ASSOCIATION OF GENETIC MARKERS WITH THE DEVELOPMENT OF METABOLIC SYNDROME AMONG YOUNG RESIDENTS OF UZBEKISTAN

Sattarov Oyatullo Xayatullo o'g'li

Assistant at the Department of Propaedeutics of Internal Diseases
Andijan State Medical Institute.

Annotation

Metabolic syndrome (MS) is a multifactorial disease that is one of the causes of the development of cardiovascular diseases. The development of this pathology is based on insulin resistance with hyperinsulinemia . The atherogenicity of the lipid profile with insulin resistance is accompanied by increased production of very low-density lipoproteins in the liver and impaired destruction of them in the periphery, which contributes to the accumulation of triglycerides and low-density lipoproteins . However, disruption of Ca2+-Na+ metabolism under conditions of peroxidation due to obesity leads to an increase in Ca2+ ions in platelets and hypertrophy of the heart muscle, thereby increasing diastolic pressure. Hyperglycemia is accompanied by the accumulation of advanced glycation end products (AGEs). Proteins with AGEs, with the assistance of cytokines , promote the proliferation of endothelial cells of the vascular wall, synthesizing endothelin-1, which causes local thrombosis and inhibits platelet aggregation. In individuals genetically predisposed to obesity and (or) insulin resistance , the development of metabolic disorders occurs slowly and constantly progresses under the influence of factors such as eating disorders and physical inactivity. Impaired endothelial properties are associated with many gene mutations, in particular the MTHFR gene, which is involved in homocysteine metabolism , and the CSK gene , which regulates cell growth and differentiation. Disruption of the expression of these genes negatively affects target cells located in the cardiovascular system, kidneys, endocrine organs and the central nervous system .

Keywords *Metabolic syndrome , MTHFR , glycosylation , hyperglycemia .*

INTRODUCTION

Metabolic syndrome (MS) is defined as a group of metabolic disorders represented by a number of risk factors for the development of cardiovascular pathologies and type 2 diabetes mellitus (T2DM). Components associated with MS include abdominal fat deposition, hypertension, carbohydrate metabolism disorders, and dyslipidemia . The relationship between MS and the development of many chronic diseases (cardiovascular pathology, non-alcoholic fatty liver disease (NAFLD), arthritis, chronic kidney disease, schizophrenia), as well as some types of cancer (endometrial cancer, prostate cancer, colorectal cancer and breast

cancer) is noted over many decades . It is known that MS also develops in parallel with obesity and T2DM.

Obesity is a worldwide metabolic disorder that is becoming a global pandemic. In 2015, 604 million adults and 108 million children were obese. Since 1980, the prevalence of obesity has doubled in 73 countries . According to the United Nations (UN), Mexico ranks first in the world in terms of the number of obese patients (32.8%), the Russian Federation is in 19th place (24.9%). With the global rise in obesity, MS has become a major public health problem worldwide .

The prevalence and mortality of diabetes also continues to increase worldwide, with important public health implications. In a study by K. Ogurtsova et al . 196 data sources from 111 countries were analyzed . In 2015, there were an estimated 415 million people with diabetes aged 20–79 years, 5 million diabetes-related deaths, and total global health care costs estimated at US$ 673 billion . About 75% of people with diabetes lived in low- and middle-income countries. The number of people with diabetes aged 20–79 years is projected to increase to 642 million by 2040 .

There are no similar global data on the prevalence of MS, but since it is approximately three times more common than diabetes, the estimated prevalence of this symptom complex is about a quarter of the world's population . About 1/5 of the population in the Asia-Pacific region, which is home to half the world's population, has MS. In other words, currently more than 1 billion people in the world suffer from MS, and the incidence of this pathology will steadily increase.

The purpose of the study was to identify possible associations between gene polymorphisms and components of the metabolic syndrome in young indigenous and non-indigenous residents of the Uzbek region .

Materials and research methods

Since 2015, 8-47 young people were examined for 3 years, whose average age was 36.62±5.12 years. Of these, 6 7 5 patients had metabolic disorders and 1 2 9 people had normal body weight and without metabolic disorders. Two groups of examined patients are presented. The first clinical group - non-indigenous residents living in the city and in rural areas . The second clinical group is indigenous people (Khanty and Mansi) living in the village. The examination included instrumental methods (determining body mass index (BMI=kg /m²), measuring waist circumference (WC) and blood pressure). All subjects underwent a study of the lipid spectrum (determination of serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG)), carbohydrate metabolism) . Table 1 presents anthropometric, laboratory and instrumental data of the examined indigenous and non-indigenous residents.

Table 1

Characteristics of the surveyed indigenous and non-indigenous residents (M ± m)

Options	Control group n = 139	Non-Indigenous n=492	Native people n=203
BMI, kg/m²	23.4 ± 0.0 1 _	32.17±0.03*	31.97±0.06
OT, cm	74.25±0.014	93.69±0.65	89.08±0.72
Fasting glucose level, mmol /l	4.37±0.001	5.63±0.001*	5.32±0.002
Glucose level 2 hours after exercise, mmol /l	5 , 15 ±0.00 3	7.16±0.002	6.91±0.001*
TC, mmol /l	3.27 ±0.00 2	5.31±0.004	5.63±0.002
TG, mmol /l	0.95 ± 0.0 02 _	2.57±0.001*	2.51±0.002
HDL cholesterol mmol /l	1.58 ± 0.00 2	1.55±0.002	1.65±0.002
LDL cholesterol, mmol /l	1.38 ± 0.00 6 _	3.12±0.003	3.03±0.001*
SBP, mm rt . Art.	1 09.75 ± 0.0 5 _	114.27±0.06	116.76±0.07
DBP, mm Hg . Art.	7 3 , 20 ±0.070	75.63±0.40	74.95±0.52

Note. p *<0.001 compared to control group

Abbreviations: SBP – systolic blood pressure, DBP – diastolic blood pressure

When studying mutations to diagnose the allelic polymorphism rs1801133 (C677T) of the MTHFR gene and rs1378942 of the CS K gene, polymerase chain reaction with restriction fragment length polymorphism (PCR with RFLP) was

used by phenol-chloroform extraction. The selection of patients for the study was based on the recommendations of the All-Russian Scientific Society of Cardiology (VNOK) (2009). The main criterion is WC>94 cm in men and over 80 cm in women - and 2 additional: arterial hypertension (BP≥130/85 mmHg) , increased TG levels (≥1.7 mmol /l), decreased levels HDL cholesterol (<1.0 mmol /l in men; <1.2 mmol /l in women), increased LDL cholesterol >3.0 mmol /l, fasting hyperglycemia ≥6.1 mmol /l . Patients provided informed consent for the examination. Statistical processing of the obtained results was carried out using the SPSS 16.0 program. The frequencies of genotypes and alleles of the studied polymorphisms in the group of patients with MS and in the control group were determined, and the odds ratio (OR) and confidence interval (CI) for the development of MS components on the frequency of alleles were calculated. The significance level was p <0.001.

Research results and discussion

The distribution of genotypes rs1801133 (C677T) of the MTHFR gene and rs1378942 of the CS K gene among the examined residents is presented in Table 1. The frequencies of genotypes rs1801133 of the MTHFR gene among patients with MS were CC - 54.1%, ST - 36.1%, TT - 9.8 %. Carriage of the T allele , associated with the risk of developing cardiovascular diseases, was noted in 27.8% of all examined patients with MS in the control group (32.7%). The frequency of carriage of the heterozygous genotype TG rs1378942 of the CS K gene in young people with MS was 50.3%, while homozygous carriage of GG was 20.4%, TT was 29.3%. In the control group, the carriage frequency of both heterozygous and homozygous variants rs1378942 of the CS K gene did not differ significantly from this parameter in patients with MS (Table 2).

table 2

Frequency of genotypes of single nucleotide polymorphisms in metabolic syndrome and in the control group

Polymorphism	Genotype	Control		MS		OR, 95% CI, p
		n	%	n	%	
CSK rs1378942	GG	22	18.2	125	20.4	1.155, 0.699 – 1.908, p=0.256
	TG	59	48.7	308	50.3	1.065, 0.721 – 1.573, p=0.199
	TT	40	33.1	179	29.3	0.837, 0.552 – 1.279,

						p=0.213
	Allele G	103	42.6	558	45.6	1.131, 0.856 – 1.494, p=0.142
	Allele T	139	57.4	666	54.4	0.793, 0.601 – 1.046, p=0.141
MTHFR rs1801133 (S677T)	SS	63	45.3	376	54.1	1.422, 0.986 – 2.050, p=0.187
	ST	61	43.9	251	36.1	0.723, 0.500 – 1.046, p=0.188
	TT	15	10.8	68	9.8	0.897, 0.496 – 1.620, p=0.302
	Allele C	187	67.3	1003	72.2	1.261, 0.956 – 1.663, p=0.141
	Allele T	91	32.7	387	27.8	0.793, 0.601 – 1.046, p=0.141

When analyzing the distribution of carriage frequencies of genotypes rs1801133 (C677T) of the MTHFR gene and rs1378942 of the CS K gene , no pronounced differences were identified among both indigenous and non-indigenous residents. However, the occurrence of the homozygous genotype TT rs1378942 of the CS K gene and rs1801133 (C677T) of the MTHFR gene among indigenous people with MS is slightly higher than among non-indigenous patients with MS (Table 3).

Table 3

Frequency of genotypes of single nucleotide polymorphisms in metabolic syndrome among non-indigenous and indigenous people with MS

Polymorphism –	Genotype	Non-Indigenous People		Native people		OR, 95% CI, p
		n	%	n	%	
CSK	GG	87	21.1	38	19.1	0.884, 0.578 – 1.35, p= 0.217

rs1378942						
	TG	214	51.8	94	47.2	0.832, 0.593 – 1.168, p= 0.173
	TT	112	27.1	67	33.7	1.364, 0.947 – 1.966, p= 0.186
	Allele G	388	47.0	170	42.7	0.842, 0.661 – 1.071, p=0.123
	Allele T	438	53.0	228	57.3	1.188, 0.934 – 1.512, p=0.123
MTHFR rs1801133 (C 677 T)	SS	249	53.4	127	55.5 –	1.085, 0.79 – 1.491, p =0.162
	ST	174	37.3	77	33, 6	0.85, 0.61 – 1.185, p= 0.1 7
	TT	43	9, 3	2 5	10.9	1 , 206 , 0.716 – 2.209, p= 0.266
	Allele C	672	72.1	331	72.3	0.992, 0.773 – 1.273, p=0.127
	Allele T	260	27.9	127	27.7	1.008, 0.786 – 1.294, p=0.127

Associations of polymorphisms rs1378942 of the CSK gene and rs1801133 C677T of the MTHFR gene with MS components were studied. The main symptom of MS is abdominal obesity (AO). Among patients with and without AO, the frequency of carriers of the heterozygous genotype T G rs1378942 of the CSK gene was 50.3% and 48.7%, respectively. Carriage of the mutant allele T rs1801133 C677T of the MTHFR gene among patients with AO was 9.8%, among patients without AO – 10.8% (OR 0.856, 95% CI 0.474 – 1.545, p = 0.302). An association of hypertension with carriage of the mutant T allele rs1801133 C677T of the MTHFR gene was identified (OR 1.367, 95% CI 1.015 – 1.841, p = 0.047). When analyzing the lipid spectrum, it turned out that carriage of the TT rs1378942 genotype of the CSK gene is associated with hypertriglyceridemia (OR 2.018, 95% CI 1.110 – 3.368, p = 0.09) (Table 4).

Table 4

Association of single nucleotide polymorphisms with MS parameters

Sign	rs1378942 CSK gene				rs1801133 (C677T) MTHFR gene			
	GG n (%)	TG n (%)	TT n (%)	OS 95%CI p	CC n (%)	ST n (%)	TT n (%)	OS 95% CI p
Abdominal obesity								
Patients with AO	125 (20.4)	308 (50.3)	179 (29.3)	0.837 0.552 – 1.270 p=0 , 213	376 (54.1)	251 (36.1)	68 (9.8)	0.856 _ _ 0.474 – _ _
Patients without AO	22 (18.2)	59 (48.7)	40 (33.1)		63 (45.3)	61 (43.9)	15 (10.8)	1,545 _ _ p=0 , 302
Arterial hypertension								
Patients with hypertension	26 (23.6)	52 (47.3)	32 (29.1)	0.963 0.620 – 1.496 p=0 , 225	51 (46.4)	42 (38.2)	17 (15.4)	1 , 367 1,015 – _ _
Patients without hypertension	147 (20.1)	367 (50.1)	219 (29.8)		415 (53.8)	285 (36.9)	72 (9.3)	1,841 _ _ p = 0.047
Hypercholesterolemia								
Patients with HCS	138 (19.9)	350 (50.6)	204 (29.5)	0.996 0.698 – 1.420 p=0 , 181	368 (53.5)	257 (37.4)	63 (9.1)	0.891 0.519 – _ _
Patients without HCS	36 (19.4)	95 (51.1)	55 (29.5)		98 (52.4)	70 (37.4)	19 (10.2)	1,530 _ _ p = 0.276
Hypertriglyceridemia								

Patients with HTG	157	398	245	2.018	425	296	82	1.365
	(19.6)	(49.8)	(30.6)	1.110-3.668 p=0.019	(52.9)	(36.9)	(10.2)	0.575 – 3.237 p=0 , 441
Patients without GTG	17 (21.8)	47 (60.2)	14 (18)		41 (52.6)	31 (39.7)	6 (7.7)	
Increased LDL cholesterol levels								
Patients with elevated LDL cholesterol	103 (20.9)	242 (49.1)	148 (thirty)	1.059 0.790 – 1.419 p = 0.149	273 (55.2)	184 (37.2)	38 (7.6)	0.559 0.358 – 0.872 p = 0.012
Patients without elevated LDL cholesterol	71 (18.4)	203 (52.7)	111 (28.9)		193 (50)	143 (37)	50 (13)	
Decrease in HDL cholesterol levels								
Patients with decreased HDL cholesterol	20 (15.4)	66 (50.8)	44 (33.8)	1.234 0.944 – 1.612 p = 0.136	67 (50.8)	48 (36.4)	17 (12.8)	1 , 153 0.868 – 1.531 _ _ _ _ p=0 , 145
Patients without a decrease in HDL cholesterol	154 (20.6)	379 (50.7)	215 (28.7)		399 (53.3)	279 (37.2)	71 (9.5)	
Hyperglycemia								

Patients with HS	47 (16.7)	151 (53.5)	84 (29.8)	1.021 0.748 – 1.392 p=0 , 158	156 (54.8)	93 (32.6)	36 (12.6)	1,513 0.964 – 2.374 _ _ _ – p=0 , 230
Patients without GG	127 (21.3)	294 (49.3)	175 (29.4)		310 (52)	234 (39.3)	52 (8.7)	

Abbreviations: AO - abdominal obesity, AG - arterial hypertension, GG - hyperglycemia, HTG - hypertriglyceridemia , HCS - hypercholesterolemia , LDL cholesterol - low-density lipoprotein cholesterol , HDL cholesterol - high-density lipoprotein cholesterol

As a result of our study, we discovered a connection between the rs1801133 C677T polymorphism of the MTHFR gene and rs1378942 of the CSK gene with individual components of MS. Thus, carriers of heterozygous T G rs1378942 CSK gene were somewhat more common among patients with obesity (50.3%) and hyperglycemia (53.5%), less often among patients with hypertriglyceridemia (49.8% vs 60.2%). Among patients with the mutant T allele rs1801133 C677T of the MTHFR gene in a heterozygous and homozygous state, an association with hypertension was detected (p = 0.047), and carriers of the TT genotype were significantly less common in the group with increased LDL cholesterol (7.6% vs 13.0% , p =0.012).

Conclusion

Thus, in young patients with MS, both indigenous and non-indigenous, no association was found with the rs1801133 C677T polymorphisms of the MTHFR gene and rs1378942 of the CSK gene. However, associative links have been identified with its individual components, such as arterial hypertension, hypertriglyceridemia , and increased LDL cholesterol levels. Timely study of the genetic predisposition of individuals to certain metabolic disorders and reducing the influence of modifiable risk factors, such as physical inactivity, eating disorders, obesity, will prevent the development of cardiovascular diseases and complications.

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