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THE PLACE OF C677T POLYMORPHISM IN THE MTHFR GENE IN THE FORMATION OF METABOLIC SYNDROME

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ABSTRACT
The material for the molecular genetic study was peripheral blood of 183 patients with metabolic syndrome and myocardial infarction (the main group) and 155 conditionally healthy donors (the control group). The main group was divided into 3 subgroups: 64 patients with MS+MI, 61 patients with MS without MI, and 58 patients with MI without MS. Testing of the C677T polymorphism in the MTHFR gene was performed on a Rotor-Gene Q device (Quagen, Germany), using a commercial test kit of Syntol LLC (Russia). DNA regions were amplified by real-time polymerase chain reaction (PCR) using TaqMan probes. Statistical processing of the results was performed using the standard OpenEpi V.9. 2 application software package.
KEYWORDS: *Metabolic syndrome, insulin resistance, abdominal obesity, myocardial infarction, C677T genetic polymorphism in the MTHFR gene.*

1. INTRODUCTION

Metabolic syndrome (MS) is a complex of metabolic, hormonal and clinical disorders that are powerful risk factors for the development of cardiovascular diseases, which are based on: high blood pressure, overweight/obesity, hyperglycemia and hyperlipidemia, which are the leading cause of death and disability worldwide [1].

According to a multicenter epidemiological study [3, 11] conducted in 22 countries of the world, the prevalence of pathological conditions/markers of MS among patients suffering from CHD was: obesity-33%, central obesity-53%, hypertension-56%, high total cholesterol - 51%, DM-25%.

Overweight and obesity are among the most common diseases at the moment. The constant increase in the number of people suffering from obesity has led to the fact that WHO considers it as a "non-communicable epidemic of the present time" [6].

According to WHO, about 30% of the world's inhabitants (16.8% of women, 14.9% of men) are overweight. The number of obese people increases progressively by 10% every 10 years. For the first time, he combined carbohydrate metabolism disorders, arterial hypertension (AH) and dyslipidemia in the concept of "X syndrome" by G. Reaven (1988), which did not consider obesity as a mandatory component. In 1989, N. Kaplan included obesity among the mandatory signs of MS [3, 7]. Thus, the leading clinical sign of MS is abdominal-visceral obesity, and the earliest manifestations, along with obesity, are dyslipidemia and hypertension.

According to a meta-analysis of 37 prospective studies, MS is associated with the risk of CVD and death and was 2 times higher than without it [10, 9]. Arterial hypertension is one of the earliest and most frequent clinical manifestations of MS [1,4]. The risk of developing cardiovascular complications in patients with hypertension in combination with other components of the metabolic syndrome (MS) is 5 times higher (25%) than in patients without metabolic disorders (5%) [5]. This fact determines the medical and social significance of studies of hypertension associated with metabolic imbalance. Frequent combination of hypertension with various components of MS can be considered an unfavorable prognostic sign for the development of diseases associated with atherosclerosis [2]. In recent years, the hypothesis that AH and IR are parallel consequences of a common cause – a genetically determined violation of the ion transport function of cell membranes-has become increasingly popular [8].

Thus, long-term population studies are required to determine the place of homocysteinemia in the pathogenesis of MS and cardiovascular diseases. It is necessary to decide on the expediency and ways to correct this condition.

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2. PURPOSE OF THE STUDY

To study the frequency of distribution and significance of the C677T polymorphism in the MTHFR gene and the level of homocysteine in the blood in the pathogenesis of metabolic syndrome.

3. MATERIAL AND METHODS OF RESEARCH

The material for the molecular genetic study was peripheral blood of 183 patients with metabolic syndrome and myocardial infarction (the main group) and 155 conditionally healthy donors (the control group). The main group was divided into 3 subgroups: 64 patients with MS+MI, 61 patients with MS without MI, and 58 patients with MI without MS. Testing of the C677T polymorphism in the MTHFR gene was performed on a Rotor-Gene Q device (Quagen, Germany), using a commercial test kit of Syntol LLC (Russia). Statistical processing of the results was performed using the standard OpenEpi OpenEpi V.9. 2 application software package.

The frequency distribution of alleles and genotypes in the studied genes was checked for compliance with the Hardy-Weinberg equilibrium.

4. THE RESULTS OBTAINED AND THEIR DISCUSSION

The study examined the C677T marker of the MTHFRgene. The C677T marker of the MTHFR gene consists of 3 genotypes C/C, C/T, and T/T (see Table 1).

According to the results of the conducted studies, in the group of patients with MS+MI and the control group, the prevalence of the major C allele of the C677T genetic marker of the MTHFR gene was 63.3% and 74.8%, respectively. The prevalence of the functionally unfavorable minor-type T allele was 36.7% and 25.2%, respectively. According to the statistical report, carriers of the minor T allele are 1.7 times more likely to develop the disease (MS+MI) than carriers of the major C allele of the C677T genetic marker of the MTHFRgene, and it was determined that the difference between them has a significant statistical significance ($\chi 2$=5.9; P=0.03; OR=1.7; 95%CI: 1.11-2.68). Studies have shown that the initial C allele of the C677T genetic marker of the MTHFR gene has a protective efficacy against the development of MS+MI ($\chi 2$=5.9; P=0.03; RR=0.6; 95%CI:0.37-0.9).

The prevalence of the wild C/C genotype of the C677T genetic marker of the MTHFR gene in the group of patients with MS+MI is significantly lower compared to the control group, which is 39.1% and 57.4%, respectively, and this indicates a protective function against the development of the disease (MS+MI) ($\chi 2$=6.1; P=0.03; OR=0.5; 95%CI0:0.26-0.86).

Table 1. Carriage of alleles and genotypes of the C677T polymorphism in the MTHFR gene in patients with MS+MI and the control group.

Alleles and genotypes	Number of examined alleles and genotypes				$\chi 2$	p	OR	95%CI
	MS + MI		MI Control group					
	n	%	n	%				
C	81	63,3	232	74,8	5,9	0,03	0,6	0,37 - 0,9
T	47	36,7	78	25,2	5,9	0,03	1,7	1,11 - 2,68
C/C	25	39,1	89	57,4	6,1	0,03	0,5	0,26 - 0,86
C/T	31	48,4	54	34,8	3,5	0,10	1,8	0,98 - 3,16
T/T	8	12,5	12	7,7	1,2	0,30	1,7	0,67 - 4,35

It should be noted that, according to the results of genetic studies of the genotypes of the C677T polymorphic marker of the MTHFR gene, a comparative analysis of the main (MS+MI) and control groups showed a probability of R=1.8 (CI95%:0.98-3.16) cause disease in functionally unfavorable heterozygous C/T genotype in the main group. And also, along with this, there was a probability of OR=1.7 (CI95%: 0.67-4.35) to cause the disease also in the mutant T/T genotype of the C677T genetic marker of the MTHFRgene.

Statistical processing of the results revealed a decrease in the frequency of the major C allele and a tendency to increase the minor T allele генетическоro of the C677T genetic marker of the MTHFR gene in MS patients without MI compared to conditionally healthy donors. Carriage of the mutant T allele was associated with a 1.33-fold increased risk of MS in the group of patients compared to the control group (χ^2=1.2; P=0.33; OR=1.33; 95%CI: 0.8282-2.0606) (see Table 2).

The frequencies of C/C, C/T T / T genotypes C677T in the MTHFR gene in the studied groups of MS patients without MI and control were: 49.2%, 41.0% and 9.8% versus 57.4%, 34.8.8% and 7.7%, respectively.

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The frequency of favorable C/C genotype among patients was not significantly lowerthan in группеthe control group (49.2%and 57.4%, respectively, with χ^2=1.2; P=0.33; OR=0.77; 95%CI:0.44-1.33).

Table 2. Carriage of alleles and genotypes of the C677T polymorphism in the MTHFR gene у пациентов с in MS patients without MI and in the control group.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	MS without		MI Control group					
	n	%	n	%				
C	85	69,7	232	74,8	1,2	0,30	0,8	0,49 - 1,23
T	37	30,3	78	25,2	1,2	0,30	1,3	0,82 - 2,06
C/C	30	49,2	89	57,4	1,2	0,30	0,7	0,4 - 1,3
C/T	25	41,0	54	34,8	0,7	0,40	1,3	0,71 - 2,38
T/T	6	9,8	12	7,7	0,3	0,70	1,3	0,47 - 3,63

The incidence of the unfavorable T/T genotype among MS patients without MI was slightly higherthan in the control group (9.8% and 7.7%, respectively, with χ^2=0.3; P=0.77; OR=1.33; 95%CI: 0.4747-3.6363) (see Table 2). Ingeneral, the listed analysis calculations showed that MS patients with this genotype are absent. There was a weak tendency to increase the number of unfavorable heterozygous C / T polymorphism C677T in the MTHFR gene in the study group, which indicates an increased (1.33-fold) risk of developing MS (χ^2=0.7; P=0.33; OR=1.33; 95%CI:0.7171-2.3838) (see Table 2).

In MI patients without MS (n=58), the occurrence of the major аллеля C677 allele генетического of the C677T genetic marker of the MTHFR gene significantly decreases to 63.8%, and the minor T677 allele increases to 36.2% (see Table 3). This conclusion is justified by the association of allelic carriage of T677генетического , the C677T genetic marker of the MTHFR gene, with a high risk (1.7 times) of MI development without MS (χ^2=5.1; P=0.3; OR=1.7; 95%CI:1.07-2.66).

In addition to these features, the proportion of genotype C677C C677c in patients with MI without MS decreased to 39.7% compared to the control, while the frequencies of unfavorable genotypesC677tand T677T677t of the C677T genetic marker of the MTHFR gene increased to 48.3% and 12.1%, respectively. These features may indicate an associationof the om genotype with677T and t677 T677T генетического of the C677T genetic marker of the MTHFR gene with the trend of the riska of MI development in comparison with conditionally healthy donors (see Table 3).

Table 3. Carriage of alleles and genotypes of the C677T polymorphism in the MTHFR gene in patients with MI without MS and in the control group.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	MI without MS		Control group					
	n	%	n	%				
C	74	63,8	232	74,8	5,1	0,03	0,6	0,38 - 0,93
T	42	36,2	78	25,2	5,1	0,03	1,7	1,07 - 2,66
C/C	23	39,7	89	57,4	5,3	0,03	0,5	0,26 - 0,9
C/T	28	48,3	54	34,8	3,2	0,10	1,8	0,95 - 3,21
T/T	7	12,1	12	7,7	1,0	0,40	1,6	0,62 - 4,35

Thus, in the presence of unfavorable genotypesC C677T and T677T генетического of the C677T genetic marker of the MTHFR gene, the risk of MI development increases by 1.8 and 1.6 times (at χ^2=3.2; P=0.11; OR=1.8; 95%CI:0.9595-3.21 and at χ^2=1.0; P=0.44; OR=1.6; 95%CI:0.62–4.35). At thesame time, our study showed that C677C the C677c genetic marker C677T of the MTHFR gene is associated with a significant contribution of this polymorphism against the risk of ИММI.

As can be seen from Table 4, theobserved difference in the frequency distribution of the minor T-type allele between the group of MS+MI patients and MS without them was characterized by its moderate increase among patients with MS+MI by 1.33 times (36.7% vs. 30.3% with χ2=1.1; P=0.33; OR=1.33; 95%CI:0.7979-2.226). Meanwhile, the increase in cases of carriage of the heterozygous C/T genotype генетического of the C677T genetic marker of the MTHFR gene among patients with MS+MI compared to those in the group of patients with MS without MI by 1.44 times (48.4% vs. 41.1% with χ2=0.7; P=0.55; OR=1.44;

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95%CI:0.667-2.74) suggests that there is a moderate tendency for its association with the risk of developing MS+MI (see Table 4).

Table 4. Carriage of alleles and genotypes of the C677T polymorphism in the MTHFR gene in patients with MS+MI and MS withoutMI.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	MS+		MI MS without					
	MI n	%	n	%				
C	81	63,3	85	69,7	1,1	0,30	0,8	0,44 - 1,27
T	47	36,7	37	30,3	1,1	0,30	1,3	0,79 - 2,26
C/C	25	39,1	30	49,2	1,3	0,30	0,7	0,33 - 1,35
C/T	31	48,4	25	41,0	0,7	0,50	1,4	0,67 - 2,74
T/T	8	12,5	6	9,8	0,2	0,70	1,3	0,43 - 4,01

This was accompanied by a slight decrease in the favorable C/C genotype (39.1% vs. 49.2%, respectively) and the major C–type allele (63.3% vs. 69.7%, respectively) in the group of patients with MS+MI (χ2=1.3; P=0.33; OR=0.7; 95%CI: 0.3333-1.35 and χ2=1.1; P=0.33; OR=0.8; 95%CI: 0.4444-1.27) compared to the same in the group of MS patients without MI. Calculation analyses showed an insignificant increase in the number of non-favorable T/T genotype in the group of patients with MS+MI than in the group of patients with MS without them. (12.5% vs. 9.8% for χ^2=0.2; P=0.77; OR=1.3; 95%CI:0.4343-4.01)

Thus, a decrease in the proportion of carriers of the major C-type allele and wild генотипа C/C genotype in the group of patients with MS+MI, and, in contrast, an increase in cases of carriage of the minor T-type allele and the unfavorable генотипа C/T genotype генетическоro of the C677T genetic marker of the MTHFR gene compared to their shares in the group of patients with MS without MI, itsuggests that they are associated with moderate development of MS+MI.

When studying the frequency of occurrence of the wild C allele and the mutant T allele генетическоro of the C677T genetic marker of the MTHFR gene between the studied groups of patients with MS+MI and MI without MS, it was found that the absolute value of the frequency of allele distribution in both cases was equal (63.3% vs. 63.8% with χ2=0.0; P=0.9; OR=1.0; 95%CI:0.58-1.65 and 36.7% vs. 36.2% at χ2=0.0; P=0.9; OR=1.0; 95%CI: 0.61-1.72) (see Table 5).

The frequency of distribution of genotypes in the MTHFR gene in groups of patients with MS+MI and MI without MS was: (wild) C / C gentoip 39.1% vs. 39.7% and (unfavorable) C/T genotype 48.4% vs. 48.3% and mutant T/T genotype 12.5% vs. 12.1%, respectively. The results obtained showed that the frequency of occurrence of alleles and genotypes of the studied genetic marker C677T of the MTHFR gene in patients with MS+MI did not differ from the group of patients with MI without MS.

Table5. Carriage of alleles and genotypes of the C677T polymorphism in the MTHFR gene in patients with MS+ИМ MI and ИМ без MCMI without MS.

Alleles and genotypes	Number of examined alleles and genotypes				χ2	p	OR	95%CI
	MS +		MI MI without MS					
	n	%	n	%				
C	81	63,3	74	63,8	0,0	0,95	1,0	0,58 - 1,65
T	47	36,7	42	36,2	0,0	0,95	1,0	0,61 - 1,72
C/C	25	39,1	23	39,7	0,0	0,95	1,0	0,47 - 2,02
C/T	31	48,4	28	48,3	0,0	0,99	1,0	0,49 - 2,05
T/T	8	12,5	7	12,1	0,0	0,95	1,0	0,35 - 3,07

Assessment of the level of association of the C677t polymorphism C677T в гене in the MTHFR gene in patients with MS without MI and MI without MS showed that the proportion of C and T alleles in the compared groups did not significantly differ from each other and amounted to 69.7% and 30.3% versus 63.8% and 36.2%, respectively.

The results of the study showed that the detection of the wild C allele and the unfavorable T allele in patients did not increase the risk of developing MS compared to MI representatives without MS (χ^2=0.9; P=0.4; OR=1.3; 95%CI:0.76–2.24 and χ^2=0.9; P=0.4; OR=0.8; 95%CI: 0.45-1.32) (see Table 6).

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Table 6. Carriage of alleles and genotypes of the C677T polymorphism in the MTHFR gene in patients with MS without MI and ИМ без MCMI without MS.

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	p	OR	95%CI
	MS without		MI MI without MS					
	n	%	n	%				
C	85	69,7	74	63,8	0,9	0,40	1,3	0,76 - 2,24
T	37	30,3	42	36,2	0,9	0,40	0,8	0,45 - 1,32
C/C	30	49,2	23	39,7	1,1	0,30	1,5	0,71 - 3,04
C/T	25	41,0	28	48,3	0,6	0,50	0,7	0,36 - 1,54
T/T	6	9,8	7	12,1	0,2	0,70	0,8	0,25 - 2,52

As can be seen from Table 6, in relation to the unfavorable haplotypes C677T and T677T полиморфизма of the C677T polymorphism in the MTHFR gene , although there were differences characterized by an almost 1-fold increase in their proportion among patients with MI without MS в 1 раз (48.3% vs. 41.0%; $\chi2$=0.6; p=0.55; OR=0.7; 95%CI: 0.3636-1.54 and 12.1% vs. 9.8%; $\chi2$=0.2; p=0.7.7; HR=0.8; 95%CI: 0.2525-2.52), however, they did not differ statistically significantly in comparison with similar values in the group of patients with MS withoutMI. The opposite situation was found in the study of the frequency of occurrence of the wild haplotype C / C polymorphism C677T in the MTHFR gene and theanalysis of calculations showed that the proportion of favorableoro haplotype C/C wasa slightly higher in patients with MS withoutMI than in the group of patients with MI without MS (see Table 6).

In general, according to the results of this study, insignificant differences in the frequency of alleles and genotypes of the C677T genetic marker of the MTHFR gene were found between MS patients without MI and the group of patients with MI without генетического маркер C677T гена MTHFRMS.

Further, the level of homocysteine in the blood of all examined patients was studied.
The study of homocysteine levels in the blood showed that in the group of patients with MS+MI, the level of this indicator was 24.6±0.8 mmol/l, in the group of patients with MS without MI – 18.4±0.8mmol/l, and in the 3rd group of patients with MI without MS-19.2±0.8 mmol / l, while in the control group, this parameter was equal to 8.7±0.5mmol / l, showing that a significant difference in the level of homocysteine in the blood serum in the group of patients was detected in relation to conditionally healthy people (p<0.001).

The mean homocysteine values in the subgroups significantly differed from each other. In the group of patients with MS+MI, the mean homocysteine values were significantly higher by 1.4 times and 1.3 times compared to other subgroups of patients with MS without MI and MI without MS.

Further, the study examined the average level of homocysteine in the main study group of patients, depending on gender (see Table 7).

Table 7. Average homocysteine level in the main study group of patients, depending on gender

Patients	Homocysteinemia level		
	MS+MI n=64	MS without MI n=61	MI without MS n=58
Men	(64/45) 24.8 ± 0.9*	(61/16) 18.3 ± 1.7	(58/45) 19.6 ± 0.9
Women	(64/19) 23.9 ± 1.7*	(61/45) 17.9 ± 0.9	(58/13) 17.9 ± 1.9

Note: * - significance of differences between male and female groups of MS+MI and MS without MI and MI without MS at p<0.001.

When studying the level of homocysteine between men and women in each subgroup of patients, this indicator was higher in men compared to the opposite sex. But despite this, the results were statistically unreliable (p >0.05) (see Table 7). The results of assessing the level of homocysteine in the section of the male sex in the studied groups of patients showed the following: (MS+MI) 24.8±0.9 mmol / l vs. (MS without MI) 18.3±1.7 mmol/l and (MI without MS) 19.6±0.9 mmol / l (see Table 7). In particular, the level of homocysteine (HC) in the blood of men in the group of patients with MS+MI was on average significantly 1.4 and 1.3 times higher compared to men in the 2nd and 3rd groups of patients with MS + MI. p<0.001, respectively. In the

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subgroup of female patients in group 1 with MS+MI (23.9±1.7 mmol/L), the level of HC was also characterized by more pronounced and significant changes in relation to women of other subgroups with MS without MI (17.9±0.9 mmol/L) and MI without MS (17.9 ± 1.9 mmol/L).

The results of assessing the level and frequency of hyperhomocysteinemia showed that patients with MS+MI with hyperhomocysteinemia accounted for 82.8%. Analysis of the obtained data showed that in group 1 of 64/53 patients had a high level of homocysteine in the blood and the average level of homocysteine in these (53) patients was 27.1 ± 0.5, which is 1.3 and 1.2 times higher than in patients with MS without MI and MI without MS. In patients with MS without MI and MI without MS, an increase in homocysteine in the blood was found in 61/44 (72.1%) and 58/42 (72.4%), respectively (8).

Table 8. Frequency and level of hyperhomocysteinemia in the main study group of patients

№	Group no. of patients	with Hyperhomocysteinemia	
		%	±
1.	MS + IM	64/53 (82.8%)	27.1 ± 0.5*
2.	MS without	MI 61/44 (72.1 %)	21.4 ± 0.6
3.	MI without MS	58/42 (72.4%)	22.4 ± 0.6

Note: * - significance of differences between male and female groups of MS+MI and MS without MI and MI without MS at $p<0.001$.

5. CONCLUSION

Thus, according to the statistical report, carriers of the minor T allele and associated unfavorable C/T and T/T genotypes are significantly more likely to develop the disease (MS+MI) b than carriers of the major C allele of the C677T genetic marker of the MTHFRgene, and it was determined that the difference between them has significant statistical significance. Studies have shown that the original C allele of the C677T genetic marker of the MTHFR gene has protective efficacy against the development of MS+MI.

Analysis of the obtained data showed that in the 1st group of patients with MS+MI out of 64/53, they had a high level of homocysteine in the blood and the average level of homocysteine in these (53) patients was 27.1 ± 0.5, which is 1.3 and 1.2 times significantly higher than in patients with MS without MI and MI without MS.

Knowing the indicators of genetic testing in patients with MS, it is possible to calculate the genetic risk of developing coronary heart disease (MI) in MS. Genetic risk assessment may contribute to the early prevention of coronary heart disease (MI) in MS.

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