
GNB3: 825	19 (47,5%)	23 (48,9%)	12 (50%)
- mutation-homozygote	4 (10%)	4 (8,5%)	-
- heterozygote	15 (37,5%)	19 (40,4%)	12 (50%)
NOS3: -786	33 (82,5%)	39 (82,9%)	23 (95,8%)
- mutation-homozygote	13 (32,5%)	23 (48,9%)	8 (33,3%)
- heterozygote	20 (50%)	16 (34%)	15 (62,5%)#
NOS3: 894	18 (45%)	19 (40,4%)	9 (37,5%)
- mutation-homozygote	4 (10%)	4 (8,5%)	1 (4,2%)
- heterozygote	14 (35%)	15 (31,9%)	8 (33,3%)

Note: * — ρ<0.05 when comparing CHF 1 and 2A, ** — ρ <0.05 when comparing CHF 1 and 2B, # — ρ <0.05 when comparing 2A and 2B of CHF stage

unfavorable course of CHF. In addition, the frequency of *AGTR2*: 1,675 and NOS3: –786 gene polymorphisms increases by 16.2% and 28.5%, respectively, at stage 2B compared to stage 2A of CHF ($\rho < 0.05$).

Thus, with the increase in CHF severity, the incidence of gene polymorphisms increases and reaches maximum values at stage 2B. This primarily pertains to *NOS3*: –786 gene polymorphism which was significantly more common in more severe manifestations of CHF.

Association of polymorphisms with a favorable course of CHF was also studied: no worsening of symptoms and signs of CHF within 1 year, no hospitalization within 1 year; and with unfavorable course: CHF progression, an increase in CHF stage or functional class (FC) within 1 year, hospitalization within 1 year.

Hospitalization was associated with an increase in the incidence of *AGTR2*: 1,675 gene polymorphism in the form of combined mutations: homozygotes and heterozygotes by 32.2%, and separately for heterozygotes by 31.1% ($\rho < 0.05$). A similar trend was observed on the part of *GNB3*: 825 gene polymorphism heterozygote by 26.9%.

The relationships between the parameters of intracardiac hemodynamics and gene polymorphisms were identified. With unfavorable echocardiographic parameters, *AGT*: 704, *NOS3*: –786 and

GNB3: 825 gene polymorphisms were the most frequently reported. These polymorphisms were associated with reduced LVEF (< 50%), increased EDD (> 57 mm) and ESD (ESD > 44 mm), LV PWD (> 12 mm) and IVST (> 12 mm). Statistically significant data were obtained in relation to LVEF and IVST. Reduced LVEF was associated with *AGT*: 704 and *GNB3*: 825 gene polymorphisms, increase in IVST with *ADD1*: 1,378 and *AGT*: 521 gene polymorphisms ($p < 0.05$). With increased LA sizes (> 40 mm) there was a tendency to an increase in the frequency of *AGT*: 521 gene polymorphism by 16%.

In the fourth study group: all patients were divided into two subgroups: carriers of the wild (T) variant of the genotype in allelic gene *SLCO1B1*5* — TT group, and carriers of C allele associated with the risk of statin-induced myopathy in the genotype — TC group. Analysis of safety parameters for the use of atorvastatin in groups separated by genetic feature, which included biochemical parameters (CPK, ALT, AST), values of hand dynamometry, did not reveal significant differences.

According to the assessment of statin pleiotropic effects in TT and TS groups, the mean value of the inflammatory reaction marker interleukin 6 was significantly higher in the TT group, the differences in this parameter were significant between the groups ((4.85 ± 1.45) pg/ml and (1.67 ± 0.26) pg/ml, respectively, $p < 0.05$).

Lower levels of interleukin 6 indicate a more pronounced anti-inflammatory (pleiotropic) effect of atorvastatin. The correlation was evaluated using the Spearman test, a statistically significant direct relationship between the level of interleukin 6 and the presence of C allele in the allele gene genotype *SLCO1B1*5* ($rs = 0.25$; $p < 0.05$) was found. Thus, C allele is associated with an additional risk of statin-induced myopathy, due to an increased plasma statin concentration compared to the carrier of the TT genotype.

Results and Discussion

In the course of our work it was possible to identify associations of genes involved in vascular wall tone: *eNOS, AGT, AGTR2* with more severe course of CHF, with early development of IHD, with the presence of adverse hemodynamic parameters. Endothelial NO-synthase produces nitric oxide, which provides vasodilation, inhibition of adhesion molecule expression and platelet aggregation, has antiproliferative, antiapoptic and antithrombotic effects. Genes involved in RAAS regulation also have a great influence on the regulation of vascular wall tone, including the mechanisms of increasing nitric oxide production [12, 13], cell proliferation and apoptosis [14, 15].

Thus, the expression of these genes has interdependent effects provided through the synthesis of nitric oxide that in the presence of their polymorphisms can significantly change both the course and rate of cardiovascular disease progression, and the dynamic response to pharmacotherapy [16].

The safety and efficacy of the drugs was also related to the presence of polymorphisms of genes involved in drug metabolism, and responsible for drug binding with the receptor. There was a link between carriership of *CYP2D6* slow alleles and more pronounced decrease in HR when taking metoprolol — greater decrease in HR was detected in carriers of slow alleles of the gene (*CYP2D6*10*, *CYP2D6*4*) in contrast to carriers of normal alleles when taking comparable doses of metoprolol: by 1.6 times for *CYP2D6*10*, by 1.7 times for *CYP2D6*4*. This is an important factor in predicting pharmacodynamic response in titration of lipophilic beta-blocker doses. Thus, an individualized approach to metoprolol administration in IHD should be carried out taking into account the results of genetic testing on the *CYP2D6* gene. The presence of slow allelic GA and CT variants of the *CYP2D6*4* and *CYP2D6*10* gene, respectively, requires the administration of lower doses of metoprolol than for GG and CC carriers

Polymorphism of *AGTR2* involved in vasodilation can also be associated with a different effect on therapy [17], with more pronounced pharmacodynamic response in patients with the homozygous GG allele of the *AGTR2* gene receiving perindopril, and ACE inhibitor doses required for a sufficient antihypertensive effect in patients with homozygous GG allele are 1.3 times lower than those for homozygous individuals with polymorphic AA variant.

Differences in the efficacy of EPL therapy in patients with the studied diseases associated with *APOE* gene polymorphism were revealed:

- Patients with alleles of the *APOE* gene predisposed to atherosclerosis (E2, E4), during EPL treatment, have significantly improved overall cholesterol, HDL and LDL, CA, and ALP levels.
- Patients with only protective alleles (E3), in relation to the development of atherosclerosis, had an improvement in cholesterol, HDL, TG, LDL, VLDL, CA and urea levels.

The development of statin-induced adverse reactions is increasingly associated with the peculiarities of organic anion carriers encoded by the *SLCO1B1* gene and carrying out statin uptake by hepatocytes [18, 19].

The indication for the use of the pharmacogenetic test is the prediction of the development of myopathies (including rhabdomyolysis) in patients who are indicated to the statins use and to the individualized selection of the maximum statin dose. *SLCO1B1*5* (c.521 T>C, rs4149056) is a variant (polymorphic marker) of the *SLCO1B1* gene (encodes polypeptide transporting organic anions involved in statin bile excretion by the liver) [20, 21].

The distribution of genotypes by *SLCO1B1*5* in the Russian population according to many authors is approximately presented as follows: TT genotype — 61%, TC — 32.5%, CC — 6.5% of patients [22, 23]. This suggests a common occurrence of C-allele of the *SLCO1B1* gene in the Russian population, and therefore patients should be expected to have a high risk of myopathy when taking statins.

As a result of our work, it was found that the carriership of genotypes for *SLCO1B1*5* variant does not affect atorvastatin markers of myopathy (CPK, pain syndrome, dynamometry data) administered in an average daily dose of (20.5 ± 5.03) mg. In general the detection of the TC and CC genotype variant of the *SLCO1B1*5* allelic gene in pharmacogenetic testing can be used to predict a more pronounced pleiotropic anti-inflammatory effect of atorvastatin. This effect is preserved by the co-administration of atorvastatin and amiodarone.

Thus, an individualized approach to the treatment of patients with diseases associated with lipid metabolism disorders based on genetic analysis can allow the prescription of more effective and safer pharmacotherapy.

Conflict of interests

The authors declare no conflict of interests.

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