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Article

Candidate Genes for Prediction of Efficacy and Safety of Statin Therapy in the Kazakh Population

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Abstract

The purpose of this research was to determine the frequency of mutation of the cytochrome *CYP3A5* genes and transport proteins SLCO1B1 and MDR1 in patients with coronary heart disease in the Kazakh nation. A prospective cohort clinical and genetic study was conducted. The study was conducted in 2017−2019. Medical records containing information about drug prescription conducted in hospitals and outpatient departments were carefully analyzed. In the examined group of 178 patients treated with statins, a significant frequency of genetic variants that determine the increased risk of complications of statin use was revealed. There was a tendency toward an increase in the activity of creatine phosphokinase (CPK) in the blood upon detection of the A6986G mutation of the cytochrome gene and *SLCO1B1* (c.521T>C) gene of the transport protein OATP1B1. In the studied Kazakh population, the presence of a homozygous mutant *SLCO1B1* gene of the transport protein can be recommended as a genetic marker for the undesirability of using antihypercholesterolemic therapy with statins, which simultaneously leads to a decrease in the effectiveness of treatment and an increase in the risk of side effects.

Keywords: Atorvastatin; pharmacogenetics; adverse effect; coronary heart disease; antihypercholesterolemic therapy

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Today, cardiovascular diseases are leading causes of mortality in the whole world. Ischemic heart disease, cerebrovascular disorders, hypertensive disease and diseases of peripheral vessels affect an increasing number of the population every year (Kowalik et al., 2019; Szczerba et al., 2021).

The use of statins for the treatment of disorders of cholesterol metabolism significantly reduced the possibility of complications such as myocardial infarction and, to a lesser extent, cerebral circulation disorders and other atherosclerotic lesions of regional arteries (Athyros et al., 2015; Navarese et al., 2014). The beneficial effect that statins have on cholesterol metabolism, as well as pathogenetic mechanisms of atherosclerosis and its complications, gives them a definite advantage over other drugs used to treat hypercholesterolemia (Correale et al., 2014). Thus, statins are an important component of the treatment of patients with cardiovascular diseases who have a high probability of atherosclerotic vascular damage, and they are included in the treatment standards for coronary heart disease and arterial hypertension in most countries with a developed healthcare system (Müller-Wieland & Merkel, 2014).

In Kazakhstan, statins, when prescribed by a doctor, are included in free medical care. However, it has been shown in cardiology practice that the percentage of prescriptions of contraindicated drug combinations is very high (Mussina et al., 2019).

Atorvastatin is a new, more effective drug from the group of hypolipidemic agents that inhibits HMG-CoAreductase and reduces the concentration of total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides.

The prescription of harmful and inappropriate combinations of drugs is widespread among the clinical practice of doctors in most countries. Hypolipidemic agents are drugs with a high probability of danger in combinations, as they have a high degree of metabolism. Increased toxicity of hypolipidemic agents is possible if they are used in combination with other drugs, especially with strong CYP3A4 inhibitors. Genetically determined changes in proteins involved in the pharmacokinetics of atorvastatin also lead to an increase in the concentration of the active substance in the blood plasma. In the healthcare structure of Kazakhstan, this problem is poorly explored, and the principle of genetic predisposition to negative effects has not been established.

Safety concerns related to statins are of particular interest due to their prevalent use globally (Adhyaru & Jacobson, 2018). Their significant effect on metabolism is a factor that determines the likelihood of side effects (Liu et al., 2019). The main side effects of taking statins include impaired muscle function, pain, weakness, and in severe cases, rhabdomyolysis is possible. Even taking into account the high probability of developing side effects of taking antilipidemic drugs, the benefit of taking statins greatly outweighs

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the harm. A number of studies on large cohorts of patients revealed genetic susceptibility to the side effects of statin therapy in patients (Jiang et al., 2016). Genes of liver cytochromes involved in drug metabolism (Licata et al., 2018) and genes of membrane transport proteins (Vrablik et al., 2014) were considered as candidates.

Furthermore, changes in the effectiveness of statins associated with certain allelic forms of the corresponding genes were revealed (Maggo et al., 2011). Genetic variation among different populations is one of the reasons for disparate drug effects and risks of side effects and complications (Hopewell et al., 2014). Until now, there has not been any study aimed at studying the factors that determine the pharmacogenetic characteristics of statin therapy in the Kazakh population.

The study aims to determine the frequency of mutation of the genes of cytochrome *CYP3A5* and transport proteins SLCO1B1 and MDR1 in patients with coronary artery disease in the Kazakh population of East Kazakhstan. The quality and safety endpoints in this study are related to the use of atorvastatin and the evaluation of its effects on patients. These endpoints include the frequency of adverse reactions, specifically myalgias and muscle weakness, as well as the levels of CPK activity in the blood.

Alternative hypothesis: There is an association between genetic variants (specifically mutations in the cytochrome *CYP3A5, SLCO1B1*, and *MDR1* genes) and the occurrence of adverse reactions and decreased effectiveness of statin therapy.

Null hypothesis: There is no association between genetic variants and the occurrence of adverse reactions and decreased effectiveness of statin therapy.

Materials and Methods

A prospective, observational, cross-sectional comparative clinical and genetic study was carried out. The research involved 178 people, including 108 men and 70 women aged 40 to 70 years (mean age 61.1; 7.8 is the standard deviation).

Inclusion criteria: Kazakh nationality (confirmed by documents of ancestors in 2 generations); coronary heart disease with a very high risk of cardiovascular complications in the anamnesis (including myocardial infarction and surgery on the coronary arteries); having disorders of cholesterol and lipid metabolism and are prescribed statins; informed consent to participate in research and conduct genetic tests.

Exclusion criteria: the presence of contraindications to statin use not related to their previously identified side effects; having serious diseases and concomitant conditions that make it impossible to verify the side effects of statin therapy; refusal to participate in the research at any stage.

The clinical side of the Emergency Hospital of Semey, the University Hospital of the Semey Medical University, and Primary Health Care (PHC) institutions participated in the study, where the study patients had outpatient observation and treatment. This study was performed for the period of March 2017 until April 2019. During the study, there was no active medical intervention in the treatment of patients carried out by family doctors, district doctors or cardiologists in PHC.

Data on the use of atorvastatin and other drugs were obtained from prescription sheets for inpatients, discharge epicrisis with recommendations for admission, and outpatient cards with information about prescriptions made by PHC doctors.

Genetic studies were performed in the PCR laboratory of the University Hospital of the NCJSC Medical University of Semey. Allelic variants of the cytochrome *CYP3A5* gene (A6986G), the OATP1B1 SLCO1B1 transport protein gene (c.521T>C), and *MDR1* (C3435T) and (C1236T) heterogeneity of alleles of the P-glycoprotein transporter protein gene encoding the key stages of biotransformation of the polymerase chain reaction PCR) on a BioRad apparatus (USA) using SNP-screen reagent kits in real time (RealTimePCR) according to the protocol of the Syntol manufacturer (Moscow).

The content of total cholesterol, lipoprotein fractions and creatine phosphokinase were measured on a PD 303S spectrophotometer in the joint educational and scientific laboratory (JESL) of the Medical University of Semey. Statin therapy was prescribed as part of the study. It should be noted that patients were not on statins before entering the study, but started statins immediately at the beginning of the study. Thereby, analyses were collected before the start of the course of statin therapy, and 2 and 6 months after the therapy.

The study used methods of descriptive statistics to determine the structure of the distribution of alleles and genotypes, as well as to describe the combinations of polymorphisms and drugs used. The analysis of the significance of differences in numerical series was carried out using the Mann-Whitney U test. The boundary level of significance for refuting the null hypothesis was taken as $p < .05$ (Glants, 1998).

The research protocol was recognized by the Ethics Committee of the State Medical University of Semey (No. 4 dated February 28, 2017). Before starting the research, all participants gave their written informed consent for the study, blood sampling and collection of data from case histories and outpatient records.

Results

Tables 1–3 show the distribution of the studied alleles and genotypes of the three genes associated with the risk of the most dangerous side effects of statins.

The prevalence of the mutant allele C of the SLCO1B1 transport protein gene was 18.0%. There were no notable differences between the defined and equilibrium distributions.

The distribution of C and T alleles of the *MDR1* transport protein gene (polymorphism C3435T) in the examined group was almost uniform with a slight excess for the nonmutant allele. The distribution of genotypes was similar, with no significant differences from the equilibrium one.

The corresponding distribution of alleles of the *MDR1* transport protein gene (C1236T) showed the prevalence of the mutant T allele (59.4%). In only 20.8% of cases were there were subjects with a homozygous no-mutant genotype, which corresponded to an equilibrium distribution. Tables 4–6 present data on the dynamics of cholesterol content and CPK activity in the examined patients, depending on the allelic forms of the studied genes.

At the beginning of the study, the studied biochemical parameters did not differ between the groups. Also, no significant differences were found in the content of total and LDL cholesterol at 2 months as well as 6 months, depending on the genotype of the cytochrome *CYP3A5* gene. Only tendencies towards a decrease in indicators were observed in the group with a homozygous mutant genotype in comparison with a homozygous nonmutant one. Differences in the content of total cholesterol within 2 months was 11.5% and LDL cholesterol within 6 months was 16.0%.

The difference in CPK activity in plasma was more notable. In this case, the presence of a homozygous mutant genotype should be considered negative. The differences in the CPK activity in plasma

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Table 1. Frequency of alleles and genotypes of the cytochrome *CYP3A5* gene (polymorphism 6986A>G)

Alleles and genotypes	Absolute number	Frequency
A	272	76.4
G	84	23.6
AA	114	64.0
AG	44	24.7
GG	20	11.2

Note: The frequency of the mutant allele G of the cytochrome *CYP3A5* gene was 23.6% in the examined group. The distribution of genotypes did not differ significantly from the equilibrium distribution of Hardy-Weinberg.

Table 2. Frequency of alleles and genotypes of transport protein SLCO1B1 (polymorphism 521T>C)

Alleles and genotypes	Absolute number	Frequency
T	292	82.0
C	64	18.0
TT	131	73.6
CT	30	16.9
CC	17	9.6

Table 3. Frequency of alleles and genotypes of transport protein MDR1

Polymorphism	Alleles and genotypes	Frequency	
C3435T	C	194	54.5
	T	162	45.5
	CC	65	36.5
	CT	64	36.0
	TT	49	27.5
C1236T	C	145	40.6
	T	211	59.4
	CC	37	20.8
	CT	71	39.9
	TT	70	39.3

at 2 months between the nonmutant homozygous and mutant homozygous and between the heterozygous genotype and homozygous mutant were 20.2% and 26.7% respectively, although the differences were not significant. After 6 months, there was a predominant increase in the CPK activity in the group with the GG genotype and the level of the aforementioned differences increased to 29.6% and 49.9% respectively.

A thorough analysis of the anamnesis and complaints revealed signs of muscular system damage in 14 patients (7.9%) at 2 months and in 19 (10.7%) at 6 months (95% confidence intervals). During the first period of the examination, 8 patients had the AA genotype, 3 patients had the AG genotype and the 3 patients had the GG genotype. In the second term, the numerical indicators were 12, 4 and 3 patients. The differences between the subgroups were not statistically significant ($p > .1$ at both periods). It should be noted that in none of the case were there any direct indications for discontinuation of statin therapy based on objective parameters (Figure 1).

A similar analysis on the genotype of the *SLCO1B1* transport protein gene showed that the total cholesterol content greatly depended on the genotype (Table 5). Having the mutant CC genotype was shown to have a negative effect. Differences in this indicator between CC and TT genotypes were 25.4 and 41.2% after 2 and 6 months respectively ($p = .047$ in the latter case). However, there was no significant difference in the content of LDL cholesterol among all selected groups (24.3% between TT and CC genotypes after 6 months).

Differences in plasma CPK activity between the groups were maximum when they were distributed according to this criterion. The group with the CC mutant genotype had the highest value. Differences in plasma CPK activity between CC mutant genotype and homozygous TT genotype were 63.3% and 239.5% after 2 and 6 months respectively ($p = .043$, $p < .001$ respectively). There was a considerable difference in the CPK activity within heterozygous mutant genotype groups after 6 months (128.6%, $p = .015$).

Distribution analysis of cases of subjective manifestations of the effect of therapy on muscle tissues showed certain variations. So, within 2 months, out of 14 patients with myalgia and/or muscle weakness, only 5 had the TT genotype (3.8% of the size of this subgroup), 2 had the CT genotype (6.6%), while 7 out of 17 patients in the subgroup had a homozygous mutant genotype (41.2%, $\chi^2 = 14.45$, $p = .005$), which is quite consistent with an increase in plasma CPK activity. Within 6 months, the corresponding distribution was: 6–4.6% (TT), 3–10.0% (CT), 10–58.8% (CC), $\chi^2 = 23.31$, $p < .001$ (Table 6).

The results of the analysis of biochemical parameters in patients, distributed depending on the genotype of the MDR1 transport protein by polymorphism C3435T, indicate the presence of a minimal effect on the efficacy and safety of treatment. There were no considerable differences between the groups at any time or in any indicator. There were only tendencies to an increase in total cholesterol and, to a lesser extent, LDL cholesterol in the group with mutant TT genotype over nonmutant CC. There were also tendencies to an increase in plasma CPK activity in the group with homozygous mutant genotype in comparison with the homozygous nonmutant one. Within 6 months, they amounted to 17.6% ($p > .05$). The distribution of the number of cases with myalgias and muscle weakness did not reveal any dependence on the genotypes of the MDR1 protein gene for this polymorphism (Table 7).

The differences in the studied parameters in the analysis depending on the presence of the C1236T polymorphism were somewhat more pronounced. It can be deduced that the presence of a nonmutant CC genotype gives a certain protective role. The difference in total cholesterol level between nonmutant CC genotype and homozygous mutant CC genotype was 17.1%, while the difference in LDL cholesterol between the two groups after 2 months was 17.3%. This showed that having a nonmutant genotype had a more positive effect on the efficacy of antihypercholesterolemic therapy.

There were practically no differences in the activity of CPK with this distribution. Moreover, after 6 months, the maximum value was determined in the subgroup with a heterozygous genotype, which confirms the fact that the indicated allele does not have an effect on CPK activity. Differences in the frequency of subjective manifestations of the effect of statin therapy on muscle tissues were also insignificant.

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Table 4. Biochemical parameters in patients depending on the genotype of the cytochrome *CYP3A5* gene (polymorphism 6986A>G)

		Genotype					
		AA, $n = 114$		AG, $n = 44$		GG, $n = 20$	
Indicator	Study period	Ā	δ	Ā	δ	Ā	δ
The content of total cholesterol in the blood (mmol/L)	Before statin prescription	7.80	1.15	7.67	0.99	7.62	1.03
	2 months	5.21	0.92	4.92	0.67	4.61	0.65
	6 months	4.69*	0.63	4.40*	0.59	4.37*	0.58
The content of LDL cholesterol in the blood (mmol/L)	Before statin prescription	4.21	0.77	4.20	0.68	4.16	0.55
	2 months	2.31	0.45	2.18	0.41	2.11	0.39
	6 months	2.19*	0.41	1.91*	0.25	1.84*	0.33
Plasma CPK activity (U/L)	Before statin prescription	86.1	9.9	79.3	10.0	91.9	11.5
	2 months	127.7	19.2	121.2	18.1	153.5*	24.0
	6 months	157.2*	27.1	136.0	23.9	203.8*	31.4

Note: *differences with the level before statin prescription are significant; U/L, units (U) of enzyme activity per liter (L) of serum.

Table 5. Biochemical parameters in patients depending on the genotype of the *SLCO1B1* transport protein gene (polymorphism 521T>C)

		Genotype					
		TT, $n = 131$		CT, $n = 30$		CC, $n = 17$	
Indicator	Study period	Ā	δ	Ā	δ	Ā	δ
The content of total cholesterol in the blood (mmol/L)	Before prescription of statins	7.71	1.44	7.92	1.38	7.73	1.09
	2 months	4.88	0.81	5.31	0.66	6.12	0.99
	6 months	4.32*	0.77	4.87*	0.70	6.10	1.03
The content of LDL cholesterol in the blood (mmol/L)	Before prescription of statins	4.18	0.69	4.27	0.65	4.25	0.87
	2 months	2.20	0.54	2.31	0.54	2.59	0.55
	6 months	2.02*	0.48	2.20*	0.47	2.51*	0.52
Plasma CPK activity (U/L)	Before prescription of statins	85.3	12.6	86.3	11.9	80.7	11.5
	2 months	120.5	14.5	134.9	16.3	196.8*#	32.9
	6 months	119.6	17.1	177.6	23.8	406.0*#@	85.0

Note: *significant difference between'before and after statin precription; #differences with the indicator in the group with the TT genotype are significant; @differences with the indicator in the group with the CT genotype are significant; U/L, units (U) of enzyme activity per liter (L) of serum

Table 6. Biochemical parameters in patients depending on the genotype of the *MDR1* transport protein gene (polymorphism C3435T)

		Genotype					
		CC, $n = 65$		CT, $n = 64$		TT, $n = 49$	
Indicator	Study period	Ā	δ	Ā	δ	Ā	δ
The content of total cholesterol in the blood (mmol/L)	Before prescription of statins	8.00	1.35	7.49	1.22	7.75	1.36
	2 months	4.92	0.74	5.10	0.84	5.23	1.02
	6 months	4.31*	0.58	4.71*	0.75	4.78*	0.95
The content of LDL cholesterol in the blood (mmol/L)	Before prescription of statins	4.23	0.62	4.20	0.69	4.17	0.81
	2 months	2.12	0.51	2.31	0.43	2.36	0.54
	6 months	2.03*	0.47	2.10*	0.39	2.13*	0.37
Plasma CPK activity (U/L)	Before prescription of statins	89.1	12.8	83.7	14.5	81.4	15.0
	2 months	122.1	17.3	133.3	19.0	132.8	16.5
	6 months	148.1*	20.7	152.2*	24.8	174.2*	25.1

Note: *significant difference between before and after statin treatment; U/L, units (U) of enzyme activity per liter (L) of serum.

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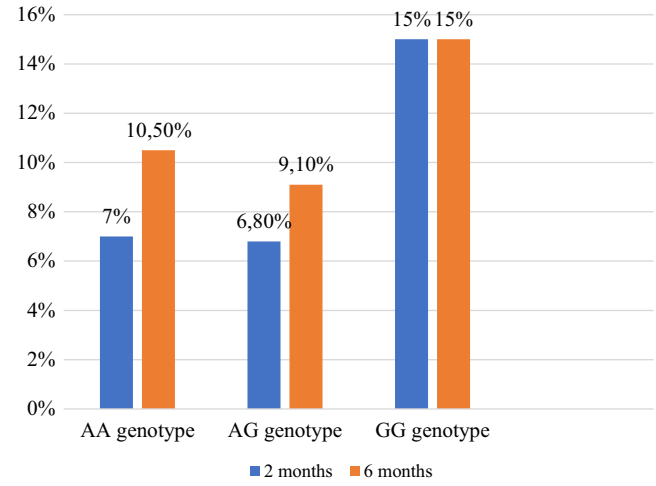

Fig. 1. Rates of muscle issues by genotype.

The distribution of polymorphisms C3435T and C1236T was completely independent. It has been found that having the second polymorphism (C1236T) does not have an effect on the studied parameters of cholesterol, LDL cholesterol and the activity of CPK in plasma in the case of their simultaneous presence in the study patients.

Furthermore, the distribution of the studied genotypes of the cytochrome *CYP3A5* gene and transport proteins SLCO1B1 and MDR1 was revealed to be independent. In the presence of various mechanisms of influence of gene dysfunction on the studied parameters, it is reasonable to consider their combined effect, aggravating the degree of biochemical changes. Table 8 shows the data of the analysis of cholesterol content and CPK activity depending on the presence of a recessive allele of the study genes in combinations of the cytochrome *CYP3A5* gene and transport proteins 6 months after the prescription of statins.

The cytochrome system promotes the metabolism of anti-hypercholesterolemic drugs in cells, while transport proteins promote their transmembrane intake. A simultaneous dysfunction of both systems increases the risk of treatment complications. Disruptions affecting the penetration of the drugs into the cell and their metabolism result in their elevated concentration in the blood increasing the risk of side effects. This is confirmed by the data presented. CPK activity in plasma was significantly higher only in groups with a combination of mutations of cytochrome gene and transport proteins compared to the subgroup without the mutations.

Discussion

The genetic components associated with a high risk of developing side effects of combinations of various drugs are a priority area of pharmacological research at the present time. It was revealed that they had an impact on the final catabolism of drugs, which terminated their action, and on intracellular transport and the reaction of cells to drugs (Bellosta & Corsini, 2018).

In this study, three genetic factors that according to recent data primarily affect the pharmacokinetics of atorvastatin were determined. These are polymorphism of genes encoding one of isozymes of cytochrome P450, which promotes avarstatin metabolism, and polymorphism of genes encoding transport proteins P-glycoprotein and OATP1B1. Together, these systems control the entry of statins into the liver and their catabolism in hepatocytes, and are the main factors determining their pharmacological activity of the drug (Hopewell et al., 2014).

When analyzing the frequency of distribution of alleles of all three studied genes among the examined individuals, no deviations from the equilibrium distribution of Hardy-Weinberg were found. Many studies showed that in different ethnic groups, they had distinct population characteristics of the frequency of alleles and genotypes of genes associated with statin metabolism. The *CYP3A* gene polymorphism was studied by Korean scientists in five different nationalities. The highest frequency of the G allele of the rs776746 polymorphism (i.e., 6986A>G) was found in the Chinese population (0.344). Korean and Japanese had the same frequency (0.255 and 0.260, respectively). In African Americans (0.198) and European Americans (0.085), the frequency of the allele was significantly lower (Lee et al., 2013). Results (frequency 0.236) are close to the Asian populations of the Far East (Koreans and Japanese).

In a study conducted in the Uzbek population, the frequency of the GG genotype in the group of patients with cardiovascular diseases and good statin tolerance was 0.120, while that in the group with clinical signs of complications was – 0.538 ($\chi^2 = 8.63$; $p = .003$) (Shek et al., 2017). If comparing these results with the cited ones (the frequency of the GG genotype is 0.112), there is no considerable difference in the frequency of the mutant homozygous genotype between the two populations.

A recent study on the Hispanic population has shown an absolute predominance of the GG genotype of the CYP3A5 gene (0.866), while the frequency of the heterozygous form was only 0.134. Furthermore, it was revealed that there were certain clinical advantages of using atorvastatin over simvastatin in the presence of the A allele (Kolovou et al., 2015).

According to several studies, the frequency of the 'slow' allele SLCO1B1*5 (i.e., allele C of polymorphism 521T>C) in the European population ranges from 15.0% to 21.6% (Turner & Pirmohamed, 2014). Research results suggest that the presence of one 'slow' allele increases the likelihood of developing statin-induced myopathy by 4.5 times, and having homozygous carrier increases that by more than 16 times. The frequency of various genotypes SLCO1B1*5 in Russia was also determined (TT – 61.0%, TC – 32.5%, CC – 6.5%) (Link et al., 2008).

In the same study conducted by Uzbek scientists (Shek et al., 2017), the group of patients with coronary artery disease and good statin tolerance had the frequency of the C allele of the 521T>C mutation equal to 0.150. The group of patients who had side effects and complications after the use of statins, the frequency of this allele was 0.385 ($\chi^2 = 5.7$; $p = .017$).

Other studies have published data characterizing the distribution of alleles C and T of C3435T and C1236T polymorphisms in the Kazakh and Russian populations of Kazakhstan, determining their association with breast cancer (Nigmatova et al., 2016). The frequency of the C allele of the C1236T polymorphism in the group of patients and controls was 0.431 and 0.454, correspondingly, in the Kazakh population, while that in the Russian population was 0.530 in patients and 0.538 in controls. There were no differences in the distribution from the Hardy-Weinberg equation. The hypothesis about the link between alleles and genotypes and the development of breast cancer was not confirmed. There was no considerable difference between this data (the frequency of the C allele is 0.406) and the above indicators. The frequency of the C allele for the C3435T polymorphism in Kazakhs was 0.560 in patients and 0.553 in controls. In the Russian population, the

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Table 7. Biochemical parameters in patients depending on the genotype of the MDR1 transport protein gene (polymorphism C1236T)

		Genotype					
		CC, $n = 37$		CT, $n = 71$		TT, $n = 70$	
Indicator	Study period	Ā	δ	Ā	δ	Ā	δ
The content of total cholesterol in the blood (mmol/L)	Before prescription of statins	7.92	1.25	7.61	1.40	7.80	1.51
	2 months	4.77	0.75	5.18	0.89	5.12	0.93
	6 months	4.15*	0.69	4.53*	0.66	4.86*	0.69
The content of LDL cholesterol in the blood (mmol/L)	Before prescription of statins	4.23	0.61	4.11	0.57	4.28	0.65
	2 months	2.03*	0.50	2.25*	0.43	2.38*	0.39
	6 months	1.90*	0.33	2.11*	0.39	2.15*	0.37
Plasma CPK activity (U/L)	Before prescription of statins	85.8	12.7	84.9	13.3	84.7	10.7
	2 months	123.2	18.4	133.7	19.5	127.4	21.3
	6 months	146.4	19.1	169.7	25.7	149.1	26.9

Note: *significant difference between before and after statin treatment; U/L, units (U) of enzyme activity per liter (L) of serum.

Table 8. Effect of combinations of the mutations on biochemical parameters in the study patients (taking atorvastatin for 6 months)

	Combination of mutations							
	No mutation, $n = 10$		Only mutations of cytochrome CYP3A5 gene, $n = 20$		Only mutations of genes of transport proteins, $n = 104$		Combinations of both mutations, $n = 44$	
Indicator	Ā	δ	Ā	δ	Ā	δ	Ā	δ
The content of total cholesterol in the blood (mmol/L)	4.74	0.49	4.22	0.52	5.27	0.61	4.99	0.67
The content of LDL cholesterol in the blood (mmol/L)	1.97	0.23	1.80	0.19	2.41	0.28	2.15	0.23
Plasma CPK activity (U/L)	144.1	22.5	212.9	30.7	219.7	35.7	259.2*	33.6

Note: *significant difference; U/L, units (U) of enzyme activity per liter (L) of serum.

frequency of the allele in patients and controls was 0.469 and 0.425 respectively, and 0.545 in this study.

A few studies by foreign researchers provide data on the frequency of alleles and genotypes of the *MDR1* gene. A study by Mexican scientists showed that the CT and TT genotypes of the C3435T polymorphism, associated with a high probability of developing complications of pharmacotherapy, were detected in 78.3% of cases, while the CC and CT genotypes of the SLCO1B1 521T>C gene polymorphism were found in 18.3% (León-Cachón et al., 2016).

An important aspect is the risk analysis of complications of statin therapy, skeletal muscle damage being the most important. It should be noted that until now, there has been no single concept of the pathogenesis of this lesion and approaches to its prevention that are not associated with the abolition of antihypercholesterolemic therapy. Furthermore, many studies and reviews doubting the role of this phenomenon in a significant number of clinical cases is questioned. However, at present, there are clinical indications for discontinuation of statins when there is a sharp increase in the activity of CPK in the blood, which are also based on evidence-based studies.

Conclusions

In this work, a number of patients who developed myalgias and muscle weakness during treatment was identified. They had increased levels of CPK activity in the blood. Having the 521T>C polymorphism of the *SLCO1B1* transport protein gene in a homozygous form has a significant effect on risk of side effects. Also, in patients with this genotype, a reduction in antihypercholesterolemic effect of statins was observed. Other genetic variants had significantly less or no effect on the risk of this side effect. The antihypercholesterolemic effect of statins was decreased in this genotype.

Management of patients with diseases of the cardiovascular system is currently characterized by two features. On the one hand, modern treatment technologies have great potential in terms of preventing and correcting developed disorders. On the other hand, there is a clear lack of a systematic approach to specific patients that would ensure the effectiveness and safety of interventions and patient management. Genetic studies reveal the degree of population risk and the need to determine specific genetic disorders in various clinical situations. Identification of the negative effect of mutations in the *SLCO1B1* transport protein gene on the degree of risk when using atorvastatin in the Kazakh population indicates the usefulness of the analysis both when prescribing statins and in case of revealing their insufficient effectiveness and signs of a negative effect on muscle tissue.

In the study, patients treated with statins, frequency of genetic variants associated with a higher probability of developing adverse reactions from the use of statins is significantly high. However, the presence of significant differences in the frequency of clinical

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manifestations of side effects of drugs on muscles was associated by only one of the studied genes (*SLCO1B1*) and only in the homozygous mutant genotype. Based on the result of the study population, it can be recommended as a genetic marker to determine the usefulness of antihypercholesterolemic therapy with statins (mainly predominantly fat-soluble drugs).

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