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Association of Lipids' Metabolism with Vitamin D Receptor (rs10735810, rs222857) and Angiotensinogen (rs699) Genes Polymorphism in Essential Hypertensive Patients

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Abstract

BACKGROUND: Cardiovascular (CV) diseases are the most spread cause of mortality in the world. Essential arterial hypertension (EAH), as a major risk factor for the development of CV diseases, is a multifactorial disease involving environmental and genetic factors together with risk-conferring behaviors.

AIM: The purpose of this study was to analyze lipid metabolism changes in patients with EAH depending on the Vitamin D receptor *(VDR* rs2228570 (*aka* rs10735810)) and angiotensinogen (*AGT* rs699) genes polymorphism.

MATERIALS AND METHODS: The single-stage study involved 100 patients suffering from Stage 2 EAH, 1–3 degrees of blood pressure increase, high and very high CV risks, 21% (21) men, and 79% (79) women. The average age of patients was 59.86 ± 6.22 years old. The control group included 60 practically healthy individuals of an appropriate age and sex distribution. To examine the *VDR* gene (rs10735810, rs2228570) and *AGT* gene (rs699) polymorphism, a qualitative real-time polymerase chain reaction was made. The lipid metabolism was studied by determining the blood plasma content of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs).

RESULTS: T allele of *AGT* gene is associated with reduced HDL-C level in men and increased TGs level in women. The EAH risk increases 4.5 times as much among the TC-genotype carriers and lowered HDL-C level (odds ratio [OR] = 6.43; p = 0.01). The EAH risk increases as far as the HDL-C level reduction, irrespective of the *VDR* gene alleles condition 1.83 times (OR = 2.37; OR 95% confidence interval [CI]: 1.02–5.51; p = 0.04) and 1.9 times (OR=2.43; OR 95% CI: 0.99–5.97; p = 0.04). HDL-C reduction and LDL-C elevation in women increase the EAH risk 2.4 times (OR = 3.27; p = 0.01) and 1.24 times (OR = 3.67; p = 0.01), respectively.

CONCLUSIONS: The EAH risk increases with a reduced HDL-C level in the TC genotype carriers of the *AGT* gene and irrespective of *VDR* gene polymorphic variants.

Introduction

Cardiovascular (CV) diseases are the most spread cause of mortality in the world and it is responsible for >4 million deaths in Europe each year [1]. Essential arterial hypertension (EAH) has a high prevalence and is a major risk factor for the development of CV diseases [2]. Hypertension affects over 1.2 billion individuals worldwide and has become the most critical and expensive public health problem [3]. Higher the long-term level of blood pressure (BP), greater the chances of hypertension complications, such as myocardial infarction, renal failure, stroke, and heart failure [4]. Reducing BP in patients with EAH is the most effective way to lower the mortality rates and hypertension-mediated organ damage [5].

EAH is a multifactorial disease involving environmental and genetic factors together with risk-conferring behaviors. EAH infrequently befalls in isolation and often combines with other CV risk factors such as dyslipidemia and glucose intolerance, or other metabolic disorders evidence [6], [7]. Obesity, lack of physical activity, and excessive salt intake are the most well-known environmental factors associated with EAH. An increased risk of CV complications is associated with dyslipidemia as well [8]. It plays an important role in the formation of the atherosclerotic lesions of the arteries in general including the kidneys and cardiac muscle [1]. The lipids' level in the blood plasma is considerably determined by genetic factors. In general, the inheritance model in patients with dyslipidemia is not indicative of the fact that there is one disorder with one gene (monogenic) causing pathology. It must originate from the inheritance of more than 1 variant of a gene that affects lipoprotein metabolism, which in itself may have a relatively small effect, but in combination with one or the other has a greater effect on triglycerides (TGs) or high-density lipoprotein cholesterol (HDL-C). The inheritance pattern is polygenic [9]. A pathogenic genes

part such as the apolipoprotein (APO) family – APOA, APOB, and APOE is the most studied, but several others are requiring further investigations.

Methods

Ethical approval

This study conforms to international bioethical standards (European Convention on Human Rights and Biomedicine, the WMA Declaration of Helsinki on ethical principles of scientific medical research involving human subjects, GCP, EUC directive #609) and approved by Commission for Bioethics in Research of the Bukovinian State Medical University, Ukraine. All patients signed written permissions and obtained full information about the study before participation.

Selection and description of participants

The single-stage study involved 100 patients. Among them, 21% (21) were men and 79% (79) were women, an average age 59.86 ± 6.22 years old (y o). The control group included 60 practically healthy individuals of an appropriate age and sex distribution.

Inclusion criteria

EAH patients were included in the current study with hypertension-mediated organ damage (target organs damage – 2nd severity stage, asymptomatic disease), from the 1st through to the 3rd grade of BP values; moderate-high CV risk; age above 30 y o. All enrolled subjects signed a consent form to participate in the study.

Exclusion criteria

Have been described in our former publications [6], [7], [10], [11]: We excluded patients with EAH Stage 3 (identified CV disease); chronic heart failure higher than II functional class (NYHA III-IV), EAH patients with complications of hypertension-mediated organ damage; secondary AH; diabetes mellitus type I (DM 1), sub- and decompensated DM 2 (with diabetes target organ damage); malignant or uncontrolled AH; sub- and decompensated diseases of the liver (3 times over the norm level of aspartate aminotransferase, alanine aminotransferase); bronchial asthma, chronic obstructive pulmonary disease of III-IV stage with C or D risk value (Gold, 2019); exacerbated infectious diseases or during unstable remission; psychological disorders; the oncologic problem of any location; taking oral corticosteroids or contraceptives; and pregnancy or lactation period.

Genotyping analysis

To examine the *VDR* gene (rs10735810, rs2228570) and *AGT* gene (704 rs699) polymorphism, a qualitative real-time polymerase chain reaction was made. The lymphocytes isolated from the peripheral venous blood stabilized by EDTA were used as the material for the study. The lymphocytes' DNA was isolated and purified according to the Thermo Scientific GeneJET Genomic DNA Purification Kit instructions (Thermo Fisher Scientific, USA) as it was described in our former publications [6], [7], [10], [11]. Amplification and genotyping were conducted on the device CFX96 Touch™ (Bio-Rad Laboratories, Inc., USA) with the use of specific complementary probes TaqMan. The software of the thermal cycler CFX96 registered the melting temperature of TaqMan probes considering fluorescence marks Fam (the samples which are homozygous for *VDR* gene A allele and *AGT* gene C allele on Fam canal) and Hex (the samples which are homozygous for *VDR* gene G allele and *AGT* gene T allele on Hex canal).

Plasma lipids included total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL- C), and TGs assessment using BioSystem S.A. reagents (Spain), on a chemiluminescent analyzer "ACCENT-200" (Poland). As "target" lipids' levels were taken as follows, according to the European and National Guidelines recommendation: TC <5.0 mmol/l for persons with moderate CV risk, <4.5 mmol/l for persons with high CV risk, <4.0 mmol/l for persons with extremely high CV risk; LDL-C <3.0 mmol/l for persons with moderate CV risk, <2.5 mmol/l – for high CV risk, <1.8 mmol/l – for extremely high CV risk; TGs generally <1.7 mmol/l; and HDL-C >1.02 mmol/l for men and >1.2 mmol/l for women [12].

Statistical analysis

Statistical analysis was performed using StatSoft Statistica 7.0 (USA) software. Estimation of the sample sets difference was performed using an odd Student's t-criterion. Analysis of qualitative data (categorical variables) and risk of pathology development were assessed by a binary logistic regression model using relative risk (RelR); risk ratio was estimated by odds ratio (OR) with 95% confidence interval [95% CI] using a Chi-square test (χ^2) (df = 1). The difference was considered reliable with $p < 0.05$.

Results

The genotype distribution depending on *VDR* and *AGT* genes polymorphic variants in the control group and in the group of patients with EAH did not differ reliably (Tables 1 and 2). More than half of patients in both groups

Table 1: Parameters of lipid metabolism depending on VDR gene (rs10735810, rs2228570) polymorphism, M ± m

Group	Genotype	Sex	TC, mmol/L	TGs, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L
Control, n = 60	AA, n = 18	M	5.92 ± 0.53	1.89 ± 0.68	1.17 ± 0.21	4.53 ± 0.47
		F	5.93 ± 0.87	1.71 ± 0.44	1.43 ± 0.1	4.3 ± 0.93
	AG, n = 28	M	5.48 ± 0.65	1.76 ± 0.38	1.32 ± 0.33	3.85 ± 0.45
		F	5.49 ± 0.53	1.49 ± 0.43	1.58 ± 0.25	3.76 ± 0.5
	GG, n = 14	F	5.2 ± 0.43	1.67 ± 0.31	1.51 ± 0.2	3.63 ± 0.4
						P_{AA}=0.04
Patients, n = 100	AA, n = 23	M	4.57 ± 0.34	2.34 ± 0.36	1.16 ± 0.17	3.12 ± 0.32
			p=0.006			p=0.003
		F	6.08 ± 0.44	2.0 ± 0.39	1.31 ± 0.25	4.59 ± 0.41
	AG, n= 50	M	5.73 ± 0.53	2.36 ± 0.4	1.06 ± 0.15	4.47 ± 0.52
			p_{AA}=0.02			p_{AA}=0.006
		F	5.65 ± 0.41	1.9 ± 0.35	1.3 ± 0.17	4.07 ± 0.37
			p_{AA}=0.001		p=0.04	p_{AA}=0.002
	GG, n = 27	M	5.55 ± 0.34	1.74 ± 0.23	1.2 ± 0.21	4.13 ± 0.32
						p_{AA}=0.04
		F	5.33 ± 0.41	1.85 ± 0.3	1.32 ± 0.19	3.91 ± 0.36
			p_{AA}=0.03			p_{AA}=0.03

M: Males; F: Females; TC: Total cholesterol; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; P – The significance of differences with a control group of the same genotype; p_{AA} – The significance of differences with AA genotype carriers in a particular group (control/patients).

were heterozygous which corresponds to the normal Hardy–Weinberg equilibrium distribution. Subjects' distribution in the groups by age and gender did not differ reliably depending on genotype either (p > 0.05).

Table 2: Parameters of lipid metabolism depending on AGT gene (rs699) polymorphism, M ± m

Group	Genotype	Sex	TC, mmol/L	TGs, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L
Control, n=48	TT, n=8	M	4.65 ± 0.37	1.89 ± 0.13	0.91 ± 0.08	3.72 ± 0.33
		F	5.45 ± 0.17	1.67 ± 0.06	1.7 ± 0.01	3.77 ± 0.09
	TC, n=25	M	6.14 ± 0.34	1.58 ± 0.58	1.2 ± 0.14	4.75 ± 0.31
			P_{TT}=0.02		P_{TT}=0.03	P_{TT}=0.04
		F	5.55 ± 0.86	1.64 ± 0.47	1.43 ± 0.1	3.97 ± 0.38
					P_{TT}<0.001	
	CC, n=15	M	5.7 ± 0.53	2.44 ± 1.06	1.56 ± 0.5	3.49 ± 0.19
						P_{TC}=0.002
		F	5.52 ± 0.41	1.83 ± 0.42	1.61 ± 0.31	3.74 ± 0.29
Patients, n=72	TT, n=10	M	5.2 ± 0.33	2.05 ± 0.54	0.87 ± 0.06	3.88 ± 0.14
		F	5.73 ± 0.46	2.04 ± 0.39	1.3 ± 0.18	4.17 ± 0.47
	TC, n=43	M	5.79 ± 0.14	2.37 ± 0.41	1.1 ± 0.15	4.45 ± 1.17
				p=0.03	P_{TT}=0.01	
		F	5.99 ± 0.39	2.06 ± 0.38	1.29 ± 0.17	4.45 ± 0.66
	CC, n=19	M	5.02 ± 0.36	1.81 ± 0.24	1.22 ± 0.26	3.68 ± 0.53
					P_{TT}=0.03	
		F	5.52 ± 0.56	1.43 ± 0.28	1.36 ± 0.59	4.06 ± 0.48
				P_{TC}=0.02		

M: Males; F: Females; TC: Total cholesterol; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; P – The significance of differences with a control group of the same genotype; pTT, pTC – The significance of differences with TT, TC genotypes carriers in a particular group (control/patients).

Lipid metabolism parameters considering *VDR* gene polymorphic variants are presented in Table 1. The parameters different from those of the normal values were found both in the control group and patients with EAH. Increased TC levels (in 76.7% of subjects in the control group and 67% of patients with EAH) and LDL cholesterol (83.3% and 89%, respectively) were found.

The men carriers of AA genotype suffering from EAH presented 22.8% lower TC than in the control group (p = 0.006) and 20.2% lower in comparison with the AG genotype carriers (p = 0.02). The women AA genotype carriers with EAH had 25.4% higher TC level in comparison with GG genotype carriers' women (p = 0.03).

Similar situation was observed with the LDL-C level: Male patients, AA genotype carriers, presented 31.1% lower values in comparison with the control group (p = 0.003); the difference with AG and GG genotypes patients carriers was 30.2% and 24.5%, respectively (p = 0.006 and p = 0.04). On the contrary, AA genotype women carriers possessed 12.8% (p = 0.002) and 17.4% (p = 0.03) higher LDL-C values in comparison with the AG and GG genotype carriers.

The TGs and HDL-C levels did not differ reliably between the *VDR* gene polymorphic variants.

Considering the above parameters, G allele of the *VDR* gene can be suggested to be associated with the TC and LDL-C levels elevation in men; AA genotype is associated with an increased level of these parameters in women.

The parameters of lipid metabolism considering *AGT* gene polymorphic variants are presented in Table 2. The TC mean values were higher than that of the normal ones practically in all the groups. The highest parameters were found in the TC genotype carriers, especially among men of the control group – 6.14 ± 0.34 mmol/L versus 5.79 ± 0.14 mmol/L in patients with EAH, though there was no reliable difference found. The TGs level was higher in the T allele carriers (especially TC genotype) in comparison with the control group by 50% among men (p = 0.03) and 25.6% among women. The HDL-C level was lower in the TT genotype men carriers in both groups than that of the threshold, while the C allele carriers (especially CC genotype) had 26.4% (p = 0.01) and 40.2% (p = 0.03) higher values in comparison with the TT genotype carriers. The LDL-C parameters were the highest among the TC genotype carriers, but in comparison with other genotypes carriers, there was no reliable difference found.

Thus, the T allele of the *AGT* gene (rs699) can be suggested to be associated with the lower HDL-C level in men and an increased TGs level.

Assessment of the EAH risks considering lipid metabolism parameters and *VDR* gene polymorphism is shown in Table 3. The EAH risk increases as far as

Table 3: Lipids values as predictors of essential arterial hypertension in observed population depending on VDR gene (rs10735810, rs2228570) polymorphism

Potential risk factor	Parameters				
	RR	95% CI RR	OR	95% CI RR	p
AA genotype					
↑ TC	1.08	0.84–1.38	1.6842	0.27–10.43	>0.05
↑ TGs	0.94	0.53–1.66	0.87	0.25–3.01	>0.05
↓ HDL-C	1.96	0.73–5.22	2.69	0.67–10.74	>0.05
↑ LDL-C	1.03	0.84–1.26	1.31	1.67–10.35	>0.05
AG genotype					
↑ TC	0.95	0.70–1.29	0.85	0.31–2.34	>0.05
↑ TGs	1.68	0.87–3.23	2.3	0.86–6.21	>0.05
↓ HDL-C	1.77	0.80–3.92	2.25	0.77–6.54	>0.05
↑ LDL-C	1.05	0.88–1.25	1.5	0.37–6.11	>0.05
GG genotype					
↑ TC	0.73	0.44–1.19	0.43	0.11–1.72	>0.05
↑ TGs	0.78	0.48–1.25	0.5	0.13–2.0	>0.05
↓ HDL-C	2.33	0.58–9.36	3.0	0.55–16.38	>0.05
↑ LDL-C	1.19	0.83–1.72	2.3	0.48–11.08	>0.05
A allele					
↑ TC	0.93	0.75–1.14	0.74	0.31–1.76	>0.05
↑ TGs	1.37	0.9–2.08	1.78	0.84–3.78	>0.05
↓ HDL-C	1.83	0.99–3.37	2.37	1.02–5.51	0.04
↑ LDL-C	1.04	0.91–1.19	1.41	0.44–4.51	>0.05
G allele					
↑ TC	0.87	0.67–1.13	0.66	0.29–1.49	>0.05
↑ TGs	0.98	0.64–1.52	0.97	0.43–2.17	>0.05
↓ HDL-C	1.91	0.96–3.81	2.43	0.99–5.97	0.04
↑ LDL-C	1.09	0.22–1.29	1.78	0.63–5.02	>0.05

RR: Risk ratio; OR: Odds ratio; 95% CI: Confidence interval; P – The significance of differences with a control group of the same genotype; TC: Total cholesterol; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

the HDL-C level reduction irrespective of the *VDR* gene alleles condition 1.83 times (OR = 2.37; OR 95% CI: 1.02–5.51; p = 0.04) and 1.9 times (OR = 2.43; OR 95% CI: 0.99–5.97; p = 0.04).

The EAH risk considering lipid metabolism parameters and *AGT* gene (rs699) polymorphism was assessed as well (Table 4). The EAH risk increases 4.5 times as much in the TC genotype carriers in case of lowered HDL-C level (OR = 6.43; OR 95% CI: 1.33–30.99; p = 0.01).

Table 4: Lipids values as predictors of essential arterial hypertension in observed population depending on AGT gene (rs699) polymorphism

Potential risk factor	Parameters				
	RR	95% CI RR	OR	95% CI RR	p
TT genotype					
↑ TC	0.8	0.42–1.53	0.5	0.07–3.85	>0.05
↑ TGs	1.2	0.51–2.83	1.5	0.23–9.8	>0.05
↓ HDL-C	0.67	0.32–1.39	0.33	0.04–2.52	>0.05
↑ LDL-C	0.9	0.73–1.11	0	-	>0.05
TC genotype					
↑ TC	0.93	0.70–1.22	0.74	0.24–2.28	>0.05
↑ TGs	0.57	0.26–1.21	0.45	0.15–1.32	>0.05
↓ HDL-C	4.53	1.13–18.26	6.43	1.33–30.99	0.01
↑ LDL-C	1.09	0.91–1.30	2.32	0.48–11.29	>0.05
CC genotype					
↑ TC	0.87	0.51–1.47	0.69	0.17–2.81	>0.05
↑ TGs	0.92	0.39–2.17	0.88	0.22–3.52	>0.05
↓ HDL-C	1.18	0.41–3.45	1.27	0.28–5.68	>0.05
↑ LDL-C	1.08	0.73–1.58	1.36	0.28–6.68	>0.05
C allele					
↑ TC	0.92	0.72–1.18	0.75	0.31–1.78	>0.05
↑ TGs	0.68	0.38–1.2	0.57	0.24–1.31	>0.05
↓ HDL-C	2.37	0.79–7.15	3.07	0.81–11.63	>0.05
↑ LDL-C	1.1	0.92–1.3	1.85	0.61–5.56	>0.05

RR: Risk ratio; OR: Odds ratio; 95% CI: Confidence interval; P – Significance of differences with control group of the same genotype; TC: Total cholesterol; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

Analysis of lipid values as EAH predictors in observed population considering sex demonstrated that HDL-C reduction and LDL-C elevation increase this risk 2.4 times (OR = 3.27; OR 95% CI: 1.22–8.73; p = 0.01) and 1.24 times (OR = 3.67; OR 95% CI: 1.27– 10.6; p = 0.01) in women, respectively (Table 5).

Table 5: Lipids values as predictors of essential arterial hypertension in observed population depending on sex

Potential risk factor	Parameters				
	RR	95% CI RR	OR	95% CI RR	p
↑ TC					
M	0.7	0.46–1.06	0.3	0.07–1.18	>0.05
F	0.94	0.74–1.2	0.82	0.34–1.95	>0.05
↑ TGs					
M	1.57	0.81–3.06	2.33	0.67–7.95	>0.05
F	1.44	0.91–2.3	1.95	0.88–4.3	>0.05
↓ HDL–C					
M	1.4	0.58–3.35	1.64	0.45–5.94	>0.05
F	2.41	1.1–5.28	3.27	1.22–8.73	0.01
↑ LDL–C					
M	0.81	0.66–1.0	0	–	>0.05
F	1.24	1.01–1.51	3.67	1.27–10.6	0.01

RR: Risk ratio; OR: Odds ratio; 95%CI: Confidence interval; P – The significance of differences with a control group of the same genotype; TC: Total cholesterol; TGs: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.

Discussion

EAH is a multifactorial disease that includes such factors as dyslipidemia, smoking, DM [10], [13], and obesity [13], [14]. Genes determine approximately 20–60% of BP variability and some peculiarities of hypertensive-mediated organs damage in different populations [6], [7], [8], [11], [15].

As for the *AGT* gene, SNP rs699 is a T to C substitution in the exon 2, resulting in a functional methionine (M) to threonine (T) exchange at codon 268 (M268T). Previously, rs699 was positioned to the amino acid 235 and the SNP is, therefore, also referred to as M235T. The rs699 threonine variant is associated with higher plasma *AGT* levels and BP [15].

The *VDR* gene is located on chromosome 12q13.1, and SNPs of this gene can affect BP. One of the most studied SNPs of the *VDR* gene is Fok I (rs228570 or rs10735810). Fok I polymorphism can generate truncated proteins and is associated with an increased risk for hypertension. Fok I polymorphism is caused by a thymine-to-cytosine transition, which leads to a translational frameshift characterized by an extension of the open reading frame to the next initiation codon (ATG), resulting in the synthesis of a truncated 424-amino acid protein [16].

The number of studies dealing with the association of lipid metabolism and *VDR* and *AGT* genes polymorphism in patients with EAH is limited. Khamlaoui *et al*. indicated the relation of *AGT* genotypes with dyslipidemia, that is, reliably higher parameters of TC and LDL-C among the TT genotype carriers [17]. Borai *et al*. stated that patients with ischemic heart disease present a considerable difference between *AGT* genotypes concerning HDL-C with the value p < 0.05 [8]. Junusbekov also affirmed that the CC genotype of rs699 was significantly related to HDL-C levels (p = 0.020) [18]. Results presented by Jia *et al.* indicated that *VDR* polymorphism correlates with the risk of an increased LDL-C level [19]. The studies carried out by Aline Hajj found that men carriers of the mutation *VDR* genotype possess a higher level of TGs and lower level of HDL-C (p = 0.0036 and p = 0.005) [20].

The optimal approach to investigate patients who present EAH symptoms depending on genetics' polymorphism remains controversial. Our prospective case–control clinical research was randomized and designed to test the hypothesis that genes polymorphism *VDR* (rs10735810, rs222857) and *AGT* (rs699) would associate with lipids metabolism pathogenic pathway. Therefore, further investigation of the gene-environment interactions and gene-metabolism associations still needs to be provided and extended.

Conclusions

T allele of *AGT* gene is associated with a lower level of HDL-C in hypertensive men and a higher level of TGs in EAH women. HDL-C lowered level increases the EAH risk 4.5 times as much in the TC genotype

carriers of *AGT* gene (rs699) (OR = 6.43; p = 0.01) and 1.83 (OR = 2.37; p = 0.04) and 1.9 times (OR = 2.43; p = 0.04) irrespective of the *VDR* gene allele condition. In women, the HDL-C low level and LDL-C elevation increase EAH risk 2.4 times (OR = 3.27; p = 0.01) and 1.24 times (OR = 3.67; p = 0.01), respectively.

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