ASSOCIATION OF *GSTP1* GENE WITH RENAL FUNCTION IN PATIENTS WITH DIABETES MELLITUS

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Introduction of point genetic associations into clinical and laboratory diagnosis will allow the physician to determine the risk of severe diabetes mellitus and its complications with a focus on detection of the genetically determined disorder. The study was aimed to identify the molecular genetic markers of severe diabetic nephropathy in patients with type 1 and 2 diabetes mellitus (DM) based on the *GSTP1* (*I105V*) gene assessment. Genotyping of the *GSTP1* gene *I105V* locus was performed in patients with type 1 and 2 DM. Then we identified the features of oxidative status, free radical oxidation, and renal function in patients with various polymorphic variants of the studied gene. Patients with type 1 DM, who were carriers of the *GSTP1* heterozygous polymorphic variant (*Ile/Val*), showed higher activity of the oxidative stress enzymes (glutathione-S-transferase, catalase) and malondialdehyde compared to homozygous carriers ($p < 0.001$, $p < 0.001$, $p < 0.05$). They also showed a significant increase in the levels of triglycerides (1.6-fold) and the glycated hemoglobin levels (1.1-fold) ($p < 0.05$). Patients with type 2 DM, who were carriers of the *GSTP1* polymorphism homozygous for allele 2 (*Val\Val*), had a higher level of malondialdehyde (100.5 μmol/L, ($p < 0.001$)), which was associated with the more severe diabetic nephropathy (average glomerular filtration rate — 48 mL/min/1.73 m2, 24-h urinary albumin excretion — 0.9 g/L; $p < 0.01$). It has been proposed to assess the *GSTP1* (*I105V*) gene in individuals with type 1 and 2 DM. This polymorphism that is heterozygous in individuals with type 1 DM and homozygous for allele 2 in individuals with type 2 DM is unfavorable in terms of the DM course and complications.

Keywords: diabetic nephropathy, oxidative stress, *GSTP1* (*I105V*) gene, personalized medicine

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СВЯЗЬ ГЕНА *GSTP1* С ФУНКЦИОНАЛЬНЫМ СОСТОЯНИЕМ ПОЧЕК У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ

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Введение в клинико-лабораторную диагностику точечных генетических ассоциаций позволит врачу определять риск тяжелого течения диабета и его осложнений, делая упор на выявление генетически детерминированного патологического состояния. Целью работы было выявить молекулярно-генетические маркеры тяжелого течения диабетической нефропатии у пациентов с сахарным диабетом (СД) 1-го и 2-го типа на основании изучения гена *GSTP1* (*I105V*). Проводили генотипирование локуса *I105V* гена *GSTP1* у пациентов с СД 1-го и 2-го типа. Далее выявляли особенности окислительного статуса, свободнорадикального окисления и функции почек у пациентов с различными полиморфными вариантами исследуемого гена. Пациенты с СД 1-го типа — носители гетерозиготного варианта полиморфизма (*Ile\Val*) гена *GSTP1* — имели более высокий уровень активности ферментов окислительного стресса (глутатион-S-трансферазы, каталазы) и малонового диальдегида по сравнению с гомозиготными носителями ($p < 0{,}001$, $p < 0{,}001$, $p < 0{,}05$). У них также выявлено значимое повышение уровня триглицеридов в 1,6 раз и повышение уровня гликированного гемоглобина в 1,1 раз ($p < 0{,}05$). Пациенты с СД 2-го типа — носители гомозиготного по аллелю 2 полиморфизма (*Val/Val*) гена *GSTP1* — имели более высокий уровень малонового диальдегида (100,5 мкмоль/л, ($p < 0{,}001$)), что сочеталось с более тяжелым течением диабетической нефропатии (среднее значение скорости клубочковой фильтрации — 48 мл/мин/1,73 м^2, уровень суточной альбуминурии — 0,9 г/л; $p < 0{,}01$). Предложено производить анализ гена *GSTP1* (*I105V*) у лиц с СД 1-го и 2-го типа. Данный полиморфизм в гетерозиготном состоянии у лиц с СД 1-го типа и в гомозиготном по аллелю 2 состоянии у лиц с СД 2-го типа неблагоприятен в отношении течения СД и его осложнений.

Ключевые слова: диабетическая нефропатия, окислительный стресс, ген *GSTP1* (*I105V*), персонифицированная медицина

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The world's clinical diagnostic laboratories (CDLs) are gradually moving toward a personalized medicine [1], which represents a modern approach to health protection considering specific features of each patient, including genetic markers and variable phenotypic traits. Such an approach makes it possible to more accurately diagnose the disease, to select optimal treatment and prevention methods, to reduce the risk of complications [2]. Introduction of the personalized medicine and specialized

CDLs will enable improving the quality of medical care, reducing the costs of public health services, and improving the patients' prognosis [3].

When discussing personalized medicine, we cannot ignore a disorder that is called the non-infectious pandemic of the 20th and 21st centuries. In 2022, there were almost 9 million people suffering from diabetes mellitus (DM) all over the world [4]. Furthermore, the increase in the number of individuals suffering from both type 2 and type 1 DM is reported [5]. It is possible to prevent type 2 DM or alleviate its course and complications through adjustment of lifestyle and diet, increase in physical activity. However, we still cannot affect the development of type 1 DM. Cardiovascular disorders, the risk of which increases 2–4-fold after the onset of diabetic nephropathy (DN), represent the main cause of mortality among patients with type 1 and type 2 DM [6, 7]. DN is a terrible complication of DM, because clinical symptoms manifest themselves at the latest stages only. According to the research, the early-stage chronic kidney disease (CKD) is missed in 20% of patients [8]. DN in patients with type 1 DM manifests itself within 10 years after the disease onset on average. In case of DM decompensation, this median is shifted, and the CKD progression takes place earlier [9]. In patients with type 2 DM, it is recommended to estimate DN severity immediately when making the diagnosis of DM. This is associated with the fact that due to mild manifestation of type 2 diabetes, patients can have hyperglycemia for a long time, which adversely affects the renal function. Inability to use modern nephroprotective drugs (sodium-glucose cotransporter 2 (SGLT-2) inhibitors; glucagon-like peptide-1 agonists, thiazolidinediones) slowing down the CKD progression is an important problem of patients with type 1 DM. The use of such drugs in patients with type 1 DM has not been sufficiently studied and is currently contraindicated [10]. As for individuals with type 2 DM, the use of nephroprotective drugs, on the contrary, has a beneficial effect on the course of DN, since these drugs maintain the glomerular filtration rate (GFR) and reduce albuminuria [11]. The methods to estimate severity of the diabetic complications, specifically DN, are used in the clinical laboratory diagnosis. However, all these methods (determination of the renal function of filtration through calculation of creatinine levels, albumin-to-creatinine ratio (ACR) in a single urinary specimen, micro- or macroalbuminuria in 24 h urine, cystatin C, etc.) become effective after the CKD onset. There are no clear markers warning physicians about the likelihood of severe diabetes and its complications, specifically DN. In our opinion, the molecular genetic markers can inform the physician about the diabetes severity. It is important to choose the genes capable of affecting the course of DN with high sensitivity and specificity amongst the multitude of genes. The leading diabetologists of our country have described the importance of the search for polygenic associations instead of individual genes and have identified the genes responsible for antioxidant protection as the candidate genes [12]. Introduction of point genetic associations into clinical laboratory diagnosis will allow the physician to determine the risk of severe diabetes and its complications, prevent these complications in a timely manner, intensify the glucose-lowering therapy, increase the number of the patients' preventive check-ups focusing on prevention and identification of the specific genetically determined complication. This represents a fundamental link of the personalized medicine in general and the personalized clinical laboratory diagnosis in particular.

When performing the search for probable candidate genes involved in the DN pathogenesis, we became interested in the role of the *GSTP1* (*I105V*) gene. This gene encodes the glutathione-S-transferase (GST) enzyme being one of the main contributors to the xenobiotic transformation process. Normally, GST contributes to the glutamate interaction with the electrophilic nitrogen (N), carbon (C), sulfur (S) and oxygen (O) atoms and ensures conjugation of sulfhydryl groups with the xenobiotic molecules. The detoxification process driven by GST is the key process of protecting cells from lipid peroxidation and protein alkylation, which increases the resistance to hypoxic states [13]. The *GSTP1* gene *I105V* (A>G) polymorphism is associated with the adenine (A) nucleotide substitution with guanine (G), which results in substitution of the amino acid in the enzyme peptide chain, thereby reducing the enzyme activity and, consequently, increasing accumulation of free radicals in the body. The increased risk of various forms of lung cancer and oral cancer is observed in the G/G genotype carriers [14]. This polymorphism is also associated with susceptibility to leukemia and Parkinson's disease. There are deletion polymorphisms (*GSTM* (*del*), *GSTT1*) that determine the nonfunctional null alleles. It is assumed that individuals with these deletions in homozygous state have a decreased ability to detoxify chemical substances. Such polymorphisms are most often found in women with endometriosis and individuals with allergy [15]. Recently, it has been found out that there are studies, in which the *GSTP1* (*I105V*) gene affects the drug pharmacokinetics, along with the genes of the P-glycoprotein transporter (MDR1), organic cations (OCT1), and organic anions (OATP-C, OAT1, OAT3) [16].

The study was aimed to identify the molecular genetic markers determining the severity of diabetic nephropathy in patients with type 1 and 2 DM based on the *GSTP1* (I105V) gene assessment.

METHODS

The study was conducted at the Department of Endocrinology of the Faculty of Advanced Training and Retraining of Specialists of the Kuban State Medical University. Patients were enrolled at the Regional Clinical Hospital of Emergency Medical Care (Krasnodar). A total of 51 individuals with type 2 DM and 49 individuals with type 1 DM were included in this open-label prospective cohort study. Inclusion criteria: patients' age 20–60 years; type 1 and 2 DM duration 10–15 years; glycated hemoglobin levels of 7.0%–9.5%; glomerular filtration rate exceeding 45 mL/min/1.73 m^2, regardless of the 24 h urinary albumin excretion rate; using drugs having no nephroprotective effects (biguanides; sulfonylureas; dipeptidyl peptidase-4 inhibitors; insulin) as glucose-lowering therapy; no severe comorbidities at the time of the study. Individuals, who did not meet these criteria, were excluded from the study. We also formed the control group of 20 conditionally healthy donors (13 females and 7 males), who were not related to the index group patients and had no history of DM or kidney disease.

Clinical laboratory testing involved the serum samples obtained by centrifuging the whole blood-containing tubes at 3000 rpm and room temperature. The fasting blood glucose levels, postprandial glycemia, complete blood counts, and blood biochemistry were assessed using the Konelab analyzer (Thermo Fisher Scientific; Finland); urinalysis and 24-h urine tests were performed using the SYNCHRON CX9 PRO biochemical analyzer (Beckman Coulter; USA) by immunoturbidimetry. GFR (mL/min/1.73 m^2) was estimated by calculation using the CKD-EPI formula.

The balance of the pro-/antioxidant system of surveyed patients and the control group was assessed based on the activity of the antioxidant defense system enzymes (superoxide

Table 1. Comparison of the *GSTP1* (*I105V*) allele frequencies in the studied groups

Genetic variant	Type 1 DM	Type 2 DM	χ^2	*p*	OR (95%CI)
GSTP1 (*Ile105Val*)					
Homozygote 1 (*ILE/ILE*), %	65.3 (32/49)	62.7 (32/51)	6.572	0.039	0.895 (0.395–2.026)
Homozygote 2 (*VAL/VAL*), %	0 (0/49)	11.8 (6/51)			–
Heterozygote (*ILE/VAL*), %	34.7 (17/49)	25.5 (13/51)			0.644 (0.272–1.524)

dismutase (SOD) [17], catalase (CAT) [18], glutathione-S-transferase (GST) [19] and malondialdehyde (MDA) levels [20]). SOD activity was determined based on the ability to inhibit autoxidation of epinephrine in the alkaline environment. The reaction rate was measured by spectrophotometry based on the resulting absorbance of the released epinephrine autoxidation products in the test sample and relative to the data obtained when there was no epinephrine in the studied blood sample. CAT measurement in the hemolysate was performed by photometry based on the ability to disrupt H_2O_2. The essence of the GST determination method was the ability of reduced glutathione (present in the substrate — 1% hemolysate of patient's red blood cells) to bind 1-chloro-2,4-dinitrobenzene, forming a stable chromogenic conjugate in the alkaline environment. The qualitative assay used to estimate MDA levels in the hemolysate involved adding thiobarbituric acid in the presence of chloroacetic acid.

The *GSTP1* (*I105V*) molecular genetic testing was performed in the molecular genetic research laboratory of the Kuban State Medical University (Krasnodar). The real-time polymerase chain reaction (qPCR) and the RotorGene real-time PCR cycler (QIAGEN; Germany) were used to perform genotyping of the *GSTP1* gene *I105V* locus from the leukocyte fraction. Two amplification reactions with the extracted DNA sample were simultaneously launched (with two pairs of allele-specific primers). The cycler automatically detected the amplification products in each amplification cycle. According to the data obtained, the control program plotted the fluorescent signal accumulation curves for the channel specified for the sample. The analysis results allowed us to draw conclusions of three types: homozygote for allele 1; heterozygote; homozygote for allele 2.

Statistical analysis

Significance of differences in the genotype frequency distribution between the groups of patients with DM and healthy individuals was assessed using the χ^2 test, and the quantitative indicators of the patients' clinical characteristics were assessed using the Student's t-test. Calculations were performed using the BIOSTAT software. The differences were considered significant at $p < 0.05$. To determine compliance with the Hardy–Weinberg principle, we calculated frequencies of all allele variants and the corresponding χ^2 values. The critical χ^2 value exceeded the estimates calculated for each group, suggesting that the Hardy–Weinberg equilibrium was preserved.

RESULTS

The following percentages of the *GSTP1* (*I105V*) polymorphism carriers were revealed among patients with type 2 DM: 25.5% were heterozygous carriers (*ILE/VAL*), 62.7% were carriers homozygous for allele 1 (*ILE/ILE*), and 11.8% were carriers homozygous for allele 2 (*VAL/VAL*). Among patients with type 1 DM, the share of patients with heterozygous gene variant (*ILE/VAL*) was 34.7%; 65.3% were homozygous for allele 1 (*ILE/ILE*); no patients homozygous for allele 2 were revealed. These data are significantly different from that of the control group, where 65% were heterozygous carriers (*ILE/VAL*), 35% were homozygous carriers (*ILE/ILE*), and where there were no carriers homozygous for allele 2 (*VAL/VAL*) (Table 1).

Then we launched the study of the relationship between the renal function and the studied gene polymorphism variant. No differences in GFR and 24 h urinary albumin excretion rate between the heterozygous carriers (ILE/VAL) and the carriers homozygous for the GSTP1 allele 1 (*ILE/ILE*) were revealed among patients with type 2 DM. The average GFR in the subgroups of individuals with type 2 DM having homozygous and heterozygous polymorphisms was 64 mL/min/1.73 m^2, and the average protein level in the 24 h urine was 0.18 g/L. However, patients with type 2 DM, who were carriers of the rare homozygote for allele 2 (*VAL/VAL*), had much worse indicators: the average GFR of this subgroup was 48 mL/min/1.73 m^2, and the 24 h urinary albumin excretion rate was 0.9 g/L. There were no significant differences in other blood biochemistry indicators between the studied gene allele variants in individuals with type 2 DM.

Assessment of the same indicators in the homo- and heterozygous carriers of the *GSTP1* (*Ile105Val*) polymorphisms in the group of patients with type 1 DM revealed no significant differences in the renal function indicators (GFR and 24 h urinary albumin excretion rate). However, a significant (1.6-fold) increase in the levels of triglycerides and a 1.1-fold increase in the glycated hemoglobin levels in the heterozygous carriers (*ILE/VAL*) of the gene compared to homozygous carriers (*ILE/ILE*) were revealed ($p < 0.05$) (Table 2).

No comparison of renal function between patients with type 1 DM, patients with type 2 DM, and the controls was performed, since the control group consisted of healthy individuals.

In the next phase we proceeded to assessing the activity of the antioxidant defense (AOD) enzymes and MDA levels as a function of the studied gene polymorphism. The most significant increase in the activity of the AOD enzymes (catalase

Table 2. Features of changes in the lipid profile indicators and glycated hemoglobin levels in patients with type 1 DM having various *GSTP1* (*I105V*) allele variants

Gene	Group	Glycated hemoglobin	VLDL	Triglycerides	Cholesterol
GSTP1 (*I105V*)	Heterozygote (*ILE/VAL*)	9.41* ± 2.13	4.07 ± 1.46	2.85 ± 1.24**	5.14 ± 0.88
	Homozygote 1 (*ILE/ILE*)	8.74 ± 2.30	3.36 ± 1.15	1.75 ± 0.67	5.00 ± 1.33

Note: * — differences between the group of patients with type 1 DM having the gene polymorphism in the heterozygous state and the patients with type 1 DM having the gene polymorphism in the homozygous state (homozygote for allele 1) at $p < 0.05$ (** — $p < 0.01$, *** — $p < 0.001$).

Table 3. Indicators of the antioxidant defense system and lipid peroxidation in individuals with various *GSTP1* (*Ile105Val*) polymorphic variants

Ile105Val	MDA (μmol/L)	CAT (nmol H_2O_2/mg Hb)	GST (μmol /min/mg of protein)	SOD (AU)
Patients with type 2 DM, genotype (*Ile/Val*), *n* = 14	24.6 ± 2.78* *p* < 0.001	40.3 ± 4.17* *p* < 0.05	30.0 ± 3.2* *p* < 0.05	81.8 ± 4.6* *p* < 0.05
Patients with type 2 DM, genotype (*Ile/Ile*), *n* = 31	34.90 ± 2.5** *p* < 0.001	40.7 ± 1.6** *p* < 0.001	42.2 ± 2.3** *p* < 0.001	89.1 ± 2.2** *p* < 0.001
Patients with type 2 DM, genotype (*Val/Val*), *n* = 5	100.5 ± 4.7*** *p* < 0.05	42.1 ± 8.3*** *p* < 0.001	29.6 ± 6.9*** *p* < 0.05	89.2 ± 8.4*** *p* < 0.05
Patients with type 1 DM, genotype (*Ile/Val*), *n* = 17	37.23 (32.37; 40.90) ### *p* < 0.001	43.36 (37.03; 51.97) # *p* < 0.05	53.02 (44.26; 59.08) ### *p* < 0.001	88.44 (81.10; 98.74)
Patients with type 1 DM, genotype (*Ile/Ile*), *n* = 32	23.30 (17.36; 28.05)	38.04 (27.82; 43.28)	29.41 (23.69; 40.38)	87.20 (73.09; 99.75)
Control group, genotype (*Ile/Val*), *n* = 13	6.4 ± 0.5	30.5 ± 1.6	28.1 ± 1.33	75.0 ± 3.07
Control group, genotype (*Ile/Ile*), *n* = 7	5.8 ± 0.49	33.08 ± 3.4	32.5 ± 3.15	73.8 ± 3.08

Note: MDA — malondialdehyde; SOD — superoxide dismutase; CAT — catalase; GST — glutathione-S-transferase. * — compared to heterozygous carriers of the studied gene in the control group; ** — compared to homozygous carriers of the studied gene in the control group; *** — compared to the indicators of the index group of genotypes (*Ile/Val*) and (*Ile/Ile*). # — differences between the group of patients with type 1 DM having the gene variant in the heterozygous state (*Ile/Val*) and the patients with type 1 DM having the gene variant in the homozygous state (*Ile/Ile*) at $p < 0.05$ (## — $p < 0.01$; ### — $p < 0.001$).

and superoxide dismutase) among patients with type 2 DM was reported for the carriers homozygous for allele 1 compared to heterozygous carriers of the *GSTP1* polymorphisms and the carriers homozygous for allele 2. However, the levels of the advanced glycation end products (MDA) in the subgroup of carriers of the rare homozygote for allele 2 (*VAL/VAL*) were significantly higher (100.5 μmol/L), than in individuals with other polymorphisms ($p < 0.001$) [21].

Among patients with type 1 DM, heterozygous carriers of the *GSTP1* polymorphism (*ILE/VAL*) had higher levels of MDA, GST, and catalase compared to homozygous carriers of the gene polymorphism ($p < 0.001$, $p < 0.001$, $p < 0.05$).

Comparison of the data obtained between patients with type 1 DM, patients with type 2 DM, and the controls revealed, quite naturally, a significant predominance of activity of the AOD enzymes and MDA levels in individuals with DM (Table 3).

DISCUSSION

The study conducted makes it possible to conclude that the abundance of heterozygous *GSTP1* polymorphism (*ILE/VAL*) in individuals with type 1 and 2 DM is significantly higher than that in controls. The genotype distributions for both polymorphisms were compliant with the Hardy–Weinberg equilibrium and showed no significant differences from the data of the SNP database [22]. Furthermore, the rare Val/Val genotype was revealed in individuals with type 2 DM, which was found in none of the surveyed patients with type 1 DM and controls ($\chi^2 = 6.572$, $p = 0.039$).

Patients with type 2 DM, carriers of the rare *GSTP1* polymorphic variant homozygous for allele 2 (*VAL/VAL*), had higher levels of MDA (free radical oxidation markers) and higher activity of the oxidative stress enzymes. One of the studies has shown a clear correlation between this polymorphic variant and the development of type 2 DM, however, the impact of this variant on the development of such complication, as diabetic polyneuropathy, has not been proven [23]. In our study, patients with the rare homozygote for allele 2 had a significantly more severe course of DN (average GFR — 48 mL/min/1.73 m^2; average 24 h urinary albumin excretion rate — 0.9 g/L). Perhaps, this is due to the fact that this specific genetic variant causes the decrease in activity of the protein produced (GST), which does not ensure adequate detoxification of xenobiotics and results in the increase in activity of free radical oxidation. This is reflected in the increase in the free radical oxidation marker (MDA) levels. Thus, conditions are being created for active lipid peroxidation in all cells, especially in the cells most sensitive to hypoxic damage, the nephrons. The multifaceted damage to the nephron structure results in the decrease in the renal functions of filtration (elevated creatinine levels and reduced GFR) and reabsorption (elevated 24 h urinary albumin excretion rate) in the cohort of patients with type 2 DM. Similar data were obtained in the study, during which the researchers confirmed the correlation between the rare homozygous polymorphism (VAL/VAL) and the end-stage kidney disease [24].

Heterozygous (*ILE/VAL*) carriers of the *GSTP1* (*I105V*) gene with type 1 DM had significantly higher activity of the AOD enzymes and MDA levels compared to the homozygous polymorphisms. GST, the antioxidant enzyme, protects the tissues against oxidative damage typical for many health conditions, especially those like type 1 DM and its chronic complications. This polymorphism is likely to be more pathogenic, when it is in heterozygous state. Similar results were obtained in the study that revealed the correlation between this genetic polymorphism and the development of the diabetic complication (cardiovascular autonomic neuropathy) in patients with type 1 DM [25]. Patients with type 1 DM and the heterozygous polymorphism variant also demonstrate a significant increase in the levels of triglycerides (1.6-fold). Based on these data, we can assume that heterozygous carriers have the reduced triacylglycerol lipase activity, which results in slower breakdown of triglycerides. This is associated with the influence of oxidative stress and some hormones, such as norepinephrine, epinephrine, glucagon, etc. it has been reported that activity of this enzyme can change under the influence of the discussed factors [26]. Furthermore, significantly higher glycated hemoglobin levels were determined in this subgroup of patients, which also correlated with elevated MDA levels and increased activity of CAT and GST.

CONCLUSIONS

The personalized medicine is based on the tailored approach to the characteristics of each patient. Introduction of the *GSTP1* (*Ile/Val*) gene molecular genetic assessment into clinical laboratory diagnosis will make it possible to identify patients

with type 1 and 2 DM having high levels of oxidative stress and increased risk of severe DN. When performing clinical laboratory diagnosis, it is recommended to determine the heterozygous (*ILE/VAL*) variant of *GSTP1* (*I105V*) in individuals with type 1 DM, which is associated with the increased free radical oxidation and activity of the AOD enzymes and can result in the significantly higher glycated hemoglobin and triglyceride levels. As for patients with type 2 DM, it is recommended to determine the rare *GSTP1* (*I105V*) gene variant homozygous for allele 2 (*VAL/VAL*) that is associated with the increased free radical oxidation and activity of the oxidative stress enzymes, as well as with the reduced renal function (increased 24 h urinary albumin excretion rate and reduced GFR). Such studies can provide the basis for development of the genetic panel, in which the polygenic sequences that improve reliability and ensure more accurate prediction of the severity and timing of the onset of diabetic complications will be determined. However, this requires expansion of the research in this field.

References

1. Ivanets NV. Nauchnoe obosnovanie sovershenstvovaniya upravleniya deyatel'nost'yu tsentralizovannoy kliniko-diagnosticheskoy laboratorii [dissertation]. Natsional'nyy nauchno-issledovatel'skiy institut obshchestvennogo zdorov'ya RAMN, 2015. Russian.
2. Paltsev MA. Personalizirovannaya meditsina. Nauka v Rossii. 2011; 1: 12–7. ISSN 0869-7078. Russian.
3. Bibikova VV, Emanuel VL. Current Status of Specialized Clinical Laboratory and its Role in Facilitating a Transition Towards Personalized Medicine. Laboratory Service. 2020; 9 (3): 16–23. Russian.
4. Heerspink HJ, Cherney DZ, Groop PH, Matthieu C, Rossing P, Tuttle KR. People with type 1 diabetes and chronic kidney disease urgently need new therapies: a call for action. The Lancet Diabetes & Endocrinology. 2023; 11 (8): 536–40.
5. Asfandiyarova NS. A review of mortality in type 2 diabetes mellitus. Diabetes mellitus. 2015; 18 (4): 12–21. DOI: 10.14341/DM6846. Russian.
6. Rawshani A, Sattar N, Franzén S, McGuire DK, Eliasson B. Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes mellitus. Circulation. 2019; 139 (16): 1900–12.
7. De Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022; 45 (12): 3075–90. DOI: 10.1016/j.kint.2022.08.012.
8. Piani MIF, Tommerdahl KL, Severn C, Chung LT, MacDonald A, et al. Aminoaciduria and metabolic dysregulation during diabetic ketoacidosis: results from the diabetic kidney alarm (DKA) study. Journal of Diabetes and its Complications. 2022; 36 (6): 108203. DOI: 10.1016/j.jdiacomp.2022.108203.
9. Dedov II, Shestakova MV, Vikulova OK, Zheleznyakova AV, Isakov MA. Diabetes mellitus in Russian Federation: prevalence, morbidity, mortality, parameters of glycaemic control and structure of glucose lowering therapy according to the Federal Diabetes Register, status 2017. Diabetes mellitus. 2018; 21 (3): 144–59. Russian.
10. Shestakova MV. Diabetes mellitus and chronic kideny disease: modern diagnostics and treatment. Annals of the Russian Academy of Medical Sciences. 2012; 67 (1): 45–9. Russian.
11. Illarioshkin SN. Modern view on etiology of parkinson's disease. Nevrologicheskiy zhurnal. 2015; 20 (4): 4–13. Russian.
12. Liu D Liu Y, Ran L, Shang H, Li D. GSTT1 and GSTM1 polymorphisms and prostate cancer risk in Asians: a systematic review and meta-analysis. Tumor Biology. 2013; 34: 2539–44.
13. Santric V, Djokic M, Suvakov S, Pljesa-Ercegovac M, Nikitovic M, Radic T, et al. GSTP1 rs1138272 polymorphism affects prostate cancer risk. Medicina. 2020; 56 (3): 128.
14. ZamekGliszczynski MJ, Giacomini KM, Zhang L. Emerging clinical importance of hepatic organic cation transporter 1 (OCT1) in drug pharmacokinetics, dynamics, pharmacogenetic variability, and drug interactions. Clinical Pharmacology & Therapeutics. 2018; 5: 758–60.
15. Mogilenkova LA, Rembovskiy VR. Role of genetic polymorphism and differences in the detoxification of chemical substances in the human body. Hygiene and Sanitation. 2016; 95 (3): 255–62. Russian.
16. Westphal C, Konkel A, Schunck WH. Cytochrome p450 enzymes in the bioactILE/VALation of polyunsaturated Fatty acids and their role in cardiovascular disease. Monooxygenase, Peroxidase and Peroxygenase Properties and Mechanisms of Cytochrome P450. 2015; 151–87.
17. Sirota TV. Novyy podkhod v issledovanii protsessa autookisleniya adrenalina i ispol'zovanie ego dlya izmereniya aktivnosti superoksiddismutazy. Voprosy meditsinskoy khimii. 1999; 45 (3): 263–72. Russian.
18. Korolyuk MA, Ivanova LI, Mayorova IG, Tokarev VE. Metod opredeleniya aktivnosti katalazy. Laboratornoe delo. 1988; 1: 16–9. Russian.
19. Karpishchenko AI. Medical laboratory technologies and diagnostics: Guide. Vol. 2: Medical laboratory technologies. St. Petersburg: Intermedica, 1999; p. 792.
20. Stalnaya ID, Garishvili TG, 1977. Method of determination of malonic dialdehyde using thiobarbityric acid. In: Modern methods in biochemistry. M.: Medicine, 1977; p. 66–8.
21. Kostyushok NY, Pavlyuchenko II, Ivanova LA, Prozorovskaya YI. The role of the gene of the second phase of the xenobiotic biotransformation system gstp1 (ile105val) in the development of diabetic nephropathy in patients with type 2 diabetes mellitus. Modern problems of science and education. 2022; 4. Available from: https://science-education.ru/ru/article/view?id=31902. Russian.
22. National Center for Biotechnology Information: Single Nucleotide Polymorphism Database (1998). Available from: https://www.ncbi.nlm.nih.gov/snp/.
23. Stoian A, Bănescu C, Bălaşa RI, Moţăţăianu A, Stoian M, Moldovan VG, et al. Influence of GSTM1, GSTT1, and GSTP1 polymorphisms on type 2 diabetes mellitus and diabetic sensorimotor peripheral neuropathy risk. Disease markers. 2015; 2015: 638693.
24. Agrawal S, Tripathi G, Khan F, Sharma R, Baburaj VP, et al. Relationship between GSTs gene polymorphism and susceptibility to end stage renal disease among North Indians. Renal failure. 2007; 29 (8): 947–53.
25. Vojtková J, Ďurdík P, Čiljaková M, Michnová Z, Turčan T, Babušíková E. The association between glutathione S-transferase T1 and M1 gene polymorphisms and cardiovascular autonomic neuropathy in Slovak adolescents with type 1 diabetes mellitus. Journal of Diabetes and its Complications. 2013; 27 (1): 44–8.
26. Perova NV, Drapkina OM. Triglitseridy: struktura, metabolizm, fiziologicheskie funktsii. M.: OOO «Vidoks», 2021; p. 192. Russian.

Литература

1. Иванец Н. В. Научное обоснование совершенствования управления деятельностью централизованной клинико-диагностической лаборатории [диссертация]. Национальный научно-исследовательский институт общественного здоровья РАМН, 2015.
2. Пальцев М. А. Персонализированная медицина. Наука в

России. 2011; 1: 12–7. ISSN 0869-7078.
3. Бибикова В. В., Эмануэль В. Л. Современное положение специализированной клинико-диагностической лаборатории и ее роль при переходе к персонализированной медицине. Лабораторная служба. 2020; 9 (3): 16–23.
4. Heerspink HJ, Cherney DZ, Groop PH, Matthieu C, Rossing P, Tuttle KR. People with type 1 diabetes and chronic kidney disease urgently need new therapies: a call for action. The Lancet Diabetes & Endocrinology. 2023; 11 (8): 536–40.
5. Асфандиярова Н. С. Смертность при сахарном диабете 2-го типа. Сахарный диабет. 2015; 18 (4): 12–21. DOI: 10.14341/DM6846.
6. Rawshani A, Sattar N, Franzén S, McGuire DK, Eliasson B. Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes mellitus. Circulation. 2019; 139 (16): 1900–12.
7. De Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022; 45 (12): 3075–90. DOI: 10.1016/j.kint.2022.08.012.
8. Piani MIF, Tommerdahl KL, Severn C, Chung LT, MacDonald A, et al. Aminoaciduria and metabolic dysregulation during diabetic ketoacidosis: results from the diabetic kidney alarm (DKA) study. Journal of Diabetes and its Complications. 2022; 36 (6): 108203. DOI: 10.1016/j.jdiacomp.2022.108203.
9. Дедов И. И., Шестакова М. В., Викулова О. К. Сахарный диабет в Российской Федерации: распространенность, заболеваемость, смертность, параметры углеводного обмена и структура сахароснижающей терапии по данным Федерального регистра сахарного диабета, статус 2017 г. Сахарный диабет. 2018; 21 (3): 144–59.
10. Шестакова М. В. Сахарный диабет и хроническая болезнь почек: современная диагностика и лечение. Вестник Российской академии медицинских наук. 2012; 67 (1): 45–9.
11. Иллариошкин С. Н. Современные представления об этиологии болезни Паркинсона. Неврологический журнал. 2015; 20 (4): 4–13.
12. Liu D Liu Y, Ran L, Shang H, Li D. GSTT1 and GSTM1 polymorphisms and prostate cancer risk in Asians: a systematic review and meta-analysis. Tumor Biology. 2013; 34: 2539–44.
13. Santric V, Djokic M, Suvakov S, Pljesa-Ercegovac M, Nikitovic M, Radic T, et al. GSTP1 rs1138272 polymorphism affects prostate cancer risk. Medicina. 2020; 56 (3): 128.
14. ZamekGliszczynski MJ, Giacomini KM, Zhang L. Emerging clinical importance of hepatic organic cation transporter 1 (OCT1) in drug pharmacokinetics, dynamics, pharmacogenetic variability, and drug interactions. Clinical Pharmacology & Therapeutics. 2018; 5: 758–60.
15. Могиленкова Л. А., Рембовский В. Р. Роль генетического полиморфизма и различия в детоксикации химических веществ в организме человека. Гигиена и санитария. 2016; 95 (3): 255–62.
16. Westphal C, Konkel A, Schunck WH. Cytochrome p450 enzymes in the bioactILE/VALation of polyunsaturated Fatty acids and their role in cardiovascular disease. Monooxygenase, Peroxidase and Peroxygenase Properties and Mechanisms of Cytochrome P450. 2015; 151–87.
17. Сирота Т. В. Новый подход в исследовании процесса аутоокисления адреналина и использование его для измерения активности супероксиддисмутазы. Вопросы медицинской химии. 1999; 45 (3): 263–72.
18. Королюк М. А., Иванова Л. И., Майорова И. Г., Токарев В. Е. Метод определения активности каталазы. Лабораторное дело. 1988; 1: 16–9.
19. Karpishchenko AI. Medical laboratory technologies and diagnostics: Guide. Vol. 2: Medical laboratory technologies. St. Petersburg: Intermedica, 1999; p. 792.
20. Stalnaya ID, Garishvili TG, 1977. Method of determination of malonic dialdehyde using thiobarbituric acid. In: Modern methods in biochemistry. M.: Medicine, 1977; p. 66–8.
21. Костюшок Н. Я., Павлюченко И. И., Иванова Л. А., Прозоровская Ю. И. Роль гена второй фазы системы биотрансформации ксенобиотиков gstp1 (ile105val) в развитии диабетической нефропатии у пациентов с сахарным диабетом 2-го типа. Современные проблемы науки и образования. 2022; 4. Доступно по ссылке: https://science-education.ru/ru/article/view?id=31902.
22. National Center for Biotechnology Information: Single Nucleotide Polymorphism Database (1998). Available from: https://www.ncbi.nlm.nih.gov/snp/.
23. Stoian A, Bănescu C, Bălaşa RI, Moţăţăianu A, Stoian M, Moldovan VG, et al. Influence of GSTM1, GSTT1, and GSTP1 polymorphisms on type 2 diabetes mellitus and diabetic sensorimotor peripheral neuropathy risk. Disease markers. 2015; 2015: 638693.
24. Agrawal S, Tripathi G, Khan F, Sharma R, Baburaj VP, et al. Relationship between GSTs gene polymorphism and susceptibility to end stage renal disease among North Indians. Renal failure. 2007; 29 (8): 947–53.
25. Vojtková J, Ďurdík P, Čiljaková M, Michnová Z, Turčan T, Babušíková E. The association between glutathione S-transferase T1 and M1 gene polymorphisms and cardiovascular autonomic neuropathy in Slovak adolescents with type 1 diabetes mellitus. Journal of Diabetes and its Complications. 2013; 27 (1): 44–8.
26. Перова Н. В., Драпкина О. М. Триглицериды: структура, метаболизм, физиологические функции. М.: ООО «Видокс», 2021; 192 с.