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Original Research

Dyslipidemia as a predictor of essential arterial hypertension depending on *AGTR1 (RS5186)* and *VDR (RS2228570)* genes polymorphism

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Abstract

Background and aims: The purpose of the work was to study lipid disorders and essential arterial hypertension (EAH) risk depending on *AGTR1 (rs5186)*, *VDR (rs2228570)* genes polymorphism. **Material and method:** One hundred subjects with EAH and target-organ damaging (2nd stage), moderate, high, or very high cardiovascular risk was involved in the case-control study. The control group consisted of 60 healthy individuals of relevant gender and age. The lipid panel was determined by the colorimetric enzymatic method. Gene polymorphism of AGTR1 (rs5186) and VDR (rs2228570) was detected by polymerase chain reaction. **Results:** The EAH risk increases in C-allele carriers of *AGTR1* (*rs*5186) gene at hypercholesterolemia 1.5 times, at an increase in low-density lipoprotein cholesterol (LDL-C) and atherogenic index (AI) – 1.58 and 2.12 times, respectively. The risk of EAH increases at hypertriglyceridemia 1.89 times and at an increase in LDL-C – 1.26 times in AA-genotype carriers of *VDR* (*rs*2228570) gene. The risk in EAH synergistically escalates almost twice in A-allele carriers of *VDR* (*rs*2228570) gene with a decrease in high-density lipoprotein cholesterol (HDL-C) and increase of AI, significantly in AG-carriers, though. **Conclusions:** The EAH risk escalates at hypercholesterolemia, elevated LDL-C and AI in C-allele carriers of *AGTR1* (*rs*5186) gene, likewise at decreased HDL-C, increased AI in A-allele carriers of *VDR* (*rs*2228570) gene in the observed.

Keywords: dyslipidemia, essential arterial hypertension, risk, AGTR1 (rs5186), VDR (rs2228570)

Background and aims

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in both Europe and Ukraine. Genetic and pathology studies, as well as observational and interventional studies have proven the role of dyslipidemia, especially hypercholesterolemia in the development of cardiovascular pathology. Increasing the level of high-density lipoprotein cholesterol (HDL-C) has a protective effect, whereas increasing the level of low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) has an atherogenic effect. There is a strong relationship between total cholesterol (TC), LDL-C, and cardiovascular risk (CVR) [1, 2]. Meta-analyzes of many studies have shown a clear dose-response relationship between LDL-C reduction and CVR. For every 1.0 mmol / l reduction of LDL-C there is a 20–25% reduction in mortality from cardiovascular complications, including EAH. Subsequent studies have confirmed that patients with very high CVR >10% reduction in LDL-C by at least 50% of baseline

(target level <1.4 mmol / l (<55 mg / dl)) is associated with the lowest risk of recurrent cardiovascular events in the population [1, 3, 4].

Essential arterial hypertension (EAH) remains the most common non-communicable planetary disease, regardless of the income level of the country and its citizens [5–8]. The overall prevalence of hypertension in the world among adults is about 30–45%, with a standardized prevalence in men and women – 24% and 20%, respectively and increases with age [6, 7, 9]. In addition to the blood pressure level, age, sex, and harmful habits, there is a number of other little-studied predictors in the stratification of the CVR: metabolic (diabetes mellitus, hyperuricemia, dyslipidemia, waist circumference), immunological (leptin-adipocytokine imbalance), hormonal (early menopause) and genetic risk factors, as well as behavioral, psychosocial, nutritional, socio-economic factors that affect the quality of life, the course of the disease and are often associated with its severity.

Therefore, early detection of EAH predictors and additional risk factors for possible complications, as well as their opportune modification, becomes a cornerstone of primary and secondary prevention of CVD on the whole and EAH in particular.

Material and method

Study design and patients

The study was conducted according to the World Medical Declaration of Helsinki on the Ethical Principles of Medical Research involving human subjects and it has complied with basic international standards of good clinical and laboratory practices (GCP, GLP). The diagnosis of EAH was established as reported by the current Ukrainian (Order of 24.05.2012 № 384) and European guidelines (ESC, ESH 2021) [5, 10]. One hundred and ten patients with EAH and hypertensive-mediated organs damaging (2nd stage), moderate, high, or very high CVR and 60 practically healthy individuals were involved in the case-control study. After screening for inclusion and exclusion criteria, which have been detailed in our publications [12–17] 100 subjects (70.84% females, 29.16% males) with EAH formed a research group. The mean age of patients was 57.86±7.81 years and ranged from 41 to 74 years. The control group consisted of 60 practically healthy individuals: 62.5% women, 37.5% men, the mean age was 46.37±6.77 years was ranged from 30 to 58 years, who did not differ by gender and age and from the group of patients ($p>0.05$). Individuals in the study and control groups were not related.

Laboratory, anthropometric and clinical data collection

The lipid panel: Total cholesterol (TC), Triglycerides (TG), Low-density lipoprotein cholesterol (LDL-C), and High-density lipoprotein cholesterol (HDL-C) were investigated in blood plasma using reagents "ACCENT-200 CHOL", "ACCENT-200 HDL Direct", "ACCENT-200 LDL Direct", "ACCENT-200 TG mono" of automated biochemistry analyzer "ACCENT 200" (CORMAY, Poland). According to the European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemias [2, 4, 10] lipid profile values were determined as follows: TC <5.0 mmol/l for individuals at low/moderate CVR, <4.5 mmol/l for individuals at high CVR, <4.0 mmol/l for individuals at very high CVR; LDL-C <3.0 mmol/l for individuals at low/moderate CVR, <2.5 mmol/l for individuals at very high CVR, <1.8 mmol/l for individuals at very high CVR; TG <1.7 mmol/l; HDL-C >1.02 mmol/l for males, 1.2 mmol/l for females. The atherogenic index (AI) was calculated by the formula: (TC – HDL-C)/ HDL-C. The "target" AI for persons younger than 30 was considered as <2.5 and for those older than 30 years – <3.5.

AGTR1 gene genotyping was performed for 120 individuals (72 patients and 48 healthy persons) and VDR gene – for 160 individuals (100 patients and 60 healthy persons). Vacutainer tubes containing K2-EDTA were used to collect the venous blood of the examined. Extraction of DNA from the nuclei of the lymphocytes of patients was performed according to the instructions in the Thermo Scientific GeneJET Genomic

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DNA Purification Kit (Thermo Fisher Scientific, USA), as it was described in our former publications [18–21]. Alleles discrimination of AGTR1 (rs5186) and VDR (*rs2228570*) genes polymorphisms, obtained by RT-PCR system CFX96 Touch (Bio-Rad, USA), was analyzed by licensed computer Software Bio-Rad Real-Time (Microsoft, USA).

Statistical analysis

The database obtained was designed in Microsoft Excel worksheets. Statistical analysis was performed using Statistica™ 7.0 (Statsoft® Inc), Primer of Biostatistics® 6.05 та MS® ExcelTM 2010. Mean values were given as M±m. A statistically significant test result was considered at a p-value less than 0.05. Pearson's criterion (χ^2) is used for the genotypes distribution comparison. Analysis of qualitative data (categorical variables), the risk of pathology development was assessed by a binary logistic regression model using relative risk (RelR); risk ratio (RR) was estimated by odds ratio (OR) with a 95% confidence interval [95% CI] using a chi-square test (χ^2) (df=1).

Results

Analyzing the lipid panel results from the examined (Table 1) we found that HDL-C in the study group was significantly lower than in the control group – by 10.56% (p<0.05). No statistically significant differences were found in other values.

Changes in the lipid profile, considering the severity of EAH, have shown that only HDL-C in hypertensive patients with 2nd and 3rd of BP elevation was significantly lower than in the control group by 14.89% (p=0.048). No statistically significant differences have been found in other values.

Dyslipidemia has not been dependent on polymorphic variants of the AGTR1 (*A1166C*) gene in patients with EAH and is characterized by hypercholesterolemia due to LDL-C, hypertriglyceridemia on the background of normal mean values of HDL-C that, however, has not affected the atherogenic index (AI) elevation (Table 2). At the same time, HDL-C has been higher in healthy individuals with the mutant C-allele, and LDL-C, on the other hand, was lower than in AA-genotype carriers by 21.97% (p_{AA}=0.042) and 13.67% (p_{AA}=0.05). The obtained data has shown that considering hemodynamic and metabolic indicators, the mutant C-allele of the AGTR1 (*rs5186*) gene in patients with EAH is a marker of damage, dysfunction, and dysregulation of RAAS activity, metabolite and proteome, but in healthy individuals, on the contrary, is a protective factor. This indicates that in conditions of pathology, protective factors might become damage factors due to a complex system of maladaptation mechanisms of malignant circuits of pathogenesis, which is enhanced by epigenomic structures and changes in the expression of involved genes.

The lipid panel values depending on polymorphic variants of the VDR (A/G) gene are shown in Table 3. In AA-genotype of carriers, the level of TC, LDL-C, and AI were marginally higher in AA-genotype carriers, than

Table 1: The lipid panel values of the examined, M±m.

Values	Control group	Study group	p-Value
TC, mmol/l	5.55±0.17	5.74±0.23	>0.05
TG, mmol/l	1.68±0.15	1.96±0.20	>0.05
HDL-C, mmol/l	1.42±0.09	1.27±0.05	<0.05
LDL-C, mmol/l	3.95±0.16	4.17±0.21	>0.05
AI	3.18±0.27	3.60±0.21	>0.05

Notes: TC – Total cholesterol; TG – Triglycerides; LDL-C – Low-density lipoprotein cholesterol; HDL-C – High-density lipoprotein cholesterol; AI – Atherogenic index. p – significance of differences with control group.

Table 2: The lipid panel values depending on polymorphic variants of the AGTR1 (A1166C) gene, M±m.

Values	AGTR1 gene genotypes in the control group		AGTR1 gene genotypes in the study group	
			AA-	AC+CC-
TC, mmol/l	AA-	5.65±0.15	5.57±0.25	6.0±0.41
	AC+CC-	5.46±032		
TG, mmol/l	AA-	1.69±0.23	1.96±0.34	2.0±0.26
	AC+CC-	1.92±0.18		
HDL-C, mmol/l	AA-	1.32±0.06	1.26±0.07	1.25±0.08 p<0.05
	AC+CC-	1.61±0.11 p_{AA}=0.042		
LDL-C, mmol/l	AA-	4.17±0.15	4.12±0.21	4.51±0.30 p<0.05
	AC+CC-	3.60±0.22 p_{AA}=0.05		
AI	AA-	3.49±0.32	3.58±0.35	3.92±0.27 p<0.05
	AC+CC-	2.71±0.44		

Notes: p – significance of differences with control group; p_{AA} – significance of differences with AA-genotype carriers. TC – Total cholesterol; TG – Triglycerides; LDL-C – Low-density lipoprotein cholesterol; HDL-C – High-density lipoprotein cholesterol; AI – Atherogenic index.

Table 3: The lipid panel values depending on polymorphic variants of the VDR (A/G) gene, M±m.

Values	VDR gene genotypes in the control group		VDR gene genotypes in the control group		
			AA	AG	GG
TC, mmol/l	AA	5.60±0.19	5.88±0.24	5.67±0.21	5.38±0.18 p_{AA}=0.05
	AG	5.52±0.31			
	GG	5.54±0.11			
TG, mmol/l	AA	1.88±0.18	2.04±0.20	2.01±0.19 p<0.05	1.82±0.15
	AG	1.52±0.24			
	GG	1.75±0.23			
HDL-C, mmol/l	AA	1.47±0.05	1.29±0.06 p<0.01	1.24±0.09 p<0.05	1.29±0.20
	AG	1.45±0.10			
	GG	1.29±0.09 p_{AA}=0.049			
LDL-C, mmol/l	AA	4.04±0.16	4.40±0.21	4.17±-0.23	3.96±0.18 p_{AA}=0.052
	AG	3.93±0.19			
	GG	3,88±0.09			
AI	AA	2.97±0.21	3.70±0.19 p<0.05	3.73±0.22 p<0.05	3.28±0.18 p_{AA}=0.049 p_{AG}=0.044
	AG	3.01±0.24			
	GG	3.79±0.56			

Notes: p – significance of differences with control group; p_{AA}, p_{AG} – significance of differences with AA-genotype carriers, AG-genotype carriers. TC – Total cholesterol; TG – Triglycerides; LDL-C – Low-density lipoprotein cholesterol; HDL-C – High-density lipoprotein cholesterol; AI – Atherogenic index.

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in individuals with GG-genotype by 9.29% (p_{AA}=0.05), 11.11% (p_{AA}=0.052), and (p_{AA}=0.049), respectively.

One-way ANOVA analysis did not confirm the association of the VDR (*rs2228570*) gene with the main indicators of cholesterol metabolism, but boundary association was established by increasing AI (F=3.80; p=0.05).

In order to study biochemical parameters as EAH risk factors depending on the allelic state of AGTR1 (*rs5186*) and VDR (*rs2228570*) genes the epidemiological analysis, as well as the correlation coefficient for two variables using -Pearson's test, one-way analysis of variance (ANOVA) were performed.

Changes in the lipid profile as a risk factor for EAH depending on polymorphic variants of the AGTR1 (*rs5186*) gene are shown in table 4. Hypercholesterolemia (TC >5.0mmol/) increases the risk of EAH regardless the polymorphic variants of the AGTR1 (*rs5186*) gene, but reliably only in C-allele carriers – 1.5 times (OR – 3.45; 95% CI OR: 0.94-12.62; p=0.055), slightly less in AA-genotype carriers – 1.44 times (OR – 3.45; 95% CI OR: 0.94-12.62; p = 0.055). The risk of EAH is escalated with an increase in LDL-C and AI, but statistically significant only in hypertensive patients C-allele carriers of the AGTR1 (*rs5186*) gene – in 1.58 and 2.12 times (OR– 10.80; 95%CI OR: 1.18-98.36; p=0.019 and OR – 3.86; 95%CI OR: 1.15-12.99; p=0.026) respectively.

Considering alleles and genotypes of the VDR (*rs2228570*) gene, the risk of EAH increases in carriers of the minor A-allele at hypertriglyceridemia (>1.7 mmol/l) and increased LDL-C, but significantly only in AA-genotype carriers almost twice and 1.26 times (OR – 2.93; 95%CI OR: 1.09-7.90; p=0.03 and OR – 3.60; 95%CI OR: 1,05-12.38; p=0.038) respectively (table 5). A similar tendency to a higher risk of EAH in patients with A-allele of the VDR (*rs2228570*) gene was found at a decrease in HDL-C (<1.2 mmol/l) and high AI – almost twice only in AG-carriers (OR – 2.88; 95%CI OR: 1.0-8.33; p=0.046 and OR – 2.70; 95%CI OR: 1.04-7.04; p=0.039), respectively.

Discussion

A number of studies have shown that carriers of the AGTR1 C-allele have higher insulin resistance [18], higher levels of LDL-C, TG, TC [19–21], more frequent development of diabetes mellitus type 2 and diabetic nephropathy [20, 22], preeclampsia in the pregnant [23], increased resistance to resistin, MCP-1, calprotectin and

Table 4: Dyslipidemia as a risk factor for essential arterial hypertension, depending on alleles, genotypes of the AGTR1 (*rs5186*) gene.

Values	Genotypes	RR	95% CI RR	OR	95% CI OR	p-Value
TC (>5.0 mmol/l)	AA	1.44	0.95–3.16	3.45	0.94–12.62	0.055
	AC, CC	1.55	0.98–2.45	2.50	1.0–6.26	0.048
TG (>1.7 mmol/l)	AA	1.38	0.86–2.22	1.88	0.76–4.65	>0.05
	AC, CC	1.58	0.91–2.76	2.81	0.87–9.10	>0.05
LDL-C (>3.0 mmol/l)	AA	0.98	0.83–1.16	0.84	0.22–3.27	>0.05
	AC, CC	1.35	1.02–1.78	10.80	1.18–98.36	0.019
-HDL-C (<1.2 mmol/l)	AA	1.35	0.78–2.34	1.67	0.67–4.20	>0.05
	AC, CC	2.25	0.69–7.31	2.84	0.66–12.20	>0.05
AI (>3.5)	AA	1.06	0.67–1.69	1.13	0.46–2.76	>0.05
	AC, CC	2.12	1.01–4.45	3.86	1.15–12.99	0.026

Notes: TC – Total cholesterol; TG – Triglycerides; LDL-C – Low-density lipoprotein cholesterol; HDL-C – High-density lipoprotein cholesterol; IA – Atherogenic index; RR – risk ratio; OR – odds ratio; 95% CI – confidence intervals.

Table 5: Dyslipidemia as a risk factor for essential arterial hypertension, depending on genotypes of the VDR (*rs2228570*) gene.

Values	Genotypes	RR	95% CI RR	OR	95% CI OR	p-Value
TC (>5.0 mmol/l)	AA	1.24	0.85–1.81	2.37	0.55–10.20	>0.05
	AG	0.95	0.70–1.29	0.85	0.31–2.34	>0.05
	GG	0.72	0.44–1.19	0.43	0.11–1.72	>0.05
TG (>1.7 mmol/l)	AA	1.89	1.0–3.58	2.93	1.09–7.90	0.03
	AG	1.17	0.61–2.24	1.36	0.39–4.70	>0.05
	GG	1.30	0.65–2.59	1.67	0.45–6.13	>0.05
LDL-C (>3.0 mmol/l)	AA	1.26	0.99–1.62	3.60	1.05–12.38	0.038
	AG	1.03	0.84–1.26	1.31	0.17–10.35	>0.05
	GG	0.99	0.76–1.30	0.96	0.15–6.0	>0.05
-HDL-C (<1.2 mmol/l)	AA	2.15	0.82–5.64	3.21	0.81–12.75	>0.05
	AG	2.05	0.96–4.46	2.88	1.0–8.33	0.046
	GG	0.86	0.40–1.88	0.78	0.21–2.92	>0.05
IA (>3.5)	AA	2.15	0.82–5.64	3.21	0.81–12.75	>0.05
	AG	1.68	0.97–2.90	2.70	1.04–7.04	0.039
	GG	0.65	0.33–1.27	0.44	0.12–1.64	>0.05

Notes: TC – Total cholesterol; TG – Triglycerides; LDL-C, HDL-C – Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol; AI – Atherogenic index; RR – risk ratio; OR – odds ratio; 95% CI – confidence intervals.

activation of nuclear factor-kB in mononuclear cells and suppressed postprandial adiponectin response to fat [21]. However, not all studies have demonstrated the association of *A1166C* polymorphism of the AGTR1 gene with hypertension, waist circumference, BP degrees, CVR, or dysmetabolic changes [24, 25]. The above is consistent with the results we have obtained that the frequency of lipid metabolism disorders in patients with EAH does not depend on polymorphic variants of the AGTR1 gene (*1166A>C*).

For the first time, we found that genotypes and alleles of the VDR gene (*rs2228570*) are not additional risk factors for EAH in the examined population. The results that we obtained were partially consistent with studies that linked VDR to hypertension, metabolic disorders, and RAAS activity [26–30]. Swapna N. et al. [31] found the association of Fok I (*rs2228570*) VDR gene polymorphism with hypertension, family history of cardiovascular diseases, smoking, and alcohol consumption in the Hindu, the mutant allele dominated in hypertensive patients and the risk of EAH was increased in 2.02 and 2.25 times in both, men and women. Jia J. et al. [32] obtained some controversial results in a study in the Chinese population of Han, which found the association of Fok I (*rs2228570*) polymorphism with reduced risk of EAH in men based on age, body mass index, TC, TG, HDL cholesterol, LDL cholesterol, smoking.

It is noteworthy that the connection of EAH with Fok I VDR gene polymorphism in a number of studies has not been proven [33]. Despite the fact the main pathogenetic aspects of EAH are common, the role of individual metabolic-hormonal messengers and genetic predictors in the pathogenesis of EAH is still insufficiently studied and requires further research, especially in the Ukrainian population.

Conclusions

Dyslipidemia increases the risk of EAH: in C-allele carriers of the AGTR1 (*rs5186*) gene

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at hypercholesterolemia (TC >5.0 mmol/l) – 1.5 times (OR–2.50; p=0.048), at an increase in LDL-C and AI – 1.58 and 2.12 times (OR–10.80; p=0.019 and OR – 3.86; p=0.026), respectively.

Risk of EAH elevates at hypertriglyceridemia (TG >1.7 mmol/l) in 1.89 times (OR–2.93; p=0.03) and at the increase in LDL-C (>3.0 mmol/l) – 1.26 times (OR–3.60; p=0.038) in AA-genotype carriers of the VDR (*rs*2228570) gene. The risk of EAH synergistically escalates almost twice in A-allele carriers of VDR (*rs*2228570) gene at a decrease of HDL-C (<1.2 mmol/l) (OR–2.88; p=0.046) and the increase of AI (>3.5) (OR–2.70; p=0.039), significantly only in AG-carriers though.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Kotseva, K., Wood, D., De Bacquer, D., et al. (2016). EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol*. 23(6):636–648. doi:10.1177/2047487315569401.
2. Mach, F., Baigent, C., Catapano, A. L., et al. (2019). ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart J*. 41(1):111–188. doi:10.1093/eurheartj/ehz455.
3. GBD 2017 Risk Factor Collaborators. (2018). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017 [published correction appears in Lancet. 2019 Jan 12;393(10167):132] [published correction appears in Lancet. 2019 Jun 22;393(10190):e44]. *Lancet*. 392(10159):1923–1994. doi:10.1016/S0140-6736(18)32225-6.
4. Arnett, D. K., Blumenthal, R. S., Albert, M. A., et al. (2019). 2019 ACC/AHA Guideline on the primary prevention of cardio- vascular disease. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 74(10):e177–e232. doi: 10.1016/j.jacc.2019.03.010.
5. Visseren, F. L. J., Mach, F., Smulders, Y. M., et al. (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 42(34):3227–3337. doi:10.1093/eurheartj/ehab484.
6. Vinther, J. L., Jacobsen, R. K., Jørgensen, T. (2018). Current European guidelines for management of cardiovascular disease: Is medical treatment in nearly half a population realistic? *Eur J Preven Cardiol*. 25(2):157–163. https://doi.org/10.1177/2047487317738826.
7. Chow, C. K., Teo, K. K., Rangarajan, S., et al. (2013). PURE Study Investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *J Am Med Assoc*. 310:959–968.
8. Bryan, W., Mancia, G., Spiering, W., et al. (2018). 2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *Eur Heart J*. 39:3021–3104. https://doi.org/10.1093/eurheartj/ehy339.
9. NCD Risk Factor Collaboration (NCD-RisC). (2017). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 389(10064):37–55. doi: 10.1016/S0140-6736(16)31919-5.
10. Nakaz MOZ Ukrayiny vid 24.05.2012 №384 "Pro zatverdzhennya ta vprova-dzhennya medyko-tekhnolohichnykh dokumentiv zi standartyzatsiyi medychnoyi dopomo-hy pry arterial'niy hipertenziyi". Nastanova ta klinichnyy protokol nadannya medychnoyi dopomohy "Arterial'na hipertenziya". Robocha hrupa z arterial'noyi hipertenziyi Ukrayins'koyi asotsiatsiyi kardiolohiv. Kyyiv:MOZ; 2012. 108[1].
11. Nakaz MOZ Ukrayiny vid 13.06.2016 № 564 «Unifikovanyy klinichnyy protokol pervynnoyi, vtorynnoyi (spetsializovanoyi) ta tretynnoyi (vysokospetsializovanoyi) medychnoyi dopomohy. Profilaktyka sertsevo-sudynnykh zakhvoryuvan'». Kyyiv:MOZ.
12. Semianiv, M. M., Sydorchuk, L. P., Dzhuryak, V. S., et al. (2021). Association of AGTR1 (rs5186), VDR (rs2228570) genes polymorphism with blood pressure elevation in patients with essential arterial hypertension. *J Med Life* 14(6):782–789. https://doi.org/10.25122/jml-2021-0018.
13. Semianiv, M., Sydorchuk, L., Fedonyuk, L., et al. (2021). Metabolic and hormonal prognostic markers of essential

arterial hypertension considering the genes polymorphism AGTR1 (rs5186) and VDR (rs2228570). *Romanian J Diabet Nutr Metabol Dis*. 28:284–291.

14. Repchuk, Y., Sydorchuk, L. P., Sydorchuk, A. R., et al. (2021). Linkage of blood pressure, obesity and diabetes mellitus with angiotensinogen gene (AGT 704T>C/rs699) polymorphism in hypertensive patients. *Bratisl Lek Listy*. 122(10):715–720. doi:10.4149/BLL_2021_114.
15. Semianiv, M., Sydorchuk, L. (2021). Clinical and metabolic parameters, Ca2+, parathormone depending on serum 25(OH)D concentration in hypertensive patients in the West-Ukrainian population. *J Educ Health Sport* 11(12):150–157. https://doi.org/10.12775/JEHS.2021.11.12.010.
16. Sydorchuk, L. P., Dzhuryak, V. S., Sydorchuk, A. R., et al (2020). Association of lipids' metabolism disorders with aldosterone synthase CYP11B2 (-344C/T) gene polymorphism in hypertensive patients depending on glomerular filtration rate. *Pharmacol OnLine*. 2:230–242 https://pharmacologyonline.silae.it/files/archives/2020/vol2/PhOL_2020_2_A023_Sydorchuk.pdf.
17. Sydorchuk, L., Dzhuryak.V., Sydorchuk, A., et al. (2020). The cytochrome 11B2 aldosterone synthase gene rs1799998 single nucleotide polymorphism determines elevated aldosterone, higher blood pressure, and reduced glomerular filtration, especially in diabetic female patients. *Endocr Regulat*. 54(3):217–226. doi:10.2478/enr-2020-0024.
18. Shakhanova, A., Aukenov, N., Nurtazina, A., Massabayeva, M., et al. (2020). Association of polymorphism genes LPL, ADRB2, AGT and AGTR1 with risk of hyperinsulinism and insulin resistance in the Kazakh population. *Biomed Reports* 13(5):35. https://doi.org/10.3892/br.2020.1342.
19. Junusbekov, Y., Bayoglu, B., Cengiz, M., et al. (2020). AGT rs699 and AGTR1 rs5186 gene variants are associated with cardiovascular-related phenotypes in atherosclerotic peripheral arterial obstructive disease. *Ir J Med Sci*. 189:885–894. https://doi.org/10.1007/s11845-019-02166-6.
20. Halder, K., Purkait, P. (2020). Association of angiotensin II type I receptor (AGTR1) gene polymorphism and type 2 diabetes & nephropathy among the Eastern Indian Bengali patients. *Diabet Obes Internat J*. 5(2):1–13. doi: 10.23880/doij-16000224.
21. Musso, G., Saba, F., Cassader, M., Paschetta, E., et al. (2019). Angiotensin II type 1 receptor rs5186 gene variant predicts incident NAFLD and associated hypertension: Role of dietary fat-induced pro-inflammatory cell activation. Am J Gastroenterol. 114(4):607–619. doi: 10.14309/ajg.0000000000000154.
22. Tziastoudi, M., Stefanidis, I., Zintzaras, E. (2020). The genetic map of diabetic nephropathy: evidence from a systematic review and meta-analysis of genetic association studies, *Clin Kidney J*. 13(5):768–781. https://doi.org/10.1093/ckj/sfaa077.
23. Mirzakhmetova, D. D., Svyatova, G. S., Berezina, G. M., Murtazaliyeva, A. V. (2020). Clinical and diagnostic significance of genetic predisposition to preeclampsia in the Kazakh population. Obstet Gynegol. 3. https://dx.doi.org/10.18565/aig.2020.3.58-63.
24. Hui, D., Feng-Zhen, W., Kun, S., et al. (2021). Association of cytochrome P450 2C9*3 and angiotensin II receptor 1 (1166A>C) gene polymorphisms with the antihypertensive effect of Irbesartan. *Am J Hypertens*. 34 (1):121 URL: https://read.qxmd.com/read/33599747/association-of-cytochrome-p450-2c9-3-and-angiotensin-ii-receptor-1-1166a-c-gene-polymorphisms-with-the-antihypertensive-effect-of-irbesartan.
25. Keping, C., Peng, X., Guochun, L., et al. (2021). Distributive characteristics of the CYP2C9 and AGTR1 genetic polymorphisms in Han Chinese hypertensive patients: a retrospective study. *BMC Cardiovasc Disord*. 21(1):73. URL: https://read.qxmd.com/read/33541272/distributive-characteristics-of-the-cyp2c9-and-agtr1-genetic-polymorphisms-in-han-chinese-hypertensive-patients-a-retrospective-study.
26. Bouillon, R. (2017). Genetic and racial differences in the vitamin D endocrine system. Endocrinol Metabol Clin N Am 46:1119–1135. https://doi.org/10.1016/j.ecl.2017.07.014.
27. Cottone, S., Guarino, L., Arsena, R., et al. (2015). Vitamin D receptor gene polymorphisms and plasma renin activity in essential hypertensive individuals. *J Hum Hypertens*. 29(8):483–487.
28. Jiang, X., O'Reilly, P. F., Aschard, H., et al. (2018). Genome-wide association study in 79,366 European-ancestry individuals informs the genetic architecture of 25-hydroxyvitamin D levels. *Nat Comm*. 9:260. https://doi.org/10.1038/s41467-017-02662-2.
29. Pilz, S., Zittermann, A., Trummer, C., et al. (2019). Vitamin D testing and treatment: A narrative review of current evidence. *Endocr Connect*. 8:R27–R43. doi: https://doi.org/10.1530/EC-18-0432.
30. Zhu, Y.-B., Li, Z.-Q., Ding, N., Yi, H.-L. (2019). The association between vitamin D receptor gene polymorphism and susceptibility to hypertension: a meta-analysis. *Eur Rev Med Pharmacol Sci*. 23:9066–9074. doi: 10.26355/eurrev_201910_19309.
31. Swapna, N., Vamsi, U. M., Usha, G., Padma, T. (2011). Risk conferred by FokI polymorphism of vitamin D receptor (VDR) gene for essential hypertension. *Indian J Hum Genet*. 17:201–206. doi: 10.4103/0971-6866.92104.
32. Jia, J., Shen, C., Mao, L., Yang, K., Men, C., Zhan, Y. (2014). Vitamin D receptor genetic polymorphism is significantly associated with decreased risk of hypertension in a Chinese Han population. *J Clin Hypertens. (Greenwich)* 16:634–639.
33. Glocke, M., Lang, F., Schaeffeler, E., et al. (2013). Impact of vitamin D receptor VDR rs2228570 polymorphism in oldest old. *Kidney Blood Press Res*. 37(4–5):311–322.

 https://doi.org/10.46389/rjd-2022-1100