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Role of the plasma level of plasminogen activator inhibitor type-1 (PAI-1) and genetic polymorphism of *PAI-1* gene in patients with ischemic heart disease in Uzbek population

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Abstract

Aim – to study the distribution of allele frequencies of the polymorphic marker 4G(-675)5G of the *PAI-1* gene among patients with coronary heart disease and individuals with risk factors for the development of coronary heart disease.

Material and methods. The study included 63 patients with diagnosed coronary heart disease, especially with stable angina (48 men and 15 women) hospitalized in the 1st Cardiology Department of the Multidisciplinary Clinic of the Tashkent Medical Academy. The average age of patients was 56.8±6.40 years (42-66 years old). The state of hypercoagulability was assessed by measures of polymorphism gene of *PAI-1* and plasma level of PAI-1.

Results. The assessment of the frequency of various variants of the 4G(-675)5G polymorphic marker of the *PAI-1* gene showed that differences in the distribution of the 5G/5G, 4G/5G, 4G/4G genotypes depending on the functional class of coronary artery disease are not statistically significant, since the chi-square test value was χ^2=1.85 (p>0.05). Based on the obtained results, it can be assumed that the presence of hetero- and homozygous variants of the 4G allele of the *PAI-1* gene does not affect the severity of the disease, in particular, the functional class of stable angina.

Conclusion. The 4G/5G polymorphism of the *PAI-1* gene was significantly associated with the risk of coronary heart disease in the Uzbek population. When stratified by angina functional class, the results showed that the 4G/5G polymorphism is associated with an increased risk of coronary heart disease and higher plasma PAI-1 levels.

Keywords: ischemic heart disease, plasminogen activator inhibitor, genetic polymorphism, hypercoagulation, risk factors.

Conflict of interest: nothing to disclose.

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Роль уровня ингибитора активатора плазминогена-1 (PAI-1) в плазме и генетического полиморфизма гена *PAI-1* у пациентов с ишемической болезнью сердца узбекской популяции

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Аннотация

Цель – изучение распределения частот аллелей полиморфного маркера 4G(-675)5G гена *PAI-1* среди пациентов с ишемической болезнью сердца (ИБС) и лиц с факторами риска развития ИБС.

Материал и методы. В исследование было включено 63 пациента с диагнозом «ишемическая болезнь сердца» (ИБС), а именно со стабильной стенокардией (48 мужчин и 15 женщин), госпитализированных в первое

кардиологическое отделение многопрофильной клиники Ташкентской медицинской академии. Средний возраст пациентов составил 56,8±6,40 года (от 42 до 66 лет). Состояние гиперкоагуляции устанавливалось по анализу полиморфизма гена *PAI-1* и уровню PAI-1 в плазме крови.
Результаты. Оценка встречаемости различных вариантов полиморфного маркера 4G(-675)5G гена *PAI-1* показала, что различия в распределении генотипов 5G/5G, 4G/5G, 4G/4G в зависимости от функционального класса ИБС не являются статистически значимыми, поскольку значение критерия хи-квадрат составило χ^2=1,85 (p>0,05). На основании полученных результатов можно предположить, что наличие гетеро- и гомозиготных вариантов аллеля 4G гена *PAI-1* не влияет на тяжесть заболевания, в частности на функциональный класс стабильной стенокардии.
Выводы. Полиморфизм 4G/5G гена *PAI-1* был достоверно ассоциирован с риском ишемической болезни сердца в узбекской популяции. При стратификации по функциональному классу стенокардии результаты показали, что полиморфизм 4G/5G связан с повышенным риском ИБС и более высокими уровнями PAI-1 в плазме.
Ключевые слова: ишемическая болезнь сердца, ингибитор активатора плазминогена, генетический полиморфизм, гиперкоагуляция, факторы риска.
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ССЗ – сердечно-сосудистое заболевание; ИБС – ишемическая болезнь сердца; ФК – функциональный класс; СС – стабильная стенокардия; ИМ – инфаркт миокарда; ТДР – тревожно-депрессивное расстройство; ГХС – гиперхолестеринемия.

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INTRODUCTION

According to a 2022 report from the State Statistics Committee of the Republic of Uzbekistan, the total number of deaths between January and December was 172,100. Among these, diseases of the circulatory system accounted for 55.5% of all registered mortality (source: State Statistics Committee of the Republic of Uzbekistan, 2022). Young survivors of arterial thrombotic events face higher mortality and morbidity rates compared to the general population, primarily due to an elevated risk of cardiovascular recurrences [1,2]. These findings emphasize the urgent need for novel diagnostic and therapeutic strategies for cardiovascular disease. This is particularly critical for younger patients, as the impact on their quality of life and the resulting socioeconomic burden are magnified by their longer life expectancy.

It is commonly known that hypercoagulability is a significant risk factor for myocardial ischemia. While hypercoagulability increases the risk of arterial thrombosis, the magnitude of this effect may vary across different clinical manifestations of arterial disease [3]. Platelets play a pivotal role in thrombus formation and propagation, making them the primary target of antithrombotic therapy in arterial disease [4]. Nevertheless, arterial thrombus formation is also driven by the activation of the plasma coagulation cascade [5].

Fibrinolysis is a process governed by the complex interplay of various plasminogen activators and inhibitors, forming an enzymatic cascade that ultimately leads to fibrin degradation. The plasminogen activator system is pivotal in numerous physiological and pathological contexts. Plasminogen activator inhibitor-1 (PAI-1), a member of the serine protease inhibitor (serpin) superfamily, is the primary physiological inhibitor of both tissue-type (tPA) and urokinase-type (uPA) plasminogen activators, the enzymes responsible for converting plasminogen into its active form, plasmin [6]. Plasminogen is mainly found in the plasma and is synthesized predominantly in the liver. Its conversion into plasmin is facilitated by two main activators: the urokinase-type plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA). The actions of these activators are tightly controlled by specific plasminogen activator inhibitors (PAIs), the most important one being plasminogen activator inhibitor type 1 (PAI-1), initially characterized as the endothelial cell-derived inhibitor [7]. Elevated PAI-1 expression in vivo inhibits fibrinolysis, leading to abnormal fibrin deposition and subsequent tissue injury [8]. PAI-1 levels are influenced by several factors, including age, renal insufficiency, systolic blood pressure, insulin resistance, obesity, and triglyceride levels, but show no association with cholesterol levels or smoking [8]. Both PAI-1 and TPA antigen levels are predictive of cardiovascular disease (CVD) events, even after adjustment for established risk factors. Furthermore, a serial increase in PAI-1 is associated with a progressively higher risk. These findings underscore the importance of the fibrinolytic system in the pathogenesis of CVD.

Additionally, there is evidence that PAI-1 plasma concentration is influenced by genetic variation. Several genetic polymorphisms have been identified at the *PAI-1* gene locus on chromosome 7 [10, 11]. Among these, a guanine insertion/deletion polymorphism known as −675 4G/5G, located in the promoter region, has been reported in numerous studies to be associated with PAI-1 plasma levels [12]. Of the known polymorphic sites in the *PAI-1* gene region, only the −675 4G/5G insertion/deletion polymorphism is suspected of having functional significance [13,14]. This polymorphism is considered an independent risk factor for ischemic heart disease and/or acute myocardial infarction (MI). A large cohort study (n=1179) demonstrated that the 4G/4G genotype is more common in first-degree relatives of patients with

Drug name	Patients, n=63
Acetylsalicylic acid 75 mg 100 mg	 8 (12,6%) 17 (26,9%)
Clopidogrel, 75 mg	38 (60,3%)
ACE inhibitors	19 (45,2%)
Angiotensin-II receptor blockers	12 (28,5%)
Beta-blockers	35 (55,5%)
Calcium channel blockers	38 (60,3%)
Statins	28 (44,4%)
Diuretics	17 (26,9%)
Nitrates	14 (22,2%)

Table 1. *Drug therapy of patients included in the study*
Таблица 1. *Фармакологическая терапия включенных в исследование пациентов*

coronary heart disease than in individuals without a family history of the condition [15].

The strength of this association may vary significantly across populations, and some ethnic groups may show a weak or absent link. This variability is likely due to the complex interaction of population-specific genetic and environmental factors.

The relationship between the PAI-1 4G/5G polymorphism and traditional ischemic heart disease risk factors in patients with stable coronary artery disease remains a subject of ongoing research. Al-Wakeel et al. found no significant association between the PAI-1 4G/5G polymorphism and coronary artery disease risk in an Egyptian population [16].

AIM

To study the distribution of allele frequencies of the polymorphic marker 4G(-675)5G of the PAI-1 gene among patients with coronary heart disease and individuals with risk factors for the development of coronary heart disease.

MATERIAL AND METHODS

Our study included 63 patients diagnosed with ischemic heart disease, specifically stable angina, who were hospitalized in the I Cardiology Department of the Multidisciplinary Clinic of Tashkent Medical Academy. The patient group consisted of 48 men and 15 women, with a mean age of 56.8 ± 6.40 years (range 42-66 years). The mean age was 56.4 ± 6.60 years for men and 58.0 ± 5.52 years for women. The control group comprised 65 apparently healthy individuals.

The diagnosis of stable angina was established according to the ischemic heart disease classification adopted at the IV Congress of Cardiologists (2000). The functional class (FC) of stable angina was determined using the Canadian Cardiovascular Society classification and exercise stress testing (bicycle ergometry).

Exclusion criteria: unstable angina, acute or chronic heart, kidney or liver failure, arrhythmia, acute cerebrovascular accident, diabetes mellitus associated myocardial infarction, malignant neoplasia.

To address the study objectives, all patients were divided into two groups based on the functional class of stable angina. The first group included 24 patients (38.1%) with FC II stable angina, while the second group consisted of 39 patients (61.9%) with FC III stable angina.

Hypercoagulability was assessed by measuring the *PAI-1* gene polymorphism and plasma PAI-1 levels. Venous blood samples (3 mL) were collected from the cubital vein for genetic analysis. DNA analysis of the *PAI-1* gene (4G/5G) was performed using multiplex PCR on CG-1-96 ("Corbett Research", Australia) and 2720 ("Applied Biosystems", USA) thermal cyclers with reagent kits from "Geno Technology" according to the manufacturer's protocol. Plasma PAI-1 levels were measured using ELISA with commercially available kits.

Additionally, our study evaluated major IHD risk factors including obesity, smoking, and anxiety-depressive disorder (ADD). Obesity was assessed using Quetelet's index. Smoking status was evaluated with the Fagerström test, while anxiety-depressive disorder was measured using the Hospital Anxiety and Depression Scale (HADS). The patients included in the study received pharmacological therapy (**Table 1**).

RESULTS

This study is the first to examine the frequency distribution of PAI-1 gene genotypes and their association with major IHD risk factors in Uzbek patients with stable angina. Patients of Uzbek nationality with stable angina were selected to identify additional prognostic criteria. To clarify the pathogenetic significance of *PAI-1* gene polymorphism across different functional classes of stable angina, PCR analysis of the PAI-1 gene was performed in the study population.

During genotyping of 63 IHD patients with stable angina, 2 patients (3.3%) were excluded from the study due to blood storage errors. The resulting data on allele and genotype frequencies of the PAI-1 4G/5G polymorphism in the specified stable angina groups are presented in **Tables 2-3**.

The population distribution of *PAI-1* gene alleles was investigated in 61 IHD patients (122 chromosomes). The frequency of the 4G allele in this group was 45.1% (n=55). We identified 13 homozygous and 29 heterozygous carriers of this allele. The frequency of the 5G allele in the main patient group was 54.9% (n=67). This allele in homozygous state was found in 19 individuals. The distribution patterns of *PAI-1* gene allele genotypes in IHD patients are visualized on the PCR product electrophoregram and presented in **Figure 1**.

Group	N	Allele frequency				Genotype distribution frequency					
		5G		4G		5G/5G		G5/G4		4G/4G	
		N	%	N	%	N	%	N	%	N	%
Main group (n=61)	61	67	54,9	55	45,1	19	31,1	29	47,5	13	21,3

Table 2. *Frequency of distribution of alleles and genotypes of G5/G4 polymorphism of PAI gene in group of patients with IHD and healthy individuals*
Таблица 2. *Частота распределения аллелей и генотипов полиморфизма G5/G4 гена PAI в группе пациентов с ИБС и здоровых пациентов*

Group	Genotype frequency distribution			Total	χ^2	P
	5G/5G	G5/G4	4G/4G			
Main group (n=61)	19	29	13	n=61	7,00	0,03
Expected frequency (n=61)	25,66	26,14	9,2			
Control group (n=65)	34	25	6	n=65		
Expected frequency (n=65)	27,34	27,86	9,8			
Total	53	54	19	n=126		

Notes: χ^2 = AMOUNT (observed - expected)2/ expected = ((19-25,66)2/25,66)+((29-26,14)2/26,14)+((13-9,2)2/9,2)+((34-27,34)2/27,34)+ ((25-27,86)2/27,86)+((6-9,8)2/9,8)=7,00.
Degree of freedom (df)=(number of columns-1)(Number of lines-1)=(3-1)*(2-1)=2*
Our indicator is in the area p<0.05, calculated with the help of Microsoft Excel p=0.03.

***Table 3.** Distribution of frequencies of genotypes under Hardy-Weinberg's law. Expected and observed frequencies of distribution of genotypes in the main and control groups*

Примечания: χ^2 = AMOUNT (набл. – ожид.)2 / ожид. = ((19-25,66)2/25,66)+((29-26,14)2/26,14)+((13-9,2)2/9,2)+((34-27,34)2/27,34)+((25-27,86)2/27,86)+ ((6-9,8)2/9,8)=7,00.
*Степень свободы (df) = (кол-во столбцов - 1) * (Кол-во строк - 1) = (3-1)*(2-1)=2*
Показатель находится в зоне p<0,05, рассчитан с помощью Microsoft Excel, p=0.03.

***Таблица 3.** Распределение частот генотипов в соответствии с законом Харди – Вайнберга. Наблюдаемые и ожидаемые частоты генотипов в основной и контрольной группах*

For this polymorphism in patients with stable angina and conditionally healthy donors, the observed genotype distribution corresponded to theoretical expectations and showed relatively high observed (Hobs) and expected (Hexp) heterozygosity under Hardy-Weinberg equilibrium (p<0.05). Based on the Chi-square statistic (χ^2=7.00), statistically significant differences in the distribution of genotypes 5G/5G, 5G/4G, and 4G/4G were established between patients in the main group and probands in the control group (p<0.05).

Genetic analysis of Uzbek individuals revealed that the 4G allele of the *PAI-1* gene occurs more frequently in IHD patients than in healthy controls. The homozygous and heterozygous states of this allele were observed in 21.3% and 47.5% of patients respectively, compared to 9.2% and 38.5% in the control group. These findings indicate the potential influence of the PAI-1 4G allele, particularly in heterozygous state, on IHD development.

The 5G/5G genotype, considered favorable, was reliably more frequent in the group of healthy controls: in 34 individuals (52.3%) vs. 19 patients (31.1%) in the IHD group. Thus, the identified differences are statistically significant and are not random (p<0.05).

The distribution of the frequencies of the polymorph marker 4G(-675)5G of the *PAI-1* gene in the IHD patient groups depending on the stable angina functional class is presented in **Table 4**.

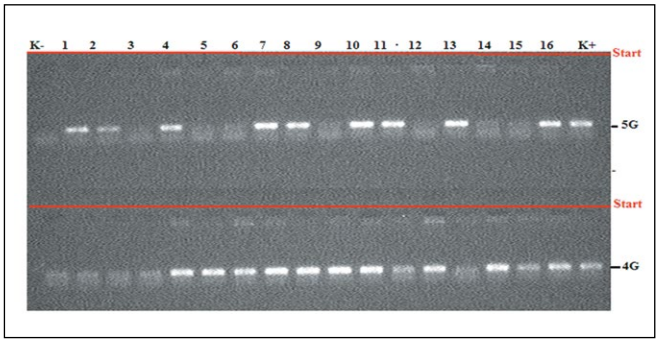

***Figure 1.** Electrophoregram of PCR products of G5/G4 polymorphism of PAI gene.*

***Рисунок 1.** Электрофореграмма продуктов ПЦР полиморфизма G5/G4 гена PAI.*

Analysis of IHD patient subgroups stratified by functional class revealed differences in allele and genotype frequency distribution of the 4G(-675)5G polymorphism of the *PAI-1* gene (rs1799768). Among 24 patients with FC II stable angina, genotype distribution was as follows: 4G/4G – 4 patients (16.7%), 4G/5G – 14 patients (58.3%), and 5G/5G – 6 patients (25.0%). In contrast, among 37 patients with FC III stable angina, the distribution was as follows: 4G/4G – 9 patients (24.3%), 4G/5G – 15 patients (40.5%), and 5G/5G – 13 patients (35.1%).

Assessment of genotype distribution for the 4G(-675)5G polymorphism in the PAI-1 gene established that differences in 5G/5G, 4G/5G, and 4G/4G genotype distribution across cardiovascular disease functional classes were not statistically significant (χ^2=1.85, p>0.05). These results suggest that the presence of heterozygous and homozygous 4G alleles of the PAI-1 gene does not influence disease severity as measured by stable angina functional class.

When genotyping the studied groups for the frequency of the favorable homozygous 5G/5G genotype of the *PAI-1* gene, a low frequency of this genotype was recorded in the group of patients with CVD at 31.1% of cases, compared to a statistically significant higher occurrence of the 5G/5G genotype at 52.3% of cases among healthy individuals. The occurrence of the heterozygous polymorphic genotype 4G/5G of the PAI-1 gene in patients with CVD was statistically significantly higher at 47.5% of cases compared to 38.5% in the control group (p<0.05), indicating the probability of high prevalence of this genotype among persons of Uzbek nationality.

Correlation of IHD risk factors and PAI-1 gene polymorphism

This study is the first to examine the frequency of mutagen genotypes of the *PAI-1* gene and to clarify their association with major IHD risk factors in cardiovascular disease development.

No clear indications of synergistic interaction effects were observed between the PAI-1 4G/5G polymorphism and the environmental exposures considered (smoking, physical inactivity, overweight, diabetes mellitus,

Group	PAI-1 gene, identified genotypes, n (%)			Total
	5G/5G	4G/5G	4G/4G	
Stable angina, II FC	6 (25%)	14 (58,3%)	4 (16,7%)	24 (39,4%)
Stable angina, III FC	13 (35,1%)	15 (40,5%)	9 (24,3%)	37 (60,6%)

Table 4. *Distribution of frequencies of genotypes of a polymorphic marker 4G(-675)5G of PAI-1 gene in the main group*

Таблица 4. *Распределение частот генотипов полиморфного маркера 4G(-675)5G гена PAI-1 в основной группе*

Group	PAI-1, gene, identified genotypes, N			Total	χ^2	P
	5G/5G	4G/5G	4G/4G			
Stable angina, II FC	6	14	4	n=24	1,85	0,39
Expected frequency	7,48	11,41	5,11			
Stable angina, III FC	13	15	9	n=37		
Expected frequency	11,52	17,59	7,89			
Total	19	29	13	n=61		

Notes: χ^2 =AMOUNT (observed - expected)2/observed = 1,85. Degree of freedom (df)=(Number of columns-1)(Number of lines-1)=(3-1)*(2-1)=2. On the p<0.05 significance level, with 2nd degree of freedom, the number in the table must be equal to 5,99. But we have 1,85. Our indicatorpis in the areap>0.05, calculated in calculations with the help of Microsoft Excel p=0.39.*

Table 5. *Distribution of frequencies of genotypes of a polymorphic marker 4G(-675)5G of PAI-1 gene in subgroups of IHD patients*

Примечания: χ^2 =AMOUNT (набл. – ожид.)2/ожид. = 1,85. Степень свободы (df)=(кол-во столбцов-1)(кол-во строк - 1)=(3-1)*(2-1)=2. При уровне значимости p<0,05 со II степенью свободы табличное значение должно быть равным 5,99. В нашем случае данная величина равна 1,85. Показатель находится в зоне p>0,05, рассчитан с помощью Microsoft Excel, p=0,39.*

Таблица 5. *Частота распределения генотипов полиморфного маркера 4G(-675)5G гена PAI-1 в подгруппах пациентов с ИБС*

hypercholesterolemia, hypertension, elevated C-reactive protein, and hypertriglyceridemia) [17].

Given the multifactorial nature of IHD pathogenesis, i.e., the presence of multiple risk factors leading to disease development and progression, we analyzed the association of the 4G(-675)5G polymorphism of the *PAI-1* gene with clinical and anamnestic data such as smoking, concomitant arterial hypertension, obesity, hypercholesterolemia, and hypodynamia in the studied groups. The analysis of genotyping for favorable (5G/5G), polymorphic (4G/5G), and mutagen (4G/4G) genotypes of the *PAI-1* gene depending on the presence of various IHD risk factors is presented in **Table 6**.

The analysis of the relationship between non-modified and modified risk factors with 5G/5G, 4G/5G and 4G/4G genotypes of the *PAI-1* gene established that genotyping between groups did not differ significantly by age, while hereditary burden for IHD was more frequently observed in heterozygous polymorphic genotype (61.5%) and also in homozygous 4G/4G genotype (65.5%) of IHD patients. Among patients of the main group with 4G/4G genotype, obesity of varying degrees was recorded in 46.2% of cases, with 4G/5G genotype in 37.9%, and with 5G/5G in 26.3%, therefore more frequently in patients with SA with obesity including third degree, the 4G/4G genotype was identified.

The association of the 4G/4G genotype with smoking was among the most significant findings: among patients with

Parameter	IHD patients (n=61)		
	4G/4G genotype n=13 (21,3)	4G/5G genotype n=29 (47,5)	5G/5G genotype n=19 (31,1)
Age, years	59,4	56,7	57,6
Hereditary burden	8 (61,5)	19 (65,5)	9 (47,4)
Obesity degree (kg/m2): Normal BMI Excess weight 1 degree 2 degree 3 degree	 1 (7,6) 6 (46,2) 4 (31) 1 (7,6) 1 (7,6)	 3 (10,3) 15 (51,7) 5 (17,2) 6 (20,7) 0	 5 (26,3) 9 (47,4) 3 (15,8) 2 (10,5) 0
Smoking, n (%)	8 (61,5)*	9 (31,0)	5 (26,3)
Arterial hypertension, n (%) Subclinical manifestations Arterial hypertension, n (%), Clinical manifestations	 3 (23,1) 9 (69,3)	 7 (24,1) 21 (72,4)	 2 (10,5) 12 (63,1)
Hypercholesterolemia	11 (84,6)*	18 (62,1)	9 (47,4)

Notes: P<0.001.

Table 6. *The characteristic of RF at patients with different genotypes of a polymorphic marker 4G(-675)5G of gene PAI-1*

Примечания: P<0.001.

Таблица 6. *Характеристика факторов риска у пациентов с различными генотипами полиморфного маркера 4G(-675)5G гена PAI-1*

the heterozygous genotype, smokers accounted for 61.5% of cases, compared to 31% and 26.3% of smokers among patients with the 4G/4G genotype and homozygous wild-type 5G/5G genotype, respectively. The presence and severity of concomitant arterial hypertension in the main patient group were highest in individuals with the 4G/4G genotype (92.4%) and 4G/5G genotype (96.5%), while among patients with the 5G/5G genotype, arterial hypertension was detected less frequently in 73.6% of cases. Additionally, we measured plasma PAI-1 levels and obtained the following results (**Table 7**).

The mean PAI-1 level in patients with the 5G/5G genotype was 33.3 ± 2.07 ng/mL, while in those with the 4G/4G genotype it was 72.0 ± 7.6 ng/mL, a statistically significant difference (P < 0.001). Plasma PAI-1 levels were significantly higher in patients with FC III stable angina compared to those with FC II. All patient groups were comparable in age, lipid profile, and coagulogram parameters. Furthermore, patients carrying the 4G/4G genotype with FC III stable angina demonstrate an increased risk of elevated PAI-1 levels.

DISCUSSION

Cardiovascular disease involving disturbances in the haemostatic system may lead to thrombotic complications with clinical manifestations such as acute myocardial infarction (AMI) and stroke [18]. Some individuals demonstrate an

Group	PAI-1 gene, identified genotypes		
	5G/5G	4G/5G	4G/4G
PAI-1 level in stable angina patients (ng/mL)	33,3±2,07*	54,8±3,47	72,0±7,6*

*Примечания: *P<0,001.*

Table 7. *Plasma level of PAI-1 depending of genotypes of PAI-1 gene in patients with ischemic heart disease*

Таблица 7. *Уровень PAI-1 в плазме в зависимости от полиморфизма гена PAI-1 у пациентов с ИБС*

*Notes: *P<0.001.*

abnormal propensity to develop venous or arterial thrombosis, experiencing thromboembolic events relatively early in life or suffering recurrent events [19]. Based on these findings, we aimed to investigate hemostasis system alterations at the genetic level in patients with stable coronary artery disease. While well-defined associations have been established between hypercoagulable states and thrombosis in the venous system, determining causative or contributing roles of these same thrombophilic conditions in arterial thrombosis has proven considerably more challenging [20].

Our findings suggest that increased coagulation tendency, associated with high plasma PAI-1 levels and polymorphic genotypes of the *PAI-1* gene (particularly 4G/4G), elevates the risk of cardiovascular events in patients with stable ischemic heart disease. The coagulation assessment included fibrinolytic markers of hypercoagulability, weighted by acute myocardial ischemia risk, as these markers proved primary in stable coronary heart disease where hypercoagulability plays a major role. Several studies have identified PAI-1 as an informative marker for assessing hypercoagulability in acute coronary syndrome patients. The first study demonstrating association between the PAI-1 4G allele and higher myocardial infarction risk in 100 young Swedish men (35-45 years) was published in 1995 [21]. Individuals homozygous for the 4G allele exhibit higher plasma PAI-1 levels than those homozygous for the 5G allele. The molecular mechanism underlying these allelic differences in PAI-1 synthesis was determined by examining allele binding capacity: both alleles bind to gene transcription activators, but the 5G allele additionally contains a binding site for a transcriptional repressor [21]. Various studies report approximately 25% higher PAI-1 levels in 4G/4G genotype carriers compared to 5G/5G carriers. Compared to the 5G allele, 4G allele carriers demonstrate higher PAI-1 concentrations and thrombosis risk. Both heterozygous and homozygous 4G allele carriers show elevated plasma PAI-1 levels [22] and increased risk of acute coronary syndromes [23].

Several studies have demonstrated the relationship between plasminogen activator inhibitor-1 levels and both stable and unstable coronary artery disease [23, 24]. In patients with myocardial infarction, a clear association exists between PAI-1 levels and response to fibrinolytic therapy, as confirmed by multiple studies [25]. However, data remain limited regarding the association between stable ischemic heart disease and both PAI-1 levels and its polymorphisms. In our study, no differences were observed between groups in terms of age or gender. Plasma PAI-1 levels and 4G/4G genotype frequency were significantly elevated, particularly in patients with FC III stable angina compared to FC II. Furthermore, patients with the 4G/4G genotype showed significantly higher plasma PAI-1 levels than those with the 5G/5G genotype [26]. A 2022 meta-analysis indicated that the PAI-1 4G>5G SNP was associated with decreased IHD risk in the overall population and in Asian, Caucasian, and Arab subgroups. In contrast, the PAI-1 gene -844 G>A polymorphism demonstrated no significant association with IHD susceptibility [27].

Our genetic analysis revealed that individuals with the 4G/4G genotype exhibit elevated plasma concentrations of PAI-1. This finding aligns with in vitro studies demonstrating that the 4G allele is associated with enhanced transcriptional activity of the PAI-1 promoter compared to the 5G allele, which creates an additional repressor-binding site in 5G carriers [28].

This finding holds clinical significance, as fibrinolysis plays a crucial role in the pathogenesis of both acute myocardial infarction and stable coronary artery disease.

CONCLUSION

The 4G/5G polymorphism of the *PAI-1* gene was significantly associated with the risk of coronary heart disease in the Uzbek population. When stratified by stable angina functional class, the results showed that the 4G/5G polymorphism is associated with an increased risk of ischemic heart disease and higher plasma PAI-1 levels.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval: The study was approved by the LEC of TMA (protocol No.85 dated 27.05.2020).	***Этическая экспертиза.*** Проведение исследования одобрено ЛЭК Ташкентской медицинской академии (протокол №85 от 27 мая 2020 г.).
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Kadirova N.A.: study design and concept, data collection; statistical analysis; wring of the manuscript; Nurillaeva N.M.: study concept, design and supervision. Petrova V.B., Lapteva E.S., Shumkov V.A.: review and editing. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Кадирова Н.А. – разработка концепции и дизайна исследования, сбор данных; проведение статистического анализа; написание текста. Нуриллаева Н.М. – руководство, разработка концепции и дизайна исследования. Петрова В.Б., Лаптева Е.С., Шумков В.А. – рецензирование и редактирование. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

REFERENCES / ЛИТЕРАТУРА

1. Hankey GJ. Stroke in young adults: implications of the long-term prognosis. *JAMA*. 2013;309(11):1171-2. DOI: 10.1001/jama.2013.2319

2. Rutten-Jacobs LC, Maaijwee NA, Arntz RM, et al. Long-term risk of recurrent vascular events after young stroke: the FUTURE study. *Ann Neurol*. 2013;74(4):592-601. DOI: 10.1002/ana.23953

3. Maino A, Rosendaal FR, Algra A, et al. Hypercoagulability Is a Stronger Risk Factor for Ischaemic Stroke than for Myocardial Infarction: A Systematic Review. *PLoS One*. 2015;10(8):e0133523.

DOI: 10.1371/journal.pone.0133523

4. Liu M, Zhao X. Platelet Glycoprotein VI: A Novel Target for Antithrombotic Therapy in Cardiovascular Disease. *Cardiology Discovery*. 2024;4(4):309-318. DOI: 10.1097/CD9.0000000000000137

5. Yamashita A, Asada Y. Underlying mechanisms of thrombus formation/growth in atherothrombosis and deep vein thrombosis. *Pathol Int*. 2023;73(2):65-80. DOI: 10.1111/pin.13305

6. Urano T, Suzuki Y, Iwaki T, et al. Recognition of Plasminogen Activator Inhibitor Type 1 as the Primary Regulator of Fibrinolysis. *Curr Drug Targets*. 2019;20(16):1695-1701. DOI: 10.2174/1389450120666190715102510

7. Griemert EV, Schwarzmaier SM, Hummel R, et al. Plasminogen activator inhibitor-1 augments damage by impairing fibrinolysis after traumatic brain injury. *Ann Neurol*. 2019;85(5):667-680. DOI: 10.1002/ana.25458

8. Tofler GH, Massaro J, O'Donnell CJ, et al. Plasminogen activator inhibitor and the risk of cardiovascular disease: The Framingham Heart Study. *Thromb Res*. 2016;140:30-35. DOI: 10.1016/j.thromres.2016.02.002

9. Nordt TK, Lohrmann J, Bode C. Regulation of PAI-1 expression by genetic polymorphisms. Impact on atherogenesis. *Thromb Res*. 2001;103(1):1-5. DOI: 10.1016/s0049-3848(01)00292-4

10. Li XN, Grenett HE, Benza RL, et al. Genotype-specific transcriptional regulation of PAI-1 expression by hypertriglyceridemic VLDL and Lp(a) in cultured human endothelial cells. *Arterioscler Thromb Vasc Biol*. 1997;17(11):3215-23 DOI: 10.1161/01.atv.17.11.3215

11. Humphries SE, Panahloo A, Montgomery HE, et al. Gene-environment interaction in the determination of levels of haemostatic variables involved in thrombosis and fibrinolysis. *Thromb Haemost*.1997;78(1):457-461. PMID: 9198196

12. Mansfield MW, Stickland MH, Grant PJ. Environmental and genetic factors in relation to elevated circulating levels of plasminogen activator inhibitor-1 in Caucasian patients with non-insulin-dependent diabetes mellitus. *Thromb Haemost*. 1995;74(3):842-847. PMID: 8571308

13. Dawson S, Hamsten A, Wiman B, et al. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator inhibitor-1 activity. *Arterioscler Thromb*. 1991;11(1):183-190. DOI: 10.1161/01.atv.11.1.183

14. Margaglione M, Cappucci G, Colaizzo D, et al. The PAI-1 gene locus 4G/5G polymorphism is associated with a family history of coronary artery disease. *Arterioscler Thromb Vasc Biol*. 1998;18(2):152-156. DOI: 10.1161/01.atv.18.2.152

15. Zhang H, Dong P, Yang X, Liu Z. Plasminogen activator inhibitor-1 4G/5G polymorphism is associated with coronary artery disease risk: a meta-analysis. *Int J Clin Exp Med*. 2014;7(10):3777-88. PMID: 25419432

16. Al-Wakeel H, Sewelam N, Khaled M, Akram A. Impact of PAI-1 4G/5G and C > G Polymorphisms in Acute ST Elevation Myocardial Infarction and Stable Angina Patients: A Single Center Egyptian Study. *Egyptian Journal of Medical Human Genetics*. 2018;19(4):325-331. DOI: 10.1016/j.ejmhg.2018.05.003

17. Boncoraglio GB, Bodini A, Brambilla C, et al. An effect of the PAI-1 4G/5G polymorphism on cholesterol levels may explain conflicting associations with myocardial infarction and stroke. *Cerebrovasc Dis*. 2006;22(2-3):191-5. DOI: 10.1159/000093604

18. Bratseth V, Pettersen AÅ, Opstad TB, et al. Markers of hypercoagulability in CAD patients. Effects of single aspirin and clopidogrel treatment. *Thrombosis J*. 2012;10:12. DOI: 10.1186/1477-9560-10-12

19. World Health Organization: Inherited Thrombophilia: Report of a Joint WHO. International Society of Thrombosis and Haemostasis (ISTH) Meeting. Geneva: World Health Organization. 1995. URL: https://www.semanticscholar.org/paper/Inherited-thrombophilia%3A-memorandum-from-a-joint-on-Memorandums/7945c86643880598ad84d8ab85c14bdae7b4bb5d

20. Reitsma PH, Rosendaal FR. Past and future of genetic research in thrombosis. *J Thromb Haemost*. 2007;5(1):264-269.

DOI: 10.1111/j.1538-7836.2007.02502.x

21. Erriksson P, Kallin B, van't Hooft FM, et al. Allele-specific increase in basal transcription of plasminogen-activator inhibitor 1 gene is associate with myocardial infarction. *Proc Natl Acad Sci USA*. 1995;92(6):1851-5. DOI: 10.1073/pnas.92.6.1851

22. Iwai N, Shimoike H, Nakamura Y, et al. The 4G/5G polymorphism of the plasminogen activator inhibitor gene is associated with the time course of progression to acute coronary syndromes. *Atherosclerosis*. 1998;136(1):109-114. DOI: 10.1016/s0021-9150(97)00191-3

23. Iacoviello L, Burzotta F, Di Castelnuovo A, et al The 4G/5G polymorphism of PAI-1 promoter gene as a risk factor for myocardial infarction: a meta-analysis. *Tromb Haemost*. 1998;80(6):1029-1030. PMID: 9869181

24. Hamsten A, Wiman B, de FU, Blomback M. Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. *N Engl J Med*. 1985;313(25):1557-63. DOI: 10.1056/NEJM198512193132501

25. Hamsten A, Blombuck M, Wiman B, et al. Haemostatic function in myocardial infarction. *Br Heart J*. 1986;55(1):58-66.

DOI: 10.1136/hrt.55.1.58

26. Roger Lijnen H, Collen DS. Impaired fibrinolysis and the risk for coronary heart disease. *Circulation*. 1996;94(9):2052-4. DOI: 10.1161/01.cir.94.9.2052

27. Lima LM, Carvalho Md, Fonseca Neto CP, et al. PAI-1 4G/5G polymorphism and plasma levels association in patients with coronary artery disease. *Arq Bras Cardiol*. 2011;97(6):462-389.

DOI: 10.1590/s0066-782x2011005000110

28. Tabaei S, Omraninava M, Mehranfar S, et al. Plasminogen Activator Inhibitor-1 Polymorphisms and Risk of Coronary Artery Disease: Evidence From Meta-Analysis and Trial Sequential Analysis. *Biochem Genet*. 2022;60(5):1409-1445. DOI: 10.1007/s10528-021-10143-x