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DOI 10.25789/YMJ.2021.73.06

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VARIANTS OF SINGLE NUCLEOTIDE SUBSTITUTIONS IN THE GENES OF MATRIX METALLOPROTEINASES (*MMP-2* AND *MMP-9*) IN ARTERIAL HYPERTENSION IN PEOPLE OF WORKING AGE

Point substitutions were studied in the genes *MMP-2* c.-1306C> T (rs243865) and *MMP-9* c.-1562C> T (rs3918242) in people under the age of 60 living in the Primorsky Territory. It was found that the differences between the shares of the *MMP-2* CC, CT, and TT genotypes in the groups of persons with AH and the control group were statistically insignificant (mid-p = 0.16), while for the *MMP-9* CC, CT, and TT genotypes, these differences were determined ($\alpha = 0.05$). In the distribution of patients with hypertension, depending on the indicators of relative cardiovascular risk (CVR) in persons with hypertension under 40 years of age in the group with a CVR value of 2, a significant increase in the minor alleles of *MMP-9* 1562 C/T was found, compared with individuals with a CVR value 1, the presence of the T allele in the *MMP-9* gene c.-1562C> T (rs3918242) is associated with a higher risk of cardiovascular catastrophes in young people with hypertension. Thus, the definition of the aforementioned polymorphism is of particular importance for young patients.

Keywords: arterial hypertension, metabolic syndrome, matrix metalloproteinases *MMP-2* and *MMP-9*, genetic polymorphisms

Introduction. One of the discussed problems in the risk of occurrence and prognosis of an unfavorable course of AH is the search for genetic polymorphisms and other significant biomarkers that allow to assess the individual cardiovascular risk with a high degree of accuracy

and timely carry out personalized corrective preventive measures [3].

The direction of predictive medicine associated with the search for genes encoding enzymes of connective tissue metabolism, the imbalance in the state of which, in turn, determines early damage to target organs, regardless of the degree of increase in blood pressure (ABP) is of interest. The processes of cardiovascular remodeling in hypertension (AH) and preclinical damage to target organs are associated with the inversion of the phenotypes of the smooth muscle cell of the vessel from contractile to proliferative, changes in the state of the cytoskeleton and cellular memory of cardiomyocytes, restructuring of the extracellular matrix as a result of the action of factors that activate hemodynamic stress, and as a result of discoordination of the response at the genetic level [3]. The family of matrix metalloproteinases (MMP) occupies a special place in the formation of the proinflammatory potential of the cell microenvironment, followed by elastin degradation and accumulation of collagen I, II, and III and fibronectin [8]. The unbalanced activity of the *MMP-2* and *MMP-9* genes caused by single nucleotide substitutions in the promoter zone

at the rs243865 and rs3918242 loci, respectively, in hypertension (AH) attracts the attention of many researchers, and their results are not unambiguous. Interest in studying the contribution of SNV to the *MMP-2* and *MMP-9* genes at the -1306 C / T and -1562 C / T loci indicates the need to accumulate data for their identification in the population of persons with AH in order to be able to use them as predictors of the risk of AH, predicting the occurrence of target organ damage and organizing personalized prevention of cardiovascular accidents, which is especially important for people of working age and young people, including due to the high prevalence of "masked" hypertension (AH) in this category of patients.

Objective: to determine the conjugation of SNV in genes *MMP-2* c.-1306C> T (rs243865) and *MMP-9* c.-1562C> T (rs3918242) with the presence of hypertension (AH) in people of working age.

Materials and methods. The study included 271 volunteers aged 25 to 60 years of Caucasian race, Slavic ethnicity, living for at least three generations in the Primorsky Territory. These individuals took part in the ESSE-RF study. Of these, 161 patients with hypertension (AH), 91 men and 70 women, the control group

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consisted of 110 practically healthy volunteers (50 men and 60 women) of the corresponding age without hypertension (AH).

For genetic studies, DNA samples were used, isolated from whole venous blood. The fragments were obtained by the polymerase chain reaction (PCR) method.

Quantitative indicators of the clinical characteristics of patients were expressed as mean (M) plus or minus standard error (SE); Student's test was used for comparative assessment. The correspondence of the observed distribution of genotype frequencies to the theoretically expected equilibrium distribution according to the Hardy – Weinberg law was evaluated using the Pearson χ^2 test. When comparing the frequencies of alleles and genotypes in the groups of healthy and sick individuals, the χ^2 test was used with Yates' correction for 2x2 contingency tables. The strength of associations of genotypic characteristics with the risk of developing hypertension (AH) was assessed by the odds ratio (OR). The confidence interval (CI) was calculated using the Woolf method with a 95% confidence interval.

Results and Discussions. The average age in the group of patients with hypertension (AH) was 39.5 ± 2.3 years (range from 33 to 44), in the control group – 39.2 ± 3.5 years (range from 35 to 46). In the group of people with AH, AH of the 1st degree prevailed, which was diagnosed in 135 individuals. Half of the 110 subjects in the control group were smokers. Among 161 patients with hypertension (AH), 92 smoked. The smoking

index in both groups did not differ and was 5.35 ± 1.6 in the group of people with hypertension (AH) and 4.75 ± 1.5 in the control group ($p > 0.05$). In the group of patients with hypertension (AH), there was a significant increase in the level of triglycerides (TG), weight, waist circumference, BMI compared with the control group ($p < 0.05$, table 1).

The frequencies of the genotypes of the studied SNV variants in the genes of metalloproteinases *MMP-2* and *MMP-9* in healthy individuals ($p = 0.7122$, $p =$

0.2109) and patients with hypertension (AH) ($p = 0.0855$, $p = 0.0821$) corresponded to equilibrium Hardy-Weinberg, which confirmed the independent distribution of alleles in the studied variants and the absence of errors during genotyping. The frequencies of the *MMP-2* CC, CT and TT genotypes in healthy subjects were 50%, 40%, and 10%, and in patients with AH, 48.3%, 35% and 16.7%, respectively (table 2). A number of authors have associated a relationship between the 1562 T alleles of *MMP-9* and AH [4,5,10]. In our

Table 1

Comparative analysis of the clinical characteristics of the examined healthy individuals and patients with hypertension (AH)

Indicators	Control group (n=110)	Patients with AH (n=161)
Age	39.2 ± 3.5	39.5 ± 2.3
Weight, kg	69 ± 3.0	$79 \pm 3.4^*$
BMI, kg/m ²	22.1 ± 3.5	$24.0 \pm 3.2^*$
Waist circumference, cm	73.7 ± 4.8	$87.3 \pm 5.6^*$
ABP (SBP and DBP), mm Hg	118 и 79 (± 9.2 и ± 7.0)	151 и 91 (± 7.5 и 8.0) [*]
HR, beats per minute	72 ± 7.0	80 ± 8.0
Smoking status (n, persons)	55	92
Smoking person index, pack / years	4.75 ± 1.5	5.35 ± 1.6
Blood glucose, mmol / l	4.82 ± 0.7	5.22 ± 0.8
GC, mmol / l	4.95 ± 0.6	5.01 ± 0.7
ApoA - g/l	1.79 ± 0.4	1.81 ± 0.3
ApoB - g/l	0.92 ± 0.3	0.83 ± 0.3
LDL, mmol / l	3.13 ± 0.8	3.35 ± 0.7
HDL, mmol / l	1.31 ± 0.5	1.28 ± 0.4
TLC, mmol / l	1.21 ± 0.7	$1.75 \pm 0.9^*$

Note: * - at $p < 0.05$ between the group of patients and control. BMI - body mass index, BP - blood pressure (systolic and diastolic), GC - general cholesterol, HR - heart rate, ApoA - apolipoprotein A, ApoB - apolipoprotein B, LDL - low density lipoproteins, HDL - high density lipoproteins, TLC - triglycerides.

Table 2

Frequency distribution of alleles and genotypes of the rs243865 polymorphic locus of the *MMP-2* gene in the population of healthy individuals and patients with hypertension (AH)

Polymorphic variant of the <i>MMP-2</i> gene c.-1306C>T (rs243865)	Frequency in healthy (n=120), absolute number (%)	Frequency in patients with arterial hypertension (n=120), absolute number (%)	χ^2	OR (95% CI)
CC	60 (50)	58 (48.3)		1
CT	48 (40)	42 (35)	0.13 $p=0.05$	0.905 (0.52-1.57)
TT	12 (10)	20 (16.7)	1.51 $p=0.05$	1.72 (0.77-3.84)
Dominant form of inheritance CT + TT versus CC	60 (50) 60 (50)	62 (51.7) 58 (48.3)	0.058 $p=0.05$	1.07 (0.64-1.77)
Recessive form of inheritance TT versus CC + CT	12 (10) 108 (90)	20 (16.7) 100 (83.3)	1.9 $p=0.05$	1.8 (0.84-3.87)
Super dominance CC+TT versus CT	72 (60) 48 (40)	78 (65) 42 (35)	0.5 $p=0.05$	1.24 (0.73-2.1)

Note: *MMP* is metalloproteinase, n is the number of groups, χ^2 (p) is the assessment of the significance of differences in the distribution of genotype frequencies between the two groups, OR is the odds ratio, 95%, CI is the confidence interval

Table 3

Frequency distribution of alleles and genotypes of the rs3918242 polymorphic locus of the MMP-9 gene in the population of healthy individuals and patients with hypertension (AH)

Polymorphic variant of the <i>MMP-2</i> gene c.-1306C>T (rs243865)	Frequency in healthy individuals (n=120), absolute number (%)	Frequency in patients with hypertension (n=120), absolute number (%)	χ^2 (P-value)	OR (95% CI)
CC	76 (63.3)	70 (58)		1
CT	38 (31.7)	34 (28.3)	0.38 p=0.05	0.971 (0.55-1.71)
TT	6 (5)	16 (13.7)	5.55* p=0.05	2.895 (1.073-7.81)
Доминантная форма наследования CT+TT versus CC	44 (36.7) 76 (63.3)	50 (42) 70 (58)	0.59 p=0.05	1.234 (0.73-2.07)
Рецессивная форма наследования TT versus CC+CT	6 (5) 114 (95)	16 (13.7) 104 (86.3)	4.47* p=0.05	2.92 (1.1-7.75)
Сверхдоминирование CC+TT versus CT	82 (68.3) 38 (31.7)	86 (71.7) 34 (28.3)	0.275 p=0.05	1.17 (0.67-2.04)

study, with regard to the distribution of the frequency of the *MMP-9* CC, CT and TT genotypes, it was determined that in the control group they were 63.3%, 31.7% and 5%, and in patients with AH 58%, 28.3% and 13.7% respectively. Thus, the differences between the proportions of the *MMP-2* CC, CT, and TT genotypes in the groups of persons with AH and the control group were statistically insignificant (mid-p = 0.16), while the indicated differences were determined for the *MMP-9* CC, CT, and TT genotypes (α = 0.05). Thus, the proportion of persons with TT genotype *MMP-9*, in whom the studied effect manifested itself, in the sample with hypertension (AH) was higher than in the control group (p = 0.045), which is consistent.

Considering the highest frequency of occurrence of the minor T allele in patients with hypertension (AH), we combined the CT + TT genotypes into one group and viewed them relative to individuals with the CC genotype. Single nucleotide substitutions in genes encoding matrix metalloproteinases can change the level of their expression, which, according to researchers, increases the susceptibility to cardiovascular diseases [1].

As follows from the data in Table 3, the odds ratio (OR) calculated from the occurrence of the T-allele *MMP-9* in patients with hypertension (AH) exceeded that in people without hypertension (AH) by 2 times (OR = 2.9) with significant differences at p = 0.05. In other words, the presence of the T allele in the *MMP-9* gene c.-1562C>T (rs3918242) correlates with the presence of AH. Along with this, with the dominant (CT + TT versus CC) and overdominant (CC + TT versus CT) models of inheritance, the carriage of the

T allele slightly increased the risk of developing AH (1.234 95% CI = 0.73-2.07; 1.17 CI = 0.67-2.04, respectively, with a significance level of p < 0.05). Whereas, in the recessive model (TT versus CC + CT) of inheritance in hypertensive patients, this risk significantly increased (2.92 95% CI = 1.1-7.75, p < 0.05), confirming the hypothesis that the presence of the T allele at the rs3918242 polymorphic locus of the *MMP-9* gene is directly related to the likelihood of developing AH. Thus, the results of this replicative study confirm the data obtained during the GWAS, which identified the polymorphic locus as a marker of an increased risk of hypertension in European and Asian populations [3, 9].

Taking into account the heterogeneity of the group of people with hypertension, depending on the degree of relative risk (for persons under 40 years old), determined on a scale for assessing the relative risk of developing cardiovascular complications and absolute (for persons aged 40 and older) cardiovascular risk (CVR) determined by the SCORE scale, we found it interesting to analyze the presence of the T allele of the genes *MMP-2* c.-1306C>T (rs243865) and *MMP-9* c.-1562C>T (rs3918242) in individuals with AH with varying degrees of CVR.

Analysis of the situation in real clinical practice demonstrates that most cardiovascular accidents occur more often in individuals with low and intermediate cardiovascular risk [2]. In our study, it was found that the vast majority of people under 40 years of age (n = 95) had a CVR value of 2 (76%, n = 72) and only 24% (n = 23) had a reference CVR value = 1. Among persons aged 40 years and older (n = 66), an opposite tendency was

observed: 35% (n = 23) had a moderate absolute CVR ($\geq 1\%$ and $< 5\%$), and 55% (n = 37) had a high ($\geq 5\%$ and $< 10\%$) and 10% (n = 6) of patients had a very high risk ($\geq 10\%$).

Alessandra M.V. Ritter et al. and Sabbatini A.R. et al. suggests that rs243865 in the *MMP-2* gene may be associated with an increase in blood pressure (ABP) in patients with resistant hypertension (AH) [6, 7]. In our study, it was found that the distribution of the frequency of the CC, CT and TT genotypes *MMP-2* c.-1306C>T (rs243865) in persons under 40, depending on the degree of relative risk, as well as in the general group of patients, did not statistically differ (table 4). When comparing the frequency of genotypes *MMP-9* c.-1562C>T (rs3918242), it was found that patients with the minor allele T (CT and TT) were more common in the subgroup with CVR = 2 (OR 2.26 95% CI = 0.42-1.84, p = 0.04). Probably, these substitutions can phenotypically manifest themselves as an imbalance in the state of connective tissue metabolism and associated damage to target organs in hypertension (AH).

In the group of patients with hypertension (AH) older than 40 years of age, no difference was found in the distribution of genotypes of the rs243865 polymorphic locus of the *MMP-2* gene depending on the degree of absolute cardiovascular risk on the SCORE scale (Table 5). Moreover, in contrast to persons under 40, there was no difference in the distribution of frequencies of genotypes *MMP-9* c.-1562C>T (rs3918242) depending on the degree of cardiovascular risk.

Conclusions. No statistically significant difference in SNV in the *MMP-2* gene c.-1306C>T (rs243865) depending on the presence of AH was found.

Table 4

Distribution of the frequency of genotypes of polymorphic loci *rs243865* of the *MMP-2* gene and *rs3918242* of the *MMP-9* gene in patients with hypertension (AH) younger than 40, depending on the degree of relative cardiovascular risk

Genotypes	Frequency in persons with CVR=2 (n=72)	Frequency in persons with CVR=1 (n=23)	OR (95% CI)	P-value
<i>MMP-2 c.-1306C>T (rs243865) TT+CT</i>	38 (52.7)	10 (43.4)	0.34 (0.16-0.71)	0.52
<i>MMP-2 c.-1306C>T (rs243865) CC</i>	34 (47.2)	13 (56.5)		
<i>MMP-9 c.-1562C>T (rs3918242) TT+CT</i>	48 (66.6)	8 (34.7)	2.26 (0.42-1.84)	0.04
<i>MMP-9 c.-1562C>T (rs3918242) CC</i>	24 (33.3)	15 (65.2)		

Note: MMP - metalloproteinase, OR - odds ratio, CI - confidence interval. P-value - significance level $p \leq 0.05$.

Table 5

Distribution of the frequency of genotypes of polymorphic loci *rs243865* of the *MMP-2* gene and *rs3918242* of the *MMP-9* gene in patients with hypertension (AH) over 40, depending on the degree of absolute cardiovascular risk (SCORE scale)

Genotypes	Frequency in persons with moderate CVR (n = 23)	Frequency in individuals with high and very high CVR (n = 43)	OR (95% CI)	P-value
<i>MMP-2 c.-1306C>T (rs243865) TT+CT</i>	13 (56.5)	22 (51.1)	0.81 (0.46-1.42)	0.35
<i>MMP-2 c.-1306C>T (rs243865) CC</i>	10 (43.4)	21 (48.8)		
<i>MMP-9 c.-1562C>T (rs3918242) TT+CT</i>	10 (43.4)	19 (44.1)	1.42 (0.59-1.82)	0.55
<i>MMP-9 c.-1562C>T (rs3918242) CC</i>	13 (56.5)	24 (55.8)		

In persons with AH, the presence of a minor *T*-allele at the *rs3918242* polymorphic locus of the *MMP-9* gene occurs 2.04 times more often than in healthy individuals. These data allow us to consider *MMP-9 c.-1562C>T (rs3918242)* as a candidate gene for detecting genetically determined connective tissue dysmetabolism with the development of hypertension (AH).

In hypertensive patients under 40 years of age with a relative cardiac risk index equal to two, the proportion of the *T* allele in the *rs3918242* polymorphic locus of the *MMP-9* gene was 2.2 times higher than that in individuals with a relative cardiovascular risk equal to one. In persons over 40 years of age, such a difference has not been distinguished. Accordingly, the presence of the *T* allele in the *MMP-9 gene c.-1562C>T (rs3918242)* is associated with a higher risk of cardiovascular catastrophes in young people with hypertension (AH).

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DIAGNOSTIC AND TREATMENT METHODS

DOI 10.25789/YMJ.2021.73.07

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RISK OF ACUTE KIDNEY INJURY IN PATIENTS WITH ISHEMIC HEART DISEASE AND CONCOMITANT METABOLIC SYNDROME AFTER ON-PUMP CORONARY BYPASS GRAFTING

The aim of the research was to study the incidence and risk factors of developing AKI, its patterns in patients with CHD and concomitant MS after the coronary artery bypass grafting off-pump.

Materials and methods. The study covered two groups: patients with CHD and MS (the main group, n=82); and patients with CHD but without MS (the control group, n=51). Here are the inclusion criteria for the study: CHD with HF of Class III-IV; normal left ventricular ejection fraction (LVEF) - 55% and above; 45-69 years of age. The exclusion criteria were as follows: complications during and after the surgery, diabetes mellitus, kidney diseases, low LVEF (<54%), over 70 years of age. The criteria for MS: central obesity, arterial hypertension, increased triglycerides (≥ 1.7 mmol/L), and impaired glucose tolerance (IGT).

Results. Signs of AKI were detected in 61 (45.9%) patients, out of which 56 (68.3%) patients had MS. The patients with MS demonstrated initial reduced in GFR (71.2 ± 13.2 ml/min/1.73 m²), with its values reducing further on the 2nd day to 55.2 ± 14 ml/min/1.73 m² and the low values remaining on the 10th day after the surgery (69.5 ± 12.8 ml/min/1.73 m²). The patients with MS had longer artificial lung ventilation (17.1 ± 9.1 hours against 10.8 ± 8.6 in the control group, $p < 0.01$), longer stay at ICU (4.1 ± 1.7 days against 2.9 ± 0.9 in the control group, $p < 0.01$) and in the hospital (24.3 ± 3.2 days against 21.39 ± 2.3 in the control group, $p < 0.015$), and higher mortality (5.4% against 1.9% in the control group). The statistically reliable risk factors were revealed: the patient's age ($p < 0.01$), high-density lipoprotein in blood ($p < 0.01$), total cholesterol ($p < 0.039$), and creatinine ($p < 0.01$).

Conclusion. The presence of MS is a factor contributing to the high probability of AKI development after coronary artery bypass grafting off-pump (68.3% of the cases), which requires monitoring of the renal function during perioperative period, as well as prevention of AKI in patients with CHD and concomitant MS.

Keywords: coronary heart disease, coronary artery bypass grafting off-pump, metabolic syndrome, risk factors, acute kidney injury.

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Relevance. Coronary heart disease (CHD) is a leader among all causes of death in the world [1]. At present, myocardial revascularization by artery bypass surgeries is a common solution for CHD. However, despite its high efficiency, there surgeries are accompanied by various undesirable dysfunctions of organs and systems in the organism, as well as the development of severe complications, including acute kidney injury (AKI) [2]. The recent data show that after coronary artery bypass grafting, AKI is observed in 17.5 % of cases [3], leading to a changed patient treatment tactic, prolonged treat-

ment duration and significantly worse prognosis, with hospital mortality rate increasing from 7.6 % to 26.3% [2].

It has been established that MS is one of the negative factors contributing to renal dysfunction in patients with cardiovascular pathologies [4]. Typically, patients with MS are overweight and suffer from dyslipidemia, insulin resistance, and arterial hypertension [5]. Due to a high risk of developing various complications in the postoperative period, this category of patients constitutes a serious medical, social, and economic challenge of the present time [2, 4].