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POPULATION FEATURES OF THE GENETIC MARKER'S DISTRIBUTION OF THE HEART FAILURE EFFECTIVENESS THERAPY WITH SGLT2 INHIBITORS IN THE KAZAKH POPULATION

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Abstract

Various approaches to cardiovascular diseases and heart failure treatment are being considered and investigated. At present, researchers note the cardio protective effect of taking a new group of drugs – SGLT2 inhibitors.

The purpose of the study: to conduct a comparative analysis of the population frequencies of alleles and genotypes of polymorphic variants of genes associated with the pharmacokinetics of dapaglifosine GWAS – SLC5A2 (rs9934336, rs3116150); PNPLA3 (rs738409); WFS1 (rs10010131); UGT2B4 (rs1080755), in an ethnically homogeneous population of Kazakhs with previously studied world populations.

A genomic database of 1800 healthy individuals of Kazakh nationality were used to analyse the population frequencies of alleles and genotypes of polymorphic variants of genes associated with the pharmacokinetics of dapagliflozin.

The results demonstrated that in the Kazakh population, the distribution of genotypes of the investigated gene polymorphisms associated with the effectiveness of heart failure therapy with SGLT2 inhibitors is in accordance with the Hardy-Weinberg equilibrium ($p>0.05$). High population frequencies of unfavourable alleles of gene polymorphisms were found – PNPLA3 rs738409, which suggests their main genetic contribution to the prognosis of the effectiveness of therapy with SGLT2 inhibitors in the treatment of heart failure in the Kazakh population.

Based on the results of the GWAS analysis and meta-studies, 5 pan-ethnic polymorphisms were selected for further replicative genotyping of patients with heart failure treated with dapagliflozin to predict the efficacy and safety of therapy with SGLT2 inhibitors in the Kazakh population.

Keywords: *SGLT2 inhibitors, pharmacokinetics, pharmacogenetics, SNP, GWAS analysis, Hardy-Weinberg equilibrium.*

Аннотация

ПОПУЛЯЦИОННЫЕ ОСОБЕННОСТИ РАСПРЕДЕЛЕНИЯ ГЕНЕТИЧЕСКИХ МАРКЕРОВ ЭФФЕКТИВНОСТИ ТЕРАПИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ ИНГИБИТОРАМИ SGLT2 У КАЗАХСКОГО НАСЕЛЕНИЯ

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Рассматриваются и исследуются различные подходы к лечению сердечно-сосудистых заболеваний и сердечной недостаточности. В настоящее время исследователи отмечают кардиопротекторный эффект приема новой группы препаратов – ингибиторов SGLT2.

Цель исследования: провести сравнительный анализ популяционных частот аллелей и генотипов полиморфных вариантов генов, связанных с фармакокинетикой дапаглифозина GWAS – SLC5A2 (rs9934336, rs3116150); PNPLA3 (rs738409); WFS1 (rs10010131); UGT2B4 (rs1080755), в этнически однородной популяции казахов с ранее изученными мировыми популяциями.

Геномная база данных 1800 здоровых лиц казахской национальности использовалась для анализа популяционных частот аллелей и генотипов полиморфных вариантов генов, связанных с фармакокинетикой дапаглифлозина.

Результаты показали, что в казахстанской популяции распределение генотипов исследуемых полиморфизмов генов, связанных с эффективностью терапии сердечной недостаточности ингибиторами SGLT2, соответствует равновесию Харди-Вайнберга (p>0,05). Выявлены высокие популяционные частоты неблагоприятных аллелей полиморфизмов генов – PNPLA3 rs738409, что свидетельствует об их основном генетическом вкладе в прогноз эффективности терапии ингибиторами SGLT2 при лечении сердечной недостаточности в казахстанской популяции. По результатам анализа GWAS и мета-исследований было отобрано 5 панэтнических полиморфизмов для дальнейшего репликативного генотипирования пациентов с сердечной недостаточностью, получавших дапаглифлозин, для прогнозирования эффективности и безопасности терапии ингибиторами SGLT2 в казахстанской популяции.

Ключевые слова: *ингибиторы SGLT2, фармакокинетика, фармакогенетика, SNP, GWAS-анализ. Равновесие Харди-Вайнберга.*

Түйіндеме

ҚАЗАҚ ТҰРҒЫНДАРЫНЫҢ ЖҮРЕК ЖЕТКІЛІКСІЗДІГІ КЕЗІНДЕ SGLT2 ИНГИБИТОРЛАРЫМЕН ТЕРАПИЯСЫНЫҢ ТИІМДІЛІГІНДЕ ГЕНЕТИКАЛЫҚ МАРКЕРЛЕРі ТАРАЛУЫНЫҢ ПОПУЛЯЦИЯЛЫҚ ЕРЕКШЕЛІКТЕРІ

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Жүрек-қан тамырлары аурулары мен жүрек жеткіліксіздігін емдеудің әртүрлі тәсілдері қарастырылып зерттелуде. Қазіргі уақытта зерттеушілер SGLT2 ингибиторларының жаңа тобын қабылдаудың жүректі қорғау әсерін атап өтеді.

Зерттеу мақсаты: бұрын зерттелген әлем популяциялары негізінде қазақ этникалық біртекті популяциясында дапаглифозин GWAS – SLC5A2 (rs9934336, rs3116150) фармакокинетикасымен байланысты гендердің полиморфты нұсқаларының аллельдері мен генотиптерінің популяциялық жиіліктеріне салыстырмалы талдау жүргізу; PNPLA3 (rs738409); WFS1 (rs10010131); UGT2B4 (rs1080755).

Дапаглифлозиннің фармакокинетикасымен байланысты гендердің полиморфты нұсқаларының аллельдерінің популяциялық жиілігін және генотиптерін талдау үшін қазақ ұлтының 1800 дені сау адамның геномдық деректер базасы пайдаланылды. Нәтижелер қазақстандық популяцияда SGLT2 тежегіштерімен жүрек жеткіліксіздігі терапиясының тиімділігіне байланысты зерттелген гендік полиморфизмдердің генотиптерінің таралуы Харди-Вайнберг тепе-теңдігіне сәйкес келетінін көрсетті (p>0,05). Гендік полиморфизмдердің қолайсыз аллельдерінің жоғары популяциялық жиіліктері анықталды – PNPLA3 rs738409, бұл олардың қазақ популяциядағы жүрек жеткіліксіздігін емдеуде SGLT2 тежегіштерімен терапия тиімділігінің болжамына негізгі генетикалық үлесін көрсетеді. GWAS талдауының және мета-зерттеулердің нәтижелері бойынша қазақстандық популяцияда SGLT2 тежегіштерімен терапияның тиімділігі мен қауіпсіздігін болжау үшін дапаглифлозинмен емделген жүрек жеткіліксіздігі бар науқастарды одан әрі репликативті генотиптеу үшін 5 панэтникалық полиморфизм таңдалды.

Түйінді сөздер: *SGLT2 ингибиторлары, фармакокинетикасы, фармакогенетика, SNP, GWAS талдауы, Харди-Вайнберг тепе-теңдігі.*

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Introduction

According to the World Health Organisation (WHO), cardiovascular diseases (CVD) account for 40% of all causes of death in Europe and 50% in Kazakhstan [5, 44]. 12% of the economically active population of the Republic of Kazakhstan suffers from CVD (about 2 million people) [2]. The high-risk group of deaths from CVD includes patients with chronic heart failure (CHF), which develops as a result of arterial hypertension (AH), coronary heart disease (CHD), rheumatic heart defects, and type 2 diabetes mellitus (DM2).

At present, various approaches to the treatment of CVD and heart failure (HF) are being considered and investigated, most researchers note the cardioprotective effect of taking a new group of drugs – SGLT2 inhibitors (sodium-glucose co-transporter 2) prescribed for the treatment of DM2 [28, 34]. Although the mechanisms of this protection are not entirely known, it has been shown that SGLT2 inhibitors cause a decrease in triglycerides, an increase in high-density lipoprotein cholesterol (HDL) [28, 10], change liver metabolism towards fatty acid oxidation and ketogenesis [42].

The most widely used drug in Europe of the SGLT2 inhibitor group – dapagliflozin (trade name Forxiga), a new class of approved oral antidiabetic drugs that specifically inhibit the function of sodium-glucose co-transporter 2 in the kidneys. Initially used for the treatment of DM2, dapagliflozin was one of the first antidiabetic drugs effective in reducing mortality from CVD and the number of hospitalisations for HF in these patients [10, 20; 22].

The Framingham Heart Study demonstrated that DM2, regardless of the level of blood pressure (BP) and cholesterol in the blood serum, increases CH by 2 times in men and 5 times in women compared with the control group of the same age. Long-term follow-up in the same cohort discovered obesity as a risk factor for the occurrence of HF in the future in both men and women [24].

According to the results of clinical trials of some hypoglycemic drugs, a decrease in body weight was shown among patients with DM2, especially those who took selective SGLT2 inhibitors (for example, dapagliflozin and empagliflozin) [21]. Meta-analysis of studies of patients with DM2, in which the effects of dapagliflozin were evaluated, body weight loss in the main group compared to the placebo group after 24 weeks ranged from 1.6 [39] to 2.2 kg [40] and from 0.8 [40] to 1.6 kg [15], respectively. In the same study, among participants taking dapagliflozin without a history of DM2, compared with the placebo group, body weight loss after 24 weeks was 4.1 kg [39].

Only a small number of studies have been conducted on the effectiveness of dapagliflozin in chronic HF, which indicates the need for more well-planned studies in this area, with a large number of subjects investigated in different groups. The results of single studies of polymorphisms of various genes are rightly interpreted with caution since they often cannot be reproduced in other cohorts and populations. The analysis of the results of genome-wide GWAS (genome-wide association study) studies and data from meta-analyses on the pharmacogenetics of dapagliflozin discovered specific polymorphisms of genes associated with the effectiveness of GWAS therapy with dapagliflozin.

In this study, a comparative analysis of the population frequencies of alleles and genotypes of polymorphic variants of genes, GWAS associated with the pharmacokinetics of dapagliflozin – SLC5A2 (Solute Carrier Family 5 Member 2, rs9934336, rs3116150); PNPLA3 (Patatin Like Phospholipase Domain Containing 3, rs738409); WFS1 (wolframin ER transmembrane glycoprotein, rs10010131); UGT2B4 (Glucuronosyltransferase Family 2 Member B4, rs1080755), in an ethnically homogeneous population of Kazakhs with previously investigated populations of the world.

Materials and Methods

This study was conducted as part of the scientific and technical program BR 11065383 "Development of innovative and highly efficient technologies to reduce the risk of premature mortality from diseases of the circulatory system, chronic respiratory diseases and diabetes" (№ 0121RK00850).

The local Ethical Commission approved the study of the Non-profit Joint Stock Company "Asfendiyarov Kazakh National Medical University" (Almaty, Kazakhstan), application No. 1121 dated April 28, 2021.

The research material was deoxyribonucleic acid (DNA) isolated from the peripheral blood of the recruited population control group, which 1800 healthy persons of Kazakh nationality represent. Criteria for selection to the control group: ethnicity – Kazakhs from 18 years and older; the ability of the subject to make an independent decision on consent to take part in the project. The DNA of the recruits is stored in the biobank "Miras" Scientific Center of Obstetrics, Gynecology and Perinatology, which was created within the framework of the project "Genetic Research on Pre-eclampsia in Central

Asian and European Populations" (InterPregGen) of the 7th Framework Program of the European Commission under Grant Agreement No. 282540 [40].

Information on possible candidate genes deposited in public databases on the pharmacogenetics of various drugs and recommendations of the Clinical Pharmacogenetics Implementation Consortium (CPIC), the European Medicines Agency (EMA); the Food and Drug Administration (FDA) (USA) were used to select substantial polymorphisms of pharmacogenetic testing when prescribing SGLT2 inhibitors in cardiology [15].

For replicative genotyping, 5 polymorphic variants of 4 genes were selected, according to GWAS data associated with the effectiveness of therapy with SGLT2 inhibitors.

DNA isolation was conducted by the M-PVA magnetic particle separation method on an automatic Prepitto analyser (Perkin Elmer) to isolate nucleic acids Chemagic Prepito (Wallac, Finland) using a set of Prepito DNA CytoPure reagents. Genotyping of each individual for ~2.5 million SNPs was conducted using OmniChip 2.5 M Illumina chips at the DECODE Iceland Genome Centre as part of the InterPregGen project. Illumina Omni2.5-8 Chip includes frequent and rare population variants of SNP from the 1000 genomes project for various world populations. Genotyping quality control was conducted with the exclusion of SNP with MAF (minimal allele frequency) below 1%, call rate<98%, significance less than $p<5x10^{-8}$, cluster plot inspection, with deviation from the Hardy-Weinberg equilibrium (HWE) ($P<0.05$) [2].

Based on the results of GWAS and meta-analysis, 5 highly significant single nucleotide polymorphisms associated with the pharmacokinetics of dapagliflozin were selected for subsequent independent replicative genotyping in an ethnically homogeneous population of Kazakhs. Statistical calculations of allele and genotype frequencies, significance tests, and analysis of the nonparametric criterion $\chi 2$ were performed using PLINK software. The assessment of the correspondence of the obtained genotype frequencies to the Hardy-Weinberg equilibrium law was calculated using the HWE test function of the PLINK programme [36].

Results

In an ethnically homogeneous population of 1800 Kazakhs, the study of population features of allelic and genotypic distribution of potentially substantial polymorphisms of genes SLC5A2 (rs9934336, rs3116150); PNPLA3 (rs738409); WFS1 (rs10010131); UGT2B4 (rs1080755), according to the GWAS analysis associated with the effectiveness of dapagliflozin therapy. Table 1 presents the genetic characteristics of the polymorphisms of the investigated genes with an indication of the identifier (SNP Identifier), the location of the polymorphism on the chromosome, the physical distance in the paired bases (base-pairposition – bp), the name of the gene.

Table 1.

Genetic characteristics of SNPs genes associated with the pharmacokinetics of dapagliflozin according to GWAS data.

No.	Name of the gene		Chromosome	rs	Position	minor
1	SLC5A2	Solute Carrier Family 5 Member 2	16	rs9934336	31484552	A
2				rs3116150	31486700	A
3	PNPLA3	Patatin Like Phospholipase Domain Containing 3	22	rs738409	43928847	C
4	WFS1	Wolframin ER transmembrane glycoprotein	4	rs10010131	6291188	A
5	UGT2B4	UDP Glucuronosyltransferase Family 2 Member B4	4	rs1080755	69478923	G

Note: rs is the SNP identifier;

As can be seen from Table 2, the highest population frequency of the minor C allele is observed in the rs738409 polymorphism of the PNPLA3 gene – 37.4%, the lowest in the rs1080755 polymorphism of the UGT2B4 gene – 8.5%.

Table 2.

Frequencies of alleles and genotypes of SNPs genes GWAS associated with the pharmacokinetics of dapagliflozin in the Kazakh population.

Name of the gene	rs	MAF	N	A1	A2	GENO
SLC5A2	rs9934336	0.188	1801	G	A	1178/569/54
	rs3116150	0.114	1800	G	A	1407/374/19
PNPLA3	rs738409	0.374	1800	G	C	700/852/248
WFS1	rs10010131	0.185	1786	G	A	1188/532/66
UGT2B4	rs1080755	0.085	1801	A	G	1505/285/11

Note: rs is the SNP identifier; MAF is the frequency of the minor allele; N is the number of samples; A1 is the wild-type allele and A2 is the minor allele; GENO is the number of identified genotypes.

The materials in Table 3 indicate that in the Kazakh population for all investigated polymorphisms, the distribution of genotypes is in accordance with the Hardy-Weinberg equilibrium since the differences between the expected and observed heterozygosity for all 5 SNPs turned out to be unreliable ($p>0.05$).

Table 4 shows the results of a comparative analysis of the calculated population frequencies of 5 minor alleles of 4 polymorphic genes associated with the pharmacokinetics of dapagliflozin in the Kazakh population compared to previously investigated populations of the world.

Allele frequencies in populations of the world are presented according to the database of 1000 genomes of the third phase [43], as well as electronic resources gnomAD [16], according to publications from world information databases, GWAS analyses.

Table 3.

Correspondence of genotype distribution to the Hardy-Weinberg equilibrium genes associated with the pharmacokinetics of dapagliflozin in the Kazakh population.

Name of the gene	rs	N	GENO	O(HET)	E(HET)	p
SLC5A2	rs9934336	1800	1178/569/54	0.3159	0.3053	0.1642
	rs3116150	1801	1407/374/19	0.2078	0.2027	0.3514
PNPLA3	rs738409	1800	700/852/248	0.4733	0.4685	0.6874
WFS1	rs10010131	1786	1188/532/66	0.2979	0.3027	0.4826
UGT2B4	rs1080755	1801	1505/285/11	0.1582	0.1559	0.65

Note: rs is the SNP identifier; MAF is the frequency of the minor allele; N is the number of genotyped individuals; GENO is the number of identified genotypes; O (HET) is the expected heterozygosity according to the Hardy-Weinberg equilibrium; E (HET) is the observed heterozygosity according to the Hardy-Weinberg equilibrium; P is p-value;

Table 4.

Comparative analysis of allelic frequencies of SNPs genes GWAS associated with the pharmacokinetics of dapagliflozin in populations of the world.

Population	N	MAF	χ2	p
SLC5A2 rs9934336				
Kazakhstan	1800	0.188		
Europe	503	0.254	10.835	<0.001*
East Asia	504	0.115	14.620	<0.001*
South Asia	489	0.181	0.361	0.548
SLC5A2 rs3116150				
Kazakhstan	1801	0.114		
Europe	503	0.237	48.459	<0.001*
East Asia	504	0.001	60.862	<0.001*
South Asia	489	0.089	2.355	0.125
PNPLA3 rs738409				
Kazakhstan	1800	0.374		
Europe	503	0.226	38.157	<0.001*
East Asia	504	0.350	1.077	0.300
South Asia	489	0.246	28.265	<0.001*
WFS1 rs10010131				
Kazakhstan	1786	0.185		
Europe	503	0.369	76.936	<0.001*
East Asia	504	0.096	22.863	<0.001*
South Asia	489	0.282	22.306	<0.001*
UGT2B4 rs1080755				
Kazakhstan	1801	0.085		
Europe	503	0.227	77.041	<0.001
East Asia	504	0.002	43.479	<0.001
South Asia	489	0.097	0.601	0.439

Note: N is the number of DNA samples; MAF is the frequency of the minor allele; χ^2 is the Chi–square criterion; p is statistical significance.

As shown in Table 4, the frequency of carrying the minor allele A rs9934336 in the SLC5A2 gene in the investigated sample of Kazakhs was 18.8%, which did not substantially differ from the similar frequency in South Asian populations – 18.1% (p>0.05), but was substantially higher than the population frequency of the minor allele A of this polymorphism in the population of East Asia – 11.5% and substantially lower than in European populations – 25.4% (p<0.001). The frequency of the minor allele A rs3116150 in the same SLC5A2 gene in the Kazakh population was 11.4%, which also had no substantial differences with the similar frequency in South Asian populations – 8.9% (p>0.05), but substantially exceeded the population frequency of the minor allele A of this polymorphism in the population of East Asia – 0.1% and it turned out to be substantially lower than in European populations – 23.7% (p<0.001).

The protein of the same name encoded by the SLC5A2 gene is the main co-transporter involved in glucose reabsorption in the kidneys, therefore, polymorphisms in this gene are associated with renal glucosuria [6]. It was shown that although dapagliflozin was the first discovered potent SGLT2 inhibitor with a beneficial effect on CVD, the pharmacogenetic mechanisms of its action have not been sufficiently investigated [32]. The results of the few studies conducted are very contradictory, from the complete absence of a link between the carriage of rs9934336 and rs3116150 of the SLC5A2 gene with a decrease in the risk of CVD to the pronounced protective effect of rs9934336 in reducing the risk of DM2 and CHD [8, 48].

The results of studies conducted to examine the course of CVD using SGLT2 inhibitors have shown a reliable relationship between the carriage of polymorphisms of SLC5A2, PNPLA3 and WFS1 with the effectiveness of HF therapy regardless of the presence of DM2 [26]. Pharmacogenetic study by *N. Zimdahl et al.* [48] the effectiveness of SGLT2 therapy (using Empagliflozin 10-25 mg/day as an example) demonstrated that the carriage of the minor A allele of rs3116150 polymorphism in the SLC5A2 gene substantially increases systolic blood pressure, increases the risk of developing DM2, which reduces the therapeutic effect of treatment. The population frequency of rs9934336, rs3116150 of the SLC5A2 gene in the Kazakh population has an intermediate value between the previously investigated populations of Europe, South and East Asia, which is likely to affect the effectiveness of therapy with SGLT2 inhibitors, which will be less substantial than for the population of South and East Asia, but more effective compared to European populations.

The materials in Table 4 indicate that the frequency of carrying the minor allele with rs738409 of the PNPLA3 in the Kazakh population was the highest and amounted to 37.4%, which had no substantial differences with the same indicator for the population of East Asia – 35.0% ($p>0.05$). Substantial differences in the higher carrier of rs738409 in Kazakhs were obtained when compared with populations of Europe – 22.6% and South Asia – 24.6% ($p<0001$). It is known that the rs738409 of the PNPLA3 has been identified as a risk factor for non-alcoholic fatty liver disease (NAFLD), while the carrier of the minor allele of the rs738409 is associated with higher therapeutic efficacy of NAFLD treatment with SGLT2 inhibitors. During therapy with dapagliflozin, statistically substantial positive correlations between the improvement of glycated haemoglobin, total cholesterol, triglycerides, AST (aspartate transaminase) and ALT (alanine transaminase) were found only in carriers of the risk allele with PNPLA3 rs738409. The frequency of the minor C allele increases to 50% and higher in Latin American populations, which explains the high incidence of steatohepatosis in this ethnic group [47]. Kazakhs have the highest population frequency of the minor allele C rs738409 of the PNPLA3 – 37.4% – suggesting a relatively higher frequency of NAFLD and a better therapeutic effect of therapy with SGLT2 inhibitors, compared with the populations of Europe and Asia.

The materials in Table 4 indicate that the frequency of the minor allele A rs10010131 of the WFS1 in the Kazakh population is 18.5%, which has a substantially low value compared to similar indicators of populations in Europe – 36.9% and South Asia – 28.2% ($p<0.001$), but substantially exceeds the similar frequency of carriage in the population of East Asia – 9.6% ($p<0.001$). The results of the GWAS studies have shown a substantial genetic contribution of rs10010131 of the WFS to the risk of developing DM2 and CVD. Pharmacogenetic analysis of the effectiveness of dapagliflozin therapy discovered the relationship between the carrier of the minor A allele associated with impaired insulin secretion with a substantial decrease in body weight, which had a greater therapeutic effect in patients with DM2 and HF [48, 37]. The comparatively low population frequency of the minor allele A rs10010131 of the WFS1 in Kazakhs – 18.5% suggests a lower efficacy of treatment with SGLT2 inhibitors in carriers of unfavourable genotypes compared to European and South Asian populations and does not allow using this polymorphism as a pharmacogenetic marker in the choice of HF therapy.

According to the results of Table 4, it is shown that the frequency of the minor allele G rs1080755 in the UGT2B4 in the investigated sample of Kazakhs was 8.5%, which did not substantially differ from the populations of South Asia – 9.7% ($p>0.05$), but it turned out to be substantially lower than the similar indicator of the European population – 22.7% and substantially higher than the similar population frequency of the Eastern Asian populations – 0.2% ($p<0.001$). It is known that the enzyme UGT-uridine diphosphate glucuronyl transferase is responsible for the metabolism of dapagliflozin in the kidneys and liver, which plays an important role in individual variability in pharmacokinetics, pharmacodynamics and response to treatment with SGLT2 inhibitors [33]. The carriage of the mutant allele G rs1080755 in the UGT2B4 reduces the rate of glucuronidation, which leads to an increase in the concentration of canagliflozin (SGLT2 inhibitor) in plasma, compared with the carriage of the "wild" type allele [14]. There are substantial ethnic differences in the population frequency of the minor allele G rs1080755, from the highest frequency – 17-38% in European, African, and Latin American populations, to very low in the Asian population [19]. The frequency of population carrier of the allele G rs1080755 of the UGT2B4 in the Kazakh population was 8.5%, which occupies an intermediate position between European and Asian populations. The results suggest the possibility of using this polymorphism in the Kazakh population as a mandatory pharmacogenetic marker for the rational dosage of dapagliflozin therapy.

Discussion

The positive effect of SGLT2 inhibitors on the prevention of HF was confirmed by the most extensive multicentre studies of CVD-REAL and CVD-REAL-2 (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors) [31] using databases of 12 countries in which the analysis of treatment outcomes of patients with DM2 was conducted [30; 46]. A meta-analysis of the results of 21 studies with dapagliflozin (5936 patients took dapagliflozin; other medicine – 3403 subjects) demonstrated that the drug reduced the likelihood of developing myocardial infarction (MI) by 43% and hospitalisation for HF by 64% [3, 29].

It was noted that dapagliflozin substantially reduces the frequency of deaths [37]: in acute and chronic HF (adjusted odds ratio (OR) = 0.75; 95% confidence interval (CI): 0.68-0.84); deaths from CVD (OR = 0.80; 95% CI: 0.68-0.93); and CH (OR = 0.72; 95% CI: 0.63-0.83).

At present, four drug SGLT2 inhibitors are available on the market – dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin. The first investigated drug of this group, Dapagliflozin (10 mg), has a bioavailability of 78%, which is not affected by a high-fat diet. It was displayed that the UGT1A9 enzyme is responsible for the metabolism of dapagliflozin in the kidneys and liver [11]. Dapagliflozin is mainly excreted in the urine [35] and is not recommended for patients with moderate to severe kidney failure (KF) or those on dialysis.

Empagliflozin (daily dose – 25 mg) is most selective to the SGLT2 enzyme, its medicinal effect is not associated

with food intake, and like other SGLT2 inhibitors, this drug prolongs liver metabolism, mainly because of glucuronidation to inactive metabolites. Kanagliflozin is recommended to be taken before the first meal at a dose of 100-300 mg, its bioavailability is 65%. It is not recommended for use in patients with severe hepatic insufficiency. Ertugliflozin has high selectivity against SGLT2 and is a new drug from the group of SGLT2 inhibitors. Its binding to plasma proteins is 93.6%, it is used once a day as monotherapy or in combination with other antihyperglycemic drugs, regardless of food intake. It is not contraindicated in patients with mild to moderate renal or hepatic insufficiency [27].

Dapagliflozin has favourable metabolic, nephroprotective and cardiovascular activity, which is explained by its inhibitory effect on SGLT2 receptors, which leads to a decrease in glucose and sodium reabsorption and increases their excretion in the urine [36]. It is noted that a decrease in glucose reabsorption contributes to a negative energy balance, contributing to weight loss and improving insulin sensitivity, which causes a favourable metabolic effect. The nephroprotective effect of dapagliflozin is explained by the reduction of the renal afferent arteriole, which reduces intraglomerular pressure and, thus, increases the excretion of albumin in the urine. The cardiovascular effect includes an improvement in hemodynamics and results from an increase in osmotic diuresis, a decrease in plasma volume and a decrease in blood pressure, which leads to preload and postload of the left ventricle. SGLT2 inhibitors increase the production of ketone bodies and enhance their utilisation in the heart, which improves the energy metabolism of cardiomyocytes and reduces the risk of development and recurrence of HF, reducing the unfavourable process of heart remodelling [27, 41, 45].

On October 15, 2020, the Committee on Medicines for Humans adopted a positive conclusion regarding dapagliflozin, expanding its indications in addition to DM2 for the treatment of HF and chronic (long-term) kidney disease in adults [13]. According to published studies, dapagliflozin is a fairly safe drug with a low incidence of side complications leading to treatment discontinuation. The most frequent non-severe side complications when taking it include fungal infections of the external genitourinary tract, the symptoms of which disappear after treatment with a topical antifungal agent or a single dose of an antifungal drug [35] and do not require discontinuation of therapy.

It was noted that a rare complication of dapagliflozin therapy in patients with DM2 is ketoacidosis, with symptoms such as polyuria, severe nausea and/or vomiting, abdominal pain, excessive thirst, respiratory distress, confusion, fatigue, and drowsiness. Although it is known that dapagliflozin does not increase the risk of hypoglycemia, the appearance of such side symptoms may require adjusting the dose of diuretics, insulin, and sulfonylureas [20, 22]. It was shown that although dapagliflozin was the first discovered potent SGLT2 inhibitor with a beneficial effect on CVD, the pharmacokinetic mechanisms of its action have not been sufficiently investigated [21]. Pharmacokinetic effects include analysis of genetic polymorphisms that lead to differences in the activity of enzymes that metabolise this drug, which affects its availability and concentration in plasma and tissues. The analysis of scientific literature indicates the need for pharmacogenetic testing to increase the effectiveness of therapy with SGLT2 inhibitors, drug selection, and dosage regiment.

According to GWAS studies, a relationship was found between the genetic variants of the SLC5A2, PNPLA3, WFS1, UGT2B4 genes and the effectiveness of dapagliflozin therapy, the use of which as pharmacogenetic markers will enhance the role of SGLT2 inhibitors in the prevention and treatment of HF regardless of the presence of DM2.

The SLC5A2 gene (rs9934336, rs3116150). The sodium-glucose co-transporter 2 protein is encoded by the SGLT2 gene, also known as SLC5A2, located on chromosome 16, having several genetic polymorphisms that may play a role in glucose homeostasis and the risk of DM2, and influence the effectiveness of treatment with SGLT2 inhibitors. The genetic assessment of the association of SGLT2 inhibitor therapy with a reduced risk of CVD included SNPs with a population frequency of the minor allele MAF>0.01: SLC5A2 rs9934336, rs3116150 [27]. A study by H. Drexel et.al. [8] on the search for associations of rs9934336, rs3813008 and rs3116150 polymorphisms of the SLC5A2 gene in 1684 patients with high risk of CVD who underwent coronary angiography demonstrated a substantial association of rs9934336 polymorphism with a decrease in glycated haemoglobin (P = 0.023) and the risk of DM2 in one-dimensional (OR = 0.82; 95% CI: 0.68-0.99; p = 0.037), and in multivariate analysis (OR = 0.79; 95% CI: 0.65-0.97; p = 0.023) [8]. Therewith, rs3813008 and rs3116150 were not substantially associated with glycemic parameters, with the risk of developing DM2, CHD, and CVD [48]. There are opposite results. Thus, J.L. Katzmann et al. [26] investigated the mechanism of reducing the risk of HF when taking drug inhibitors of SGLT2 and carrying SLC5A2 rs9934336 and rs3116150. A large sample of 416737 DNA from the UK Biobank and DNA of 3316 patients with CVD from the LURIC study [26] discovered a substantial association of rs9934336 and rs3116150 with the level of glycated haemoglobin, cholesterol, uric acid, systolic blood pressure, waist circumference, increased risk of HF by 35%, but did not affect the frequency and outcomes of coronary heart disease. According to a large multinational study conducted in 6 European countries on a sample of over 300000 patients with DM2, treatment with SGLT2 inhibitors compared to other hypoglycemic drugs was more effective. It reduced the frequency of CVD by 39% [31].

The PNPLA3 gene (rs738409). The protein encoded by this gene is a triacylglycerol lipase, which mediates the hydrolysis of triacylglycerol in adipocytes, the main cells of adipose tissue [9]. It should be clarified that in all HapMap populations, dbSNP and SNPedia data, the common rs738409 allele of the PNPLA3 is the C allele on the plus chain (encoding 148I), which means G on the minus chain. However, in the scientific literature, most authors incorrectly refer to rs738409 (G) as a minor allele. The genotypes defined in SNPedia were used, although they may be the opposite of what is indicated in the scientific literature. In 2017, the results of the EFFECT-II study were published to evaluate the effects of therapy with dapagliflozin and omega-3 carboxylic acids on liver fat content in individuals

with DM2 and NAFLD [1]. The effect of rs738409 of the PNPLA3 on a decrease in the level of biomarkers of hepatocyte damage, including alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase [38], a decrease in body weight, and abdominal fat volume [20] with dapagliflozin monotherapy was noted. It is known that NAFLD is associated with an increased risk of fatal/nonfatal CVD and arrhythmic complications (left ventricular hypertrophy, aortic valve sclerosis and other arrhythmias) regardless of the general risk factors for CVD. The presence of a number of main mechanisms, including hepatic/systemic insulin resistance, atherogenic dyslipidemia, hypertension and proatherogenic, procoagulant and proinflammatory mediators released from steatous/inflamed liver, may be associated with the possible effect of PNPLA3 rs738409 on lipoprotein metabolism during dapagliflozin therapy, has been suggested [17].

The WFS1 gene (rs10010131). WFS1 is a gene encoding a transmembrane protein that takes part in the regulation of Ca2+ homeostasis in cells, negatively regulates the stress response in the endoplasmic reticulum and positively regulates the stability of V–ATPase, preventing their degradation through a proteasome-independent mechanism [17]. According to the results of GWAS studies rs10010131, the polymorphism of the WFS1 gene is associated with the risk of developing DM2, and the risk of CVD ($p<0.05$) [7]. The correlation between the carriage of the minor allele A rs10010131 polymorphism of the WFS1 gene and a decrease in body weight when taking dapagliflozin was discovered, which amounted to 2.4 kg for each minor allele ($p<0.05$) [18]. Among patients with DM2 [12], estimated caloric intake increases by an average of 10-15% during continuous intake of SGLT2 inhibitors, which compensates for approximately 9 kg of expected body weight loss in 1 year caused by glucosuria [18, 37]. Dapagliflozin is a substrate for various CYP enzymes (the highest metabolism with CYP1A2, CYP2C9, CYP2D6, and CYP3A4) and various UGT (UDP-glucuronosyltransferase) enzymes (UGT1A9, UGT2B4, and UGT2B7). It has been shown that the excretion of dapagliflozin largely depends on the formation of dapagliflozin 3-O-glucuronide, which is mediated by the UGT1A9 enzyme [12].

UGT2B4 gene (rs1080755). Due to the extremely low population frequency of the rs72551330 polymorphism of the UGT1A9 gene in the populations of the world – less than 1.0% [13], in the Kazakh population, according to the genomic database of the DNA biobank Miras – 0.1, extensive inhibitors of this polymorphism 3*/3* they are very rare, which does not allow using it as a prognostic marker of the response to treatment with inhibitors SGLT2. Therefore, only the most common polymorphism rs1080755 of the UGT2B4 gene is included in this study. UDP-glucuronosyltransferase (UGT) catalyses phase II biotransformation reactions in which lipophilic substrates are conjugated with glucuronic acid, which increases the solubility of the metabolite in water, thereby facilitating their excretion in urine or bile. UGT is necessary for the excretion and detoxification of drugs, xenobiotics and endogenous compounds. It is known that less than 1% of the dose of SGLT2 inhibitors is excreted unchanged in the urine. The

4. populations of the world, suggests a relatively high frequency of NAFLD in Kazakhs and the best therapeutic rs1080755 polymorphism in the UGT2B4 gene catalyses the formation of glucuronidated metabolites, which affects the pharmacokinetics of SGLT2 inhibitors [25, 32]. On the contrary, in the study by S. Imamovic Kadric et al., plasma concentrations of the SGLT2 inhibitor did not differ between carriers of the wild-type allele and the minor UGT2B4 allele, even though carriers of the mutant allele had reduced levels of O-glucuronide metabolites [23].

Conclusions

The comparative analysis of genotypic and allelic frequencies of polymorphisms of genes associated with the pharmacogenetics of SGLT2 inhibitors demonstrated that the formation of the genetic structure of Kazakhs occurred as a result of active migration processes between populations of Asia and Europe under the influence of natural selection, mixing, genetic drift, and adaptive evolution. As a result of clinical pharmacogenetic studies, substantial associations of SGLT2 inhibitors and gene polymorphisms – UGT1A9, SLC5A2, PNPLA3, CNR1, SORCS1, WFS1, and TCF7L2 were discovered. Since most of these studies were conducted based on a very limited design and sample size and thus demonstrated often contradictory results, additional large-scale genotypic and GWAS studies are needed to identify new genetic biomarkers in choosing the most optimal therapeutic strategy and improving the effectiveness of HF therapy.

A comparative analysis of a genome-wide study demonstrated that in the Kazakh population, an intermediate population frequency of minor allele carriers between European and Asian populations was found for most gene polymorphisms associated with the pharmacogenetics of dapagliflozin - SLC5A2 rs9934336; SLC5A2 rs3116150; WFS1 rs10010131; UGT2B4 rs1080755. Compared with the previously investigated populations of Europe and Asia, the Kazakh population has a substantially higher population frequency of carrying unfavourable alleles of polymorphism of gene PNPLA3 rs738409. Thus, the analysis of the population features of the frequency distribution of alleles and genotypes of polymorphic genetic variants of genes, according to the GWAS analysis associated with the pharmacogenetics of dapagliflozin in the treatment of HF, in the Kazakh population, demonstrated:

1. The distribution of genotypes of 5 investigated gene polymorphisms associated with the effectiveness of HF therapy with SGLT2 inhibitors, obtained as a result of statistical processing in the PLINK-HWE test programme, is in accordance with the Hardy-Weinberg equilibrium ($p>0.05$).

2. The results of the conducted genome-wide studies demonstrated that the high population frequencies of unfavourable allele of gene polymorphisms found in the Kazakh population – PNPLA3 rs738409 suggest it main genetic contribution to the prognosis of the effectiveness of therapy with SGLT2 inhibitors in the treatment of HF.

3. The highest frequency of carriage of the minor allele with rs738409 polymorphism of the PNPLA3 gene – 37.4% in the Kazakh population compared to the investigated

effect of therapy with SGLT2 inhibitors, compared with the investigated populations of Europe and Asia.

5. The frequency of population carrier of allele A rs72551330 polymorphism of the UGT2B4 gene in the Kazakh population was 8.5%, which occupies an intermediate position between the previously investigated European and Asian populations and will allow using this polymorphism as a mandatory pharmacogenetic marker for rational dosage of the drug in dapagliflozin therapy.

Thus, the inconsistency of the available results of GWAS studies and pronounced ethnic stratification determined the choice of 5 pan-ethnic polymorphisms for further replicative genotyping of patients with HF treated with dapagliflozin in an independent Kazakh population. Notably, the main studies on the pharmacokinetics of SGLT2 inhibitors have been conducted in European populations and cannot be extrapolated when prescribed to the Kazakh population. The results will serve as a basis for developing effective methods for selecting drugs and predicting the effectiveness and safety of treatment with SGLT2 inhibitors in the Kazakh population.

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