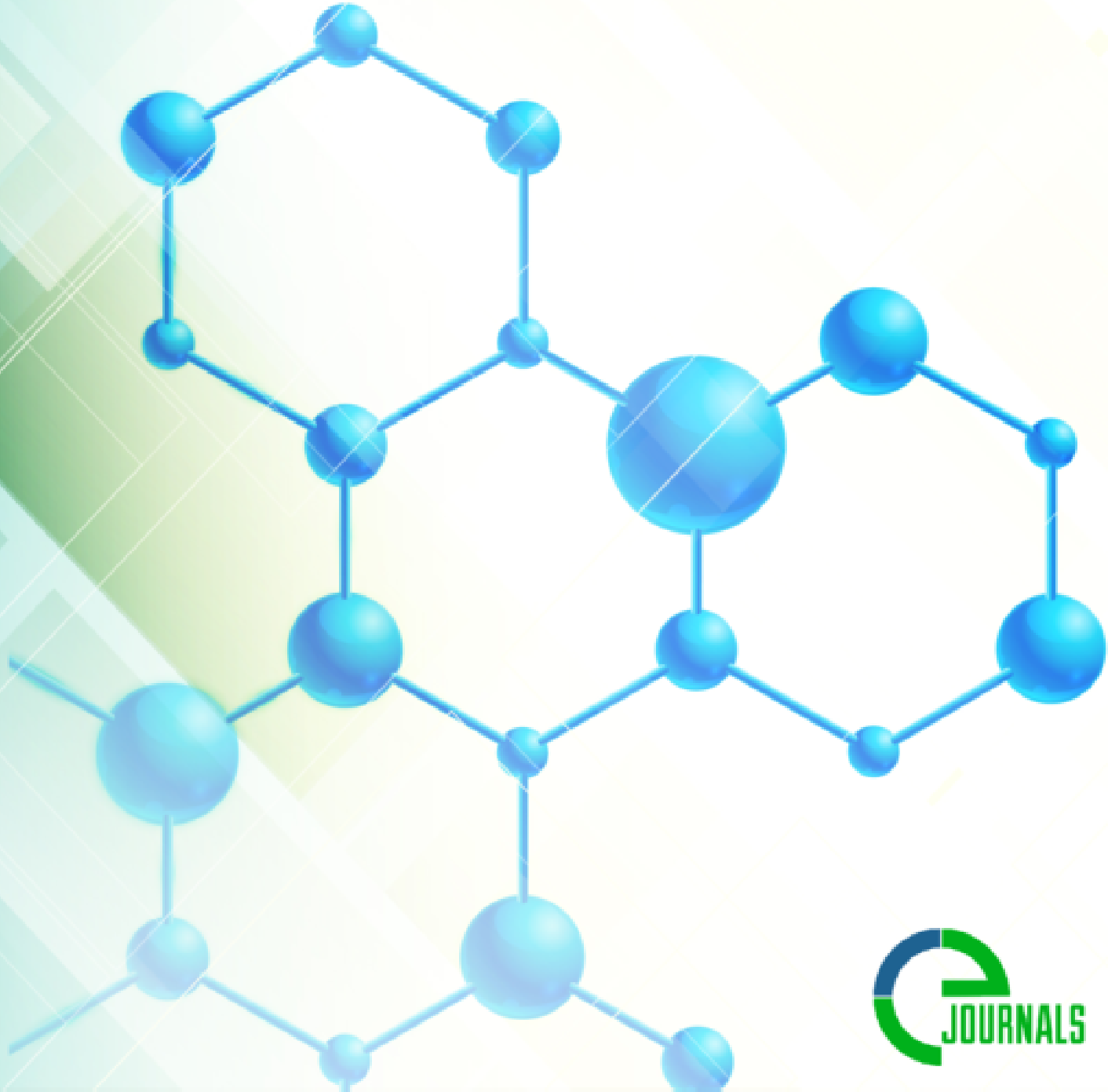
EUROPEAN JOURNAL OF

MOLECULAR MEDICINE



JOURNALS

European Journal of Molecular medicine

Volume 5, No.1, February 2025

Internet address: ttp://ejournals.id/index.php/EJMM/issue/archive
E-mail: info@ejournals.id
Published by ejournals PVT LTD
DOI prefix: 10.52325
Issued Bimonthly
Potsdamer Straße 170, 10784 Berlin, Germany

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THE SIGNIFICANCE OF POLYMORPHISM RS17576 OF THE MMP-9 GENE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AFTER MYOCARDIAL INFARCTION.

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Abstract: The aim of our study was to evaluate the role of polymorphism rs17576 MMP-9 gene in patients with type 2 diabetes mellitus after myocardial infarction (MI). In patients with type 2 diabetes mellitus after myocardial infarction 86 Uzbeks have been studied the alleles and genotypes rs17576 MMP-9 gene. According to it, according to the result of the oddsratio (OR - odds ratio), in carriers of the minor allele G the probability of developing the disease decreased by 29% (OR =0.71, 95% CI: 0.45-1.12), this means that the minor allele G has a protective effect against the development of coronary heart disease. On the other hand, the wild-type A allele of the MMP-9 gene polymorphism rs17576 increased the like-lihood ofdeveloping MI by 42% (OR = 1.42; 95% CI: 0.91-2.21) and turned out to be a significant risk factor for developing MI.

Keywords: Matrix metalloproteinases, Type 2 diabetes mellitus, Myocardial infarction, Gene

1.Introduction Matrix metalloproteinases (MMPs) are a family ofprotease enzymes consisting of more than 25 individualmembers. All MMPs have the following functional features:they degrade extracellular matrix (ECM) components;almost all of them are secreted in a latent form and requireactivation to exhibit proteolytic activity (the exception isMMP-11, which is released into the extracellular matrix asan active enzyme); all MMPs belong to zinc-containingproteins, which is located in the active center of the enzyme,and calcium is required to stabilize their tertiary structure;exhibit high functional activity at neutral pH values.Theyare regulated enzymes and are inhibited by tissue-specificinhibitors of metalloproteinases (TIMPs) [1].MMPs areidentified in the myocardium and promote changes in theECM, resulting in myocardial remodeling.Over the pastfew decades, increasing evidence from basic and clinicalresearch has demonstrated the important role of MMPs in theprogression of left ventricular hypertrophy, remodeling, andmortality after myocardial infarction (MI). In the presentstudy, we examine MMP expression after MI and its role as apossible prognostic marker [2,3]. The nature of collagen in the ECM is determined by thebalance between MMPs and TIMPs. Imbalance betweenMMPs and TIMPs is a major factor responsible forcardiomyocyte and interstitial changes after MI in infarcted and distant regions, since increased levels of some MMPs may contribute to maladaptive remodeling, making it anunfavorable prognostic factor [4,5]. One member of theMMP that may play an important role during acute MI and/orthe remodeling process after MI is MMP-9.Active MMP-9 enzymatically degrades numerous ECMsubstrates, including collagen, fibronectin and laminin, tofacilitate ECM turnover and scar formation during cardiacwound healing [6,7]. MMP-9, also known as gelatinase B orcollagenase type IV, has a molecular weight of 92 kDa and isone of the important members of MMPs that can contributeto ECM degradation [8].The aim of our study was to evaluate the role of rs17576polymorphism MMP-9 gene in patients with type 2 diabetesmellitus after myocardial infarction (MI).

2.Materials and Methods. In patients with type 2 diabetes mellitus after MI 86of Uzbek nationality have been studied the geneticdeterminants of alleles and genotypes

rs17576 of theMMP-9 gene. The control group consisted of 83 healthyindividuals- men of Uzbek nationality. The study wasperformed according to the standards of Good ClinicalPractice (Good Clinical Practice) and the Declaration ofHelsinki. The study protocol was approved by the ethicscommittees of all participating clinical centers. Beforeinclusion in the study all participants provided writteninformed consent. Study polymorphism rs17576 MMP-9gene gene was conducted using polymerase chain reaction1658 Khusanov R. A. and Nuritdinov N. A.: Studying the Polymorphism rs17576 MMP 9Gene in Patients with Type 2 Diabetes Mellitus after Myocardial Infarctionon programmable thermocycler CG-1-96 "CorbettResearch" (Australia) and 2720 "Applied Biosystems"(USA), using kits LLC "Medlab" (St. Petersburg), accordingto the manufacturer's instructions. In our work allelepolymorphism G/T894 revealed after digestion of theamplified fragment of 206 bp containing the polymorphicsite. Evaluation of deviation of the distribution of genotypesof studied polymorphisms of DNA from the canonicaldistribution of Hardy-Weinberg equilibrium was performedusing the computer program for the analysis of genetic data"GenePop" ("Genetics of Population"). To calculate the"odds ratio" (OR - odds ratio) with 95% confidenceintervals (CI-confidenceinterval), ?2 and pvalues usedstatistical package statistical software package "OpenEpi 2009, Version 2.3".3.Results The conducted studies showed that the distribution ofalleles in the main and control groups differed significantly.Thus, the percentage of the wild type A allele in the maingroup was 41.3%, which is 1.25 times higher than in thecontrol group (33.0%). The percentage of the G allele inpatients with prior MI was lower (58.7%) than in the controlgroup (67.0%) (Table 1).

Table 1. Expected and observed frequencies of distribution of alleles andgenotypes of MMP-9 gene polymorphism (rs17576) in the group of patientswith type 2 diabetes mellitus after MI

Alleles				Allele frequency	
A				0.413	
G				0.587	
Genotype	Genotype frequency				
	ObservedHo	ExpectedHe	$\chi 2$	p	df
A/A	0.198	0.179	0.03	0.298	1
A/G	0.43	0.485	0.06		
G/G	0.372	0.344	0.03		
Total	1	1	1.08		

Analysis of the distribution of rs17576 genotypes of theMMP-9 gene in donors of the control group showed that thewild-type homozygous AA genotype was detected in 13.2%of those examined, the heterozygous A/G genotype in 39.8%and the homozygous GG genotype in 47.0% of donors.At the same time, in the main group, 19.8% of patientshad a homozygous

wild-type AA genotype, 43.0% had aheterozygous A/G genotype, and 37.2% had a homozygousGG genotype. Analysis of the distribution of rs17576 genotypes of theMMP-9 gene in donors of the control group showed that thewild-type homozygous AA genotype was detected in 13.2%of those examined, the heterozygous A/G genotype in 39.8%and the homozygous GG genotype in 47.0% of donors.At the same time, in the main group, 19.8% of patientshad a homozygous wild-type AA genotype, 43.0% had aheterozygous A/G genotype, and 37.2% had a homozygousGG genotype. Similarly, the percentage of genotypes AA,AG and GG in patients with FC-2 was 17.8; 37.8 and 44.4%,respectively, while in patients with FC-3 these figures were21.9; 48.8 and 29.3%. Similarly, for the tested polymorphism, it was found thatthe level of the heterozygous genotype in the main groupof patients was slightly lower than the expected result(0.43/0.485; D = -0.113), on the other hand, the expected andobserved results for the heterozygous genotype in the controlgroup did not differ significantly (0.398/0.427; D=-0.067).According to these indicators, the difference between theobserved - empirical and expected - theoretical results in themain and control groups was not statistically significant($\chi 2<3.84$; $p>0.05$), which showed that the results determinedduring the study correspond to Hardy-Weinberg. Thus, usingthe results obtained during the study, the pathogeneticsignificance of the rs17576 polymorphism of the MMP-9gene in patients with myocardial infarction associated withtype 2 diabetes mellitus was analyzed. According to it,according to the result of the odds ratio (OR - odds ratio), incarriers of the minor allele G the probability of developingthe disease decreased by 29% (OR = 0.71, 95% CI:0.45-1.12), this means that the minor allele G has aprotective effect against the development of coronary heartdisease. On the other hand, the wild-type A allele of theMMP-9 gene polymorphism rs17576 increased thelikelihood of developing MI by 42% (OR = 1.42; 95% CI:0.91-2.21) and turned out to be a significant risk factorfor developing MI. Although chi-square did not reveal astatistically significant positive association between thedistribution of alleles of the rs17576 polymorphism of theMMP-9 gene and the development of the disease MI ($\chi 2$ =2.4, p = 0.12), the chi-square index was higher than therandom variation between the factor and the disease, as wellas the wild allele of the MMP-9 gene, which indicatespolymorphism rs17576 (A) demonstrates a tendency todevelop MI. This suggests that the reason for the lack ofassociation between the MMP-9 gene in our study may bedue to the relatively small number of patients studied. Whenanalyzing the rs17576 polymorphism of the MMP-9 gene forthe pathogenetic significance of various genotypes in thedevelopment of the disease, the wild type A/A genotypeshowed a 61% increase (OR=1.61, 95% CI 0.71-3.69) in theprobability of developing MI. Similarly, the heterozygousA/G genotype increased the likelihood of developing thedisease by 14% (OR=1.14; 95% CI 0.62-2.11), while thehomozygous G/G genotype reduced the likelihood by33% (OR=0,67; 95% CI 0.62-2.11). This means that wildhomozygous A/A and heterozygous A/G genotypes increasethe risk of developing MI, on the other hand, thehomozygous G/G genotype has a protective effect on thedevelopment of the disease, but the presented results werenot statistically significant ($\chi 2<3.84$, $p>0.05$).

4.DiscussionMMP-9 is secreted by macrophages of a fibrous capsuleand is supposed to be involved in remodeling processes afterit, and can also increase the risk of myocardial infarctionassociated with atherosclerosis and the breakdown ofplaques [9]. MMP-9 contributes to the vulnerability ofplaques, and high expression of MMP-9 is associated withthe destabilization of coronary plaques. Thus, the MMP-9 isable to spread inflammatory signals with it, therefore it isnecessary to maintain its activity at an adequate level,otherwise it can cause uncontrolled inflammation, as well asdestabilize potentially dangerous coronary plaques [10].In this regard, we investigated one of the commonpolymorphisms of the MMP

-9 gene - RS17576 A> G (orGl279arg), located on the exon 6, is a replacement A with G,which leads to a replacement of unrowned glutamine with apositively charged arginine in a catalytic domain MMP -9[11]. Consequently, this mutation can change enzymaticfunctional proportions and/or the level of expression, whichcan play an important role in the pathogenesis of them, aswell as in remodeling after transferred

[12].**5.Conclusions**This means that wild homozygous A/A and heterozygousA/G genotypes increase the risk of developing MI.According to it, according to the result of the odds ratio (OR-odds ratio), in carriers of the minor allele G the probabilityof developing the disease decreased by 29% (OR = 0.71,95% CI: 0.45-1.12), this means that the minor allele G hasa protective effect against the development of coronaryheart disease. On the other hand, the wild-type A allele ofthe MMP-9 gene polymorphism rs17576 increased thelike-lihood of developing MI by 42% (OR = 1.42; 95% CI:0.91-2.21) and turned out to be a significant risk factor fordeveloping MI.

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