ORIGINAL ARTICLE

THE EFFECT OF NOS3 AND AGTR1 GENOTYPES ON THE COURSE OF THE ARTERIAL HYPERTENSION FOR THE OVERWEIGHT OR OBESE PATIENTS

DOI: 10.36740/WLek202202137

Viktoriia S. Potaskalova[1], Nick V. Khaitovych[1], Larysa V. Natrus[1], Tsira B. Abdriakhimova[1], Kateryna I. Kleban[1], Vitalii Y. Lunov[1], Oleg A. Korop[2]

[1]BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

[2]KHARKIV MEDICAL ACADEMY OF POSTGRADUATE EDUCATION, KHARKIV, UKRAINE

ABSTRACT

The aim: Objective of the research is to determine the effect of NOS3 and AGTR1 genotypes of patients with arterial hypertension and high body mass index in the course of the disease.

Materials and methods: 58 patients (22 men and 36 women) with AH and high BMI were examined. The average age of the examined patients was 53.6±8.7 years. The analysis of rs1799983 polymorphisms of the NOS3 gene (localization 7q36.1; 7:150999023) and AGTR1 (type 1 receptor for angiotensin 2 1166 A>C) was performed using TaqMan assay (Thermo Fisher Scientific, USA) by real-time PCR (Applied Biosystems, USA) using TaqMan probe amplification products. Genomic DNA samples were isolated from stabilized blood using a Genomic DNA Mini Kit reagent (Invitrogen, USA). The Statistica 10 program (StatSoft Inc.) was used for statistical processing of the obtained data, USA). The independent samples were compared using the Mann-Whitney (U) criterion. In all cases of statistical evaluation, the reliability of differences was taken into account at a value of $p<0.05$.

Results and conclusions: Polymorphism of the NOS3 and AGTR1 genes is associated with early development and complicated course of cardiovascular pathology. The combination of NOS3 and AGTR1 gene polymorphism in patients with the high body mass index increases the risk of complications in hypertension. Using a mathematical model to predict the probability (95%) of genetic mutations in two genes (NOS3 and AGTR1) increases the effectiveness of diagnosis for patients with the high risk of developing cardiovascular complications.

KEY WORDS: arterial hypertensions, NOS3 and AGTR1 genotypes, body mass index

Wiad Lek. 2022;75(2):533-539

INTRODUCTION

The cardiovascular diseases, as arterial hypertension(AH), determine the mortality and disability of the adult population. The number of the patients with AH increases with age, which is associated with a violation of the response to vasodilating factors, this problem leads to the development of vascular diseases, accompanied by pathological vascular remodeling, impaired tissue perfusion. An early predictor of atherosclerosis and complications of cardiovascular pathology is endothelial disfunction. Vascular endothelium supports hemostasis, and endothelial dysfunction affects vascular tone, immune inflammation, and platelet activation [1, 2]. During the aging process of the endothelium, both structural and functional changes occur, in particular, angiogenesis, vascular wall tone are disrupted, and mitochondrial dysfunction occurs. In addition, endothelial disorders are affected by oxidative stress, hyperuricemia, activation of the renin-angiotensin system, and vascular inflammation [3-6].

The disorders of NO synthesis by endotheliocytes may be genetically determined The replacement of guanine with thymine at 894 positions in exon 7 of the NOS3 gene leads to a change of the enzyme activity due to a change in the amino acid sequence (glutamine is replaced with arginine at 298 positions) [7-10]. The existing T allele in patients with AH and a high body mass index (BMI) is associated with an early (on average 4.5 years) development of the disease, which was found among 39,7% of patients.

The gene AGTR1 polymorphism is associated with high vascular stiffness [11] and endothelial disfunction [12] and cardiovascular complications in pathology, which also affects the development and severity of hypertension [13-15].

Therefore, better understanding of the pathophysiology of cardiovascular diseases can be useful for optimizing prevention and treatment, and patients with AH will be provided optimal blood pressure (BP) control. Routine examinations of patients with AH can identify damage of the target-organs and determine the risks of complications, analyze the effectiveness of antihypertensive therapy, but the examinations do not show additional information on the personal treatment of such patients. A data variety about the contribution of the NOS3 and AGTR1 genes polymorphisms to the development of the disease and its complications, and the course of concomitant pathology,

in particular the 2nd type of the diabetes, obesity, hypercholesterolemia, chronic renal failure, are aimed to find a pharmacogenetic basis for the treatment choice strategy for patients with AH [16-24].

THE AIM

Objective of the research is to determine the effect of NOS3 and AGTR1 genotypes of patients with arterial hypertension and high body mass index in the course of the disease.

MATERIALS AND METHODS

58 patients (22 men and 36 women) with AH and high BMI were examined. The average age of the examined patients was 53.6±8.7 years. The analysis of rs1799983 polymorphisms of the NOS3 gene (localization 7q36.1; 7:150999023) and AGTR1 (type 1 receptor for angiotensin 2 1166 A>C) was performed using TaqMan assay (Thermo Fisher Scientific, USA) by real-time PCR (Applied Biosystems, USA) using TaqMan probe amplification products. Genomic DNA samples were isolated from stabilized blood using a Genomic DNA Mini Kit reagent (Invitrogen, USA). The Statistica 10 program (StatSoft Inc.) was used for statistical processing of the obtained data, USA). The independent samples were compared using the Mann-Whitney (U) criterion. In all cases of statistical evaluation, the reliability of differences was taken into account at a value of $p<0.05$.

RESULTS AND DISCUSSION

The Endothelial nitric oxide synthase (NOS3) is a dimeric enzyme, the activity and expression of which are regulated at the transcriptional, post – transcriptional, and prost-translational levels. The gene encoding NOS3 includes polymorphic sites (single-nucleotide polymorphisms, tandem repeats, microsatellites, and inserts). Nitric oxide synthesis may be affected by some polymorphisms due to NOS3 activity or expression. NOS3 haplotypes can increase the risk of developing diseases [25] based on endothelial dysfunction, in particular ischemic heart disease (CHD), myocardial infarction, ischemic brain stroke, hypertension, and chronic kidney disease [26-31] (table. I).

The data of the research of gene polymorphism and the link between them with risks for patients with a Cardiological profile alter in different populations. Even on the territory of the same continent and the same country, depending on the region, the population may have different genotypes of the same gene, so it is not possible to extrapolate statistics on the polymorphism of a particular gene to the entire population of the country.

Mutations in the Nos3 gene can become predictors of the 2nd type diabetes mellitus (DM) [32, 33], although the dominant AG genotype of the NOS3 rs1800779 and T2D polymorphisms is protective [34], while the GT polymorphism of the NOS3 gene is associated with the development of arterial hypertension in Brazilian women [35]. The presented meta-analysis data in the European population according to Mendelian randomization indicate an association of exon polymorphism in NOS3 (rs1799983, p.Glu298Asp) and in intron COL4A1 (rs9521634) and near DYRK1A (rs720470) with ischemic brain stroke due to changes in blood pressure levels [36]. In patients in the Antalya population, the NOS3 GT and TC polymorphism (rs2070744) is associated with hypertension [37].

Also, a prospective study shows the role of nos3 gene polymorphism in the formation of cerebral artery aneurysms, their rupture or the development of vasospasm, and the existing polymorphism can be considered a risk factor for the development of vascular complications along with smoking, hypertension, and diabetes [38]. The RS2070744 NOS3 polymorphism may be considered a factor of genetic predisposition in Sudan to hypertension [39].

A high risk of CHD was shown in Caucasians, South Asian populations, and Middle Eastern people with the existing TT and GT nos3 polymorphism. TT polymorphism significantly increases the risk (odds ratio >2) of developing ASF in 10 countries (Ukraine, Brazil, Great Britain, Egypt, India, Iran, Chile, South Korea, Morocco, Japan, etc.) [40]. A strong correlation exists in the TG Enos and AG polymorphism in Morocco [41]. Conflicting data on NOS3 polymorphism and the risk of myocardial infarction. A meta-analysis revealed an association of TC polymorphism in the NOS3 gene with the risk of myocardial infarction in Asian and European populations [42]. In patients with CHD from Pakistan, the Glu298Asp variant of the NOS3 gene showed no association with hypertension and dyslipidemia, but had a strong correlation with systolic blood pressure [43]. NOS3 polymorphism in Iranian patients is associated with the development of multiple sclerosis [44], GT, TC, and 4a/4b polymorphisms were not associated with the risk of CHD in residents of northern Iran [45]. Patients with CHD are more likely to have the rs1799983 t and rs2070744 G alleles than the GG genotype, and diastolic blood pressure increases with increasing BMI [46].

Among the examined patients, the wild allele of the NOS3 gene was found inside 35 (60.3%) individuals, the GT genotype - inside 20 (34.5%) patients, and the TT genotype – inside 3 (5.2%) subjects. It is known that the TT genotype increases the risk of hypertension by 2.3 times: the no level is lower in patients with hypertension and diabetes with GT and TT polymorphism [47, 48].

The early development of CHD with a gt gene polymorphism was found [49-51], although among the Tunisian population, the GT polymorphism is not associated with the development of CHD [52].

The pathogenesis contribution arguable data of cardiovascular diseases are presented in numerous literature reviews of the polymorphism of the AGTR1 gene. Thus, GT (rs275652) and AG (rs275653) polymorphisms are associated with severe atherosclerotic vascular damage among patients in the Mexican population [53, 54] (table. II).

Also, polymorphism of the AGTR1 gene causes sodium reabsorption in the distal tubules and the development of vascular stiffness, regardless of the level of blood pressure [55, 56]. The activation of renin-angiotensin of the aldoste-

Table I. Association of NOS3 gene polymorphisms with the development of pathological conditions

Genotype	Result	Reference
NOS3 gene polymorphism	Cerebral artery aneurysms, rupture or development of vasospasm; disseminated sclerosis	Subhas K. Konar etc., 2019; Mohammad Mehdi Heidari etc., 2017;
TT polymorphism of the NOS3 gene	AH	Jelita Siregar etc.., 2020;
GT polymorphism of the NOS3 gene	AH; the early development of IXC	Abel Barbosa Lira Neto etc. 2019; Sanaa Nassereddine etc., 2018; Boqian Zhu etc., 2017; Khalil Mahmoodi etc. 2016; Sherif Arafa etc., 2018;
Alleles rs1799983 T and rs2070744 G of the NOS3 gene	Increased diastolic blood pressure among patients with high BMI	G L Zhao and etc, 2016;
NOS3 haplotypes G894T/T-786C	Reduced NO level among patients with hypertension and diabetes; CHD; myocardial infarction; ischemic cerebral stroke; hypertension; chronic kidney disease	Robin Johns etc, 2018; Omneya Moguib etc, 2017; Jelita Siregar etc, 2020; Cecilia Vecoli, 2014; Alejandro Marín Medina etc, 2018; E A Trifonova etc, 2019; N Yu etc, 2019; Beáta Soltész etc; Gustavo H Oliveira-Paula etc, 2016; Xiang-Zhen Kong etc, 2017; Dalia El-Lebedy etc, 2018; Süleyman Ömer Anlıaçık etc, 2019; Sahar Gamil etc, 2017; Rainer Malik etc, 2018;
AG polymorphism NOS3 rs1800779 and T2D	High systolic blood pressure	Saleem Ullah Shahid etc, 2017;

Table II. Association of agtr1 gene polymorphisms with the development of pathological conditions

Genotype	Result	Reference
AGTR1 gene polymorphism	Increased vascular stiffness; Hypoxia resistance	Marcin Cwynar etc, 2016; Tatiana I Baranova etc, 2017;
Agtr1 GT (rs275652) and agtr1 AG (rs275653) polymorphisms	Systemic atherosclerosis	Tatiana S Rodríguez-Reyna etc, 2016; Zhongping Shi та ін., 2021;
genotype CC AGTR1	High renin levels; Complications of concomitant diseases	Tatyana Mulerova etc, 2020; Ana Célia Sousa etc, 2018; Keping Chen etc, 2021; Samantha Kohli etc, 2016; Sandrita Simonyte etc, 2017; Benjamin Goldstein etc, 2016; Sudhir Jain etc, 2018; Elena V Zholdybayeva etc, 2016; Roseline Wai Kuan Yap etc, 2017; Hsien-Feng Chang etc, 2018;
AC polymorphism of the AGTR1 gene	Liver damage; Insulin resistance; Endothelial dysfunction; Adipokine activation; Diabetic nephropathy; Hypertriglyceridemia; Increased low-density lipoproteins	Giovanni Musso etc,2019; Dana de Gracia Hahn etc, 2019; Yan Zhuang etc, 2018; H-L Xu etc, 2020; Xun Li etc, 2016;
Alel C in rs5186 of the AGTR1 gene	High mortality and cardiovascular complications among patients with end-stage kidney disease	Sharon M Moe etc, 2019.

rone system (RAAS) is connected with AH. The results of a meta-analysis of the genetic association between RAAS genes and chronic kidney disease indicated a reduced risk of kidney damage in the presence of the AGT rs699-T allele and the AGTR1 rs5186-a allele [57], which also depends on the population [58]. The genetic polymorphism of AGTR1 in many researches is not associated with the development of hypertension [59, 60], although the CC genotype of this gene is associated with high level of renin, which contributes to the development of hypertension, at least in some populations [61-65] and negatively affects the course of concomitant diseases [66-69].

The collected data result for the dominant type of AA homozygote of the AGTR1 gene was detected inside 39 (67.2%) patients, and the heterozygous AC polymorphism was detected inside 19 (37.8%) of the examined patients.

A number of researches have shown no association between AGTR1 gene polymorphism and insulin resistance [70], although another study found the effect of AGTR1 AC polymorphism on liver damage, the development of insulin resistance and endothelial dysfunction, the effect on the activation of adipokines, chemokines and pro-inflammatory cells in response to fat consumption [71, 72], which is important while choosing drugs. The AGTR1 gene mutation is associated with the development of diabetic nephropathy among the Asian population [73]. The research result linked the existing polymorphism to high levels of triglycerides and low-density lipoproteins [74, 75]. The C allele in rs5186 of the AGTR1 gene is associated with high mortality and cardiovascular complications in patients with end-stage kidney disease, both in the European and African populations [76]. Also, according to other authors, polymorphism of the AGTR1 gene can cause resistance to hypoxia [77].

It is known about the link of myocardial remodeling with AH, which is determined among patients with hypertension to determine the stage and control the course of the disease, namely, the relative thickness of the left ventricle (VTS LV), left ventricular myocardial mass (MMLSH), and the left ventricular myocardial mass index (MMLSH) [78, 79]. Hypercholesterolemia is also a risk factor for hypertension and requires pharmacological correction in overweight patients, even at normal blood pressure values [80-82]. Hyperuricemia increases the risk of developing complications of hypertension, and it is advisable to determine the level of uric acid (uric acid) in all patients with increased blood pressure [83-85]. Both hypertension and obesity are associated with increased immune inflammation, which promotes remodeling of the vascular wall and increases its stiffness [86-88]. Obese patients have a high risk of developing insulin resistance and diabetes of the 2nd type [89-91].

According to the results of the analysis of indicators obtained during the examination of patients with AH, the heart rate (HR) has a likely relationship with the prediction of the existing polymorphism of the NOS3 and AGTR1 genes.

As a result of performing logistic regression to model the differentiation of existing polymorphism by NOS3 or AGTR1 genes separately, no statistically significant results were found. However, with the simultaneous polymorphism of these genes, we obtained strong correlations with the given risk factors for the course of hypertension. we created a mathematical equation according to which the probability of genetic mutations for two genes (NOS3 and AGTR1) can be predicted with a probability of 95%:

$$Y = 38{,}8 \times \text{BLP HD} + 21{,}8 \times \text{BLP HD} + 0{,}75 \times \text{BLP LD} + 5{,}6 \times \text{AI} - 0{,}009 \times \text{ILVMM} - 0{,}069 \times \text{LVMM} + 0{,}86 \times \text{N} + 0{,}009 \times \text{urinary capacity} + 0{,}21 \times \text{HD AH} - 1{,}84 \times \text{TC} + 2{,}8 \times \text{FBG} + 0{,}006 \times \text{HR} - 122{,}1$$

Where:

Y is the theoretical probability of mutations;
BLP HD - high-density beta-lipoproteins;
BLP LD - low-density beta-lipoproteins;
AI - atherogenicity index;
N – neutrophil count;
HD AH - hypertension-duration of arterial hypertension;
TC - total cholesterol;
FBG - fasting blood glucose;
HR - heart rate;
LVMM - left ventricular myocardial mass;
ILVMM - left ventricular myocardial mass index;

The inclusion in the formula of the indicator – the duration of the disease, can become a criterion for an early prognosis of the AH development in this category of patients.

The definition of gene polymorphism is associated not only with the risk of developing the disease, in particular, certain gene mutations can be protective in nature. Information about the gene polymorphism helps in choosing pharmacogenetic treatment for patients with the high risk of developing cardiovascular complications.

Since these indicators can be determined while examining a patient at the primary level and do not require high economic costs, this formula will help identify individuals with the likely presence of polymorphism for two genes (NOS3 and AGTR1) and, if need, send them for additional genetic examination to correct the treatment.

CONCLUSIONS

1. Polymorphism of the NOS3 and AGTR1 genes is associated with early development and complicated course of cardiovascular pathology.
2. The combination of NOS3 and AGTR1 gene polymorphism in patients with the high body mass index increases the risk of complications in hypertension.
3. Using a mathematical model to predict the probability (95%) of genetic mutations in two genes (NOS3 and AGTR1) increases the effectiveness of diagnosis for patients with the high risk of developing cardiovascular complications.

REFERENCES

1. Ungvari Z., Tarantini S., Kiss T. et al. Endothelial dysfunction and angiogenesis impairment in the ageing vasculature. Nat Rev Cardiol. 2018;15(9):555-565. doi: 10.1038/s41569–018–0030–z.
2. Heaps C.L., Bray J.F., McIntosh A.L., Schroeder F. Endothelial nitric oxide synthase protein distribution and nitric oxide production in endothelial cells along the coronary vascular tree. Microvasc Res. 2019; 122:34-40. doi: 10.1016/j.mvr.2018.11.004
3. Annayya G.J., Cassie R.A., James J., Sowersabcd R. Endothelial cell senescence in aging– related vascular dysfunction. Biochim Biophys Acta Mol Basis Dis. 2019; 1865(7): 1802-1809. doi: 10.1016/j.bbadis.2018.08.008.
4. Mazurek-Mochol M., Kozak M., Sawczuk M. et al. Nos3 Gene Rs1799983 and Rs2070744 Polymorphisms in Patients with Periodontal Disease. Folia Biol (Praha). 2018;64(2): 59-64.

5. Gao L., Zhao Z., Guo F. et al. Association of endothelial nitric oxide synthase polymorphisms with an increased risk of erectile dysfunction. Asian J Androl. 2017;19(3): 330-337. doi: 10.4103/1008-682X.163300.
6. ZhouS., Mu G., Wei Sh. et al. Associations Between Polymorphisms of Endothelial Nitric Oxide Synthase, Matrix Metalloproteinase 3, Angiotensinogen, and Angiotensin II Type 1 Receptor and Risk of Restenosis After Percutaneous Coronary Intervention: A Meta– analysis. Clin Ther. 2020;42(3): 458-474. doi: 10.1016/j.clinthera.2020.01.018.
7. Bautista L.E. Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. Journal of Human Hypertension. 2003;17: 223-230.
8. Li Y.Y. Endothelial nitric oxide synthase G894T gene polymorphism and essential hypertension in the Chinese population: a meta– analysis involving 11,248 subjects. Intern. Med. 2011;50 (19): 2099-2106.
9. Mahmoodi K., Nasehi L., Karami E., Soltanpour M.S. Association of Nitric Oxide Levels and Endothelial Nitric Oxide Synthase G894T Polymorphism with Coronary Artery Disease in the Iranian Population. Vasc Specialist Int. 2016;32(3): 105-112.
10. Potaskalov V.S., Khaitovich M.V., Natrus L.V., Yu. S. Osadchuk The frequency of G894T polymorphic variants of the endothelial NO-synthase gene in patients with arterial hypertension and epidermal mastitis. Family Medicine. 2019; 3 (83): 47-51.
11. CwynarM., Gąsowski J., Głuszewska A. et al. Blood pressure, arterial stiffness and endogenous lithium clearance in relation to AGTR1 A1166C and AGTR2 G1675A gene polymorphisms. J Renin Angiotensin Aldosterone Syst. 2016; 17(2): 1470320316655669. doi: 10.1177/1470320316655669.
12. Li Y., Chen F., Zhang X. et al. Angiotensin type 1 receptor A1166C gene polymorphism is associated with endothelial dysfunction and in-stent restenosis after percutaneous coronary intervention. Int J Clin Exp Pathol. 2015;8(6):7350-7357.
13. Bahramali E., Firouzabadi N., Rajabi M. et al. Association of renin-angiotensin-aldosterone system gene polymorphisms with left ventricular hypertrophy in patients with heart failure with preserved ejection fraction: A case-control study. Clin Exp Hypertens. 2017;39(4): 371– 376. doi: 10.1080/10641963.2016.1267196.
14. Karpov R.S., Puzyrev K.V., Koshel'skaia O. A. et al.Polymorphic markers of GNB3 (C825T), AGTR1 (A1166C) and ACE (A2350G and I/D) genes in patients with arterial hypertension combined with diabetes mellitus type 2. Ter Arkh. 2004;76(6): 5-30.
15. Barbarash O.L., Mulerova T.A., Maksimov V.N. et al. Left Ventricular Myocardial Hypertrophy as a Result of Arterial Hypertension Among Mountain Shoria Population. The Role of Genetic Polymorphism. Kardiologiia. 2018;58(9): 37-46.
16. De Becker B., Borghi C., Burnier M., van de Borne Ph. Uric acid and hypertension: a focused review and practical recommendations. J Hypertens. 2019;37(5):878-883. doi: 10.1097/HJH.0000000000001980.
17. Kuwabara M., Kanbay M., Hisatome I. Uric Acid and Hypertension Because of Arterial Stiffness. Hypertension. 2018; 72:582–584.
18. An Li– Na, Rong N., Ning M. et al.High serum uric acid is associated with increased arterial stiffness in hypertension. Aging (Albany NY). 2020; 12(14): 14569– 14581. doi: 10.18632/aging.103506.
19. Yang Wang A.E., Jia– Wen Hu A.E., Yong-Bo L.E.F. et al. The Role of Uric Acid in Hypertension of Adolescents, Prehypertension and Salt Sensitivity of Blood Pressure. Med Sci Monit. 2017; 23: 790– 795.
20. Chau K., Girerd N., Zannad F. et al. Health-related determinants of undiagnosed arterial hypertension: a population-based study. Family Practice. 2019;36(3): 276-283. doi:10.1093/fampra/cmy075.
21. Cacanyiova S., Krskova K., Zorad S. et al. Arterial Hypertension and Plasma Glucose Modulate the Vasoactive Effects of Nitroso-Sulfide Coupled Signaling in Human Intrarenal Arteries. Molecules. 2020;25(12): 2886. doi:10.3390/molecules25122886.
22. Kucharska A., Gajewska D., Kiedrowski M. et al. The impact of individualised nutritional therapy according to DASH diet on blood pressure, body mass, and selected biochemical parameters in overweight/obese patients with primary arterial hypertension: a prospective randomised study. Kardiol Pol. 2018;76(1): 158– 165. doi: 10.5603/KP.a2017.0184.
23. Chuhunov V. V., Markova M. V., Kurilo V. O. et al. Peculiarities of the structure and distribution of we akness in the structure of type 2 diabetes mellitus among different social groups. Problemi Endokrinnoi Patologii. 2020;2:89-94.
24. Kozhyna H., Markova M., Yavorska T. et al.Analysis of stress-potentiating factors in the dynamics of cerebrovascular pathology development. European Psychiatry. The Journal of the European Psychiatric Association. 2019;565:91.
25. Oliveira-Paula G. H., Lacchini R., Tanus-Santos J. E. et al. Endothelial nitric oxide synthase: From biochemistry and gene structure to clinical implications of NOS3 polymorphisms. Gene. 2016;575(2 Pt 3): 584– 99. doi: 10.1016/j.gene.2015.09.061.
26. Vecoli C. Endothelial nitric oxide synthase gene polymorphisms in cardiovascular disease. Vitam Horm. 2014; 96: 387– 406. doi: 10.1016/B978-0-12– 800254-4.00015-5.
27. Medina A. M., Zubero E. E., Alatorre Jiménez M.A.N. et al.OS3 Polymorphisms and Chronic Kidney Disease. J Bras Nefrol. 2018;40(3): 273– 277. doi: 10.1590/2175-8239-JBN-3824.
28. Trifonova E. A., Swarovskaya M. G., Ganzha O. A. et al. The interaction effect of angiogenesis and endothelial dysfunction– related gene variants increases the susceptibility of recurrent pregnancy loss. J Assist Reprod Genet. 2019;36(4): 717– 726. doi: 10.1007/s10815-019-01403-2.
29. Yu N., Fan L., Wu J.– L. Analysis on the correlations of ENOS and ET– 2 gene polymorphisms with eclampsia. Eur Rev Med Pharmacol Sci. 2019; 23(16): 6800– 6805. doi: 10.26355/eurrev_201908_18718.
30. Soltész B., Pikó P., Sándor J. et al. The genetic risk for hypertension is lower among the Hungarian Roma population compared to the general population. PLoS One. 2020; 15(6): e0234547. doi: 10.1371/journal.pone.0234547.
31. El-Lebedy D. Interaction between endothelial nitric oxide synthase rs1799983, cholesteryl ester– transfer protein rs708272 and angiopoietin– like protein 8 rs2278426 gene variants highly elevates the risk of type 2 diabetes mellitus and cardiovascular disease. Cardiovasc Diabetol. 2018;17(1): 97. doi: 10.1186/s12933-018-0742-8.
32. Chen F., Li Y.-M., Yang L.-Q. et al. Association of NOS2 and NOS3 gene polymorphisms with susceptibility to type 2 diabetes mellitus and diabetic nephropathy in the Chinese Han population. IUBMB Life. 2016;68(7): 516. doi: 10.1002/iub.1513.
33. Bregar D., Cilenšek I., Mankoč S. et al. The joint effect of the endothelin receptor B gene (EDNRB) polymorphism rs10507875 and nitric oxide synthase 3 gene (NOS3) polymorphism rs869109213 in Slovenian patients with type 2 diabetes mellitus and diabetic retinopathy. Bosn J Basic Med Sci. 2018;18(1): 80-86. doi: 10.17305/bjbms.2017.2244.
34. Garme Y., Saravani R., Galavi H. R. Association of nitric oxide synthase 3 gene polymorphism with the risk of type 2 diabetes. Biomed Rep. 2017; 7(1): 85-89. doi: 10.3892/br.2017.916.
35. Neto A.B. L., Farias M.C.O., Vasconcelos N.B.R. et al. Prevalence of endothelial nitric oxide synthase (ENOS) gene G894T polymorphism and its association with hypertension: a population-based study with Brazilian women. Arch Med Sci Atheroscler Dis. 2019;4: e63-e73. doi: 10.5114/amsad.2019.84539.

36. Malik R., Rannikmäe K., Traylor M. et al. Genome-wide meta-analysis identifies 3 novel loci associated with stroke. Ann Neurol. 2018; 84(6):934-939. doi: 10.1002/ana.25369.
37. Anlıaçık S.Ö., Tokgöz S., Zamani A.G. et al. Investigation of the relationship between ischemic stroke and endothelial nitric oxide synthase gene polymorphisms [G894T, intron 4 VNTR and T786C]. Turk J Med Sci. 2019;49(2): 589-594. doi: 10.3906/sag-1808-57.
38. Konar S.K., Ramesh Sh., Christopher R. et al.The Correlation of Endothelial Nitric Oxide Synthase (eNOS) Polymorphism and Other Risk Factors with Aneurysmal Subarachnoid Hemorrhage: A Case– Control Study. Neurology India. 2019; 67(4): 1006-1012.
39. Gamil S., Erdmann J., Abdalrahman I. B., Mohamed A. O. Association of NOS3 gene polymorphisms with essential hypertension in Sudanese patients: a case control study. BMC Med Genet. 2017;18(1): 128. doi: 10.1186/s12881– 017-0491-7.
40. Johns R., Chen Z.-F., Young L. et al. Meta-Analysis of NOS3 G894T Polymorphisms with Air Pollution on the Risk of Ischemic Heart Disease Worldwide. Toxics. 2018:6(3): 44. doi: 10.3390/toxics6030044.
41. Nassereddine S., Idrissi H., Habbal R. et al. The polymorphism G894 T of endothelial nitric oxide synthase (eNOS) gene is associated with susceptibility to essential hypertension (EH) in Morocco. BMC Med Genet. 2018;19(1): 127. doi: 10.1186/s12881-018-0638-1.
42. Kong X.-Z., Zhang Z.-Y., Wei L.-H. et al.The Endothelial Nitric Oxide Synthase Gene T-786C Polymorphism Increases Myocardial Infarction Risk: A Meta-Analysis. Med Sci Monit. 2017;23: 759– 766. doi: 10.12659/msm.899905.
43. ShabanaS.U.Sh., Rehman A. Association Patterns of Endothelial Nitric Oxide Synthase Gene (NOS3) Variant Glu298Asp with Blood Pressure and Serum Lipid Levels in Subjects with Coronary Artery Disease from Pakistan. Ann Hum Genet. 2017;81(4):129-134. doi: 10.1111/ahg.12192.
44. Heidari M.M., Khatami M., Tahamtan Y. Molecular Analysis of rs2070744 and rs1799983 Polymorphisms of NOS3 Gene in Iranian Patients With Multiple Sclerosis. Basic Clin Neurosci. 2017; 8(4): 279– 284. doi: 10.18869/nirp.bcn.8.4.279.
45. Joshaghani H.R., Salehi A., Samadian E. et al. Association between NOS3 G894T, T-786C and 4a/4b Variants and Coronary Artery Diseases in Iranian Population. Iran J Public Health. 2018; 47(12): 1891-1898.
46. Zhao G.L., Li Q.J., Lu H.Y. Association between NOS3 genetic variants and coronary artery disease in the Han population. Genet Mol Res. 2016;15(2): 1-7. doi: 10.4238/gmr.15028044.
47. Siregar J., Ganie R.A., Lindarto D. et al. Association of endothelial nitric oxide synthase gene (G894T) polymorphism and hypertension in diabetic Bataknese patients. Med Glas (Zenica). 2020;17(2): 316-320. doi: 10.17392/1088-20.
48. Moguib O., Raslan H.M., Rasheed I.A. et al. Endothelial nitric oxide synthase gene (T786C and G894T) polymorphisms in Egyptian patients with type 2 diabetes. J Genet Eng Biotechnol. 2017;15(2): 431-436. doi: 10.1016/j.jgeb.2017.05.001.
49. Zhu B., Si X., Gong Y. et al. An association between the endothelial nitric oxide synthase gene G894T polymorphism and premature coronary artery disease: a meta– analysis. Oncotarget. 2017;8(44):77990-77998. doi: 10.18632/oncotarget.20400.
50. Mahmoodi K., Nasehi L., Karami E., Soltanpour M.S. Association of Nitric Oxide Levels and Endothelial Nitric Oxide Synthase G894T Polymorphism with Coronary Artery Disease in the Iranian Population. Vasc Specialist Int. 2016;32(3): 105-112. doi: 10.5758/vsi.2016.32.3.105.
51. Arafa Sh., Abdelsalam Sh., El-Gilany A.-H. et al. Endothelial nitric oxide synthase Glu 298 Asp (G894T) and Apolipoprotein E gene polymorphism as possible risk factors for coronary heart disease among Egyptians. Egypt Heart J. 2018; 70(4): 393-401. doi: 10.1016/j.ehj.2018.08.001.
52. Afef L., Leila B., Bassem Ch. et al. Endothelial nitric oxide gene polymorphisms and their association with coronary artery disease in Tunisian population. Anatol J Cardiol. 2017;17(1):31-36. doi: 10.14744/AnatolJCardiol.2016.6946.
53. Rodríguez-Reyna T.S., Núñez-Alvarez C., Cruz-Lagunas A. et al. Angiotensin II Type 1 receptor (AGTR1) gene polymorphisms are associated with vascular manifestations in patients with systemic sclerosis (SSc). J Renin Angiotensin Aldosterone Syst. 2016;17(3): 1470320316659954. doi: 10.1177/1470320316659954.
54. Shi Zh., Wang J., Chen Sh. et al. Relationship between A1166C polymorphism of angiotensin II type 1 receptor gene and arteriosclerosis: A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021;100(4): e24407. doi: 10.1097/MD.0000000000024407.
55. Cwynar M., Gąsowski J., Głuszewska A. et al. Blood pressure, arterial stiffness and endogenous lithium clearance in relation to AGTR1 A1166C and AGTR2 G1675A gene polymorphisms. J Renin Angiotensin Aldosterone Syst. 2016;17(2): 1470320316655669. doi: 10.1177/1470320316655669.
56. Cwynar M., Gąsowski J., Głuszewska A. et al. Blood pressure, arterial stiffness and endogenous lithium clearance in relation to AGTR1 A1166C and AGTR2 G1675A gene polymorphisms. J Renin Angiotensin Aldosterone Syst. 2016; 17(2): 1470320316655669. doi: 10.1177/1470320316655669.
57. Smyth L.J., Cañadas-Garre M., Cappa R.C. et al. Genetic associations between genes in the renin-angiotensin-aldosterone system and renal disease: a systematic review and meta-analysis. BMJ Open. 2019;9(4): e026777. doi: 10.1136/bmjopen-2018-026777.
58. Chang H.-F., Hsiao P.-J., Hsu Y.-J. et al. Association between angiotensin II receptor type 1 A1166C polymorphism and chronic kidney disease. Oncotarget. 2018; 9(18): 14444-14455. doi: 10.18632/oncotarget.24469.
59. Ji L.-D., Li J.-Y., Yao B.-B. et al. Are genetic polymorphisms in the renin– angiotensin– aldosterone system associated with essential hypertension? Evidence from genome– wide association studies. J Hum Hypertens. 2017;31(11): 695-698. doi: 10.1038/jhh.2017.29.
60. Charoen P., Eu-Ahsunthornwattana J., Thongmung N. et al. Contribution of Four Polymorphisms in Renin-Angiotensin-Aldosterone-Related Genes to Hypertension in a Thai Population. Int J Hypertens. 2019; 4861081. doi: 10.1155/2019/4861081.
61. Mulerova T., Uchasova E., Ogarkov M., Barbarash O. Genetic forms and pathophysiology of essential arterial hypertension in minor indigenous peoples of Russia. BMC Cardiovasc Disord. 2020;20(1):169. doi: 10.1186/s12872-020-01464-7.
62. Sousa A.C., Reis R.P., Pereira A. et al.Genetic Polymorphisms Associated with the Onset of Arterial Hypertension in a Portuguese Population. Acta Med Port. 2018;31(10):542-550. doi: 10.20344/amp.9184.
63. Chen K., Xiao P., Li G. et al. Distributive characteristics of the CYP2C9 and AGTR1 genetic polymorphisms in Han Chinese hypertensive patients: a retrospective study. BMC Cardiovasc Disord. 2021;21(1): 73. doi: 10.1186/s12872-021-01895-w.
64. Kohli S., Kumar R., Gupta M. et al. Impact of interactions between risk alleles on clinical endpoints in hypertension. Heart Asia. 2016;8(1): 83-9. doi: 10.1136/heartasia-2016-010723.

65. Simonyte S., Kuciene R., Medzioniene J. et al. Renin– angiotensin system gene polymorphisms and high blood pressure in Lithuanian children and adolescents. BMC Med Genet. 2017; 18(1):100. doi:10.1186/s12881-017-0462-z.
66. Goldstein B., Speth R. C., Trivedi M. et al. Benjamin Goldstein Renin-angiotensin system gene expression and neurodegenerative diseases. J Renin Angiotensin Aldosterone Syst. 2016;17(3):1470320316666750. doi: 10.1177/1470320316666750.
67. Jain S., Rana A., Jain K. et al. Age-Related Expression of Human AT1R Variants and Associated Renal Dysfunction in Transgenic Mice. Am J Hypertens. 2018;31(11): 1234-1242. doi: 10.1093/ajh/hpy121.
68. Zholdybayeva E.V., Talzhanov Y.A., Aitkulova A.M. et al. Genetic risk factors for restenosis after percutaneous coronary intervention in Kazakh population. Hum Genomics. 2016;10(1): 15. doi: 10.1186/s40246-016-0077-z.
69. Yap R.W.K., Shidoji Y., Yap W.S., Masaki M. Association and Interaction Effect of AGTR1 and AGTR2 Gene Polymorphisms with Dietary Pattern on Metabolic Risk Factors of Cardiovascular Disease in Malaysian Adults. Nutrients. 2017;9(8): 853. doi:10.3390/nu9080853.
70. Shakhanova A., Aukenov N., Nurtazina A. et al.Association of polymorphism genes LPL, ADRB2, AGT and AGTR1 with risk of hyperinsulinism and insulin resistance in the Kazakh population. Biomed Rep. 2020;13(5):35. doi:10.3892/br.2020.1342.
71. Musso G., Saba F., Cassader M. 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. 2019; 114(4): 607– 619. doi:10.14309/ajg.0000000000000154.
72. de Gracia Hahn D., Duret A., Mann J.P. An AGTR1 Variant Worsens Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome. Am J Gastroenterol. 2019; 114(4):556-559. doi:10.14309/ajg.0000000000000193.
73. Zhuang Y., Niu F., Liu D. et al.Association between AGTR1 A1166C polymorphism and the susceptibility to diabetic nephropathy: Evidence from a meta-analysis. Medicine (Baltimore). 2018;97(41):e07689. doi: 10.1097/MD.0000000000007689.
74. Xu H.– L., Cui J., Jia R. et al. Relationship between onset of eclampsia and AGTR1 gene polymorphisms. Eur Rev Med Pharmacol Sci. 2020; 24(24): 12638– 12644. doi: 10.26355/eurrev_202012_24160.
75. Li, X. Tan H., Zhou Sh. et al. Renin-angiotensin-aldosterone system gene polymorphisms in gestational hypertension and preeclampsia: A case-control gene-association study. Sci Rep. 2016; 6:38030. doi: 10.1038/srep38030.
76. Moe Sh.M., Long J., Linus Schwantes-An T.-H. et al. Angiotensin-related genetic determinants of cardiovascular disease in patients undergoing hemodialysis. Nephrol Dial Transplant. 2019; 34(11): 1924-1931. doi: 10.1093/ndt/gfy191.
77. Baranova T.I., Berlov D.N., Glotov O.S. et al.Genetic determination of the vascular reactions in humans in response to the diving reflex. Am J Physiol Heart Circ Physiol. 2017;312(3):622– 631. doi: 10.1152/ajpheart.00080.2016.
78. González A., Ravassa S., López B. et al. Myocardial Remodeling in Hypertension. Hypertension. 2018;72(3):549– 558. doi: 10.1161/HYPERTENSIONAHA.118.11125.
79. Nwabuo Ch.C., Vasan R.S. et al. Pathophysiology of Hypertensive Heart Disease: Beyond Left Ventricular Hypertrophy. Curr Hypertens Rep. 2020; 22(2): 11. doi: 10.1007/s11906-020-1017-9.
80. Ivanovic B., Tadic M. et al. Hypercholesterolemia and Hypertension: Two Sides of the Same Coin. Am J Cardiovasc Drugs. 2015;15(6): 403–14. doi: 10.1007/s40256-015-0128-1.
81. van Rooy M.-J., Pretorius E. Obesity, hypertension and hypercholesterolemia as risk factors for atherosclerosis leading to ischemic events. Curr Med Chem. 2014; 21(19): 2121-9. doi: 10.2174/09298673216613122716295O.
82. Eamranond P.P., Legedza A.T.R., Diez– Roux A.V. et al.Association between language and risk factor levels among Hispanic adults with hypertension, hypercholesterolemia, or diabetes. Am Heart J. 2009; 157(1): 53– 59. doi: 10.1016/j.ahj.2008.08.015.
83. Kuwabara M., Kuwabara R., et al. Different Risk for Hypertension, Diabetes, Dyslipidemia, and Hyperuricemia According to Level of Body Mass Index in Japanese and American Subjects. Nutrients. 2018; 10(8): 1011. doi: 10.3390/nu10081011.
84. Mortada I. Hyperuricemia, Type 2 Diabetes Mellitus, and Hypertension: an Emerging Association. Curr Hypertens Rep. 2017; 19(9): 69. doi: 10.1007/s11906-017-0770-x.
85. Feig D.I., Kang D.-H., Johnson R.J. Uric acid and cardiovascular risk. N Engl J Med. 2008; 359(17):1811– 1821. doi: 10.1056/NEJMra0800885.
86. McMaster W.G., Kirabo A., Madhur M. S., Harrison D.G. Inflammation, immunity, and hypertensive end– organ damage. Circ Res. 2015;116(6): 1022-1033. doi: 10.1161/CIRCRESAHA.116.303697.
87. Nosalski R., Siedlinski M., Denby L. et al. T-Cell-Derived miRNA-214 Mediates Perivascular Fibrosis in Hypertension. Circ Res. 2020; 126(8): 988-1003. doi: 10.1161/CIRCRESAHA.119.315428.
88. Zanoli L., Briet M., Empana J.P. et al. Vascular consequences of inflammation: a position statement from the ESH Working Group on Vascular Structure and Function and the ARTERY Society. J Hypertens. 2020; 38(9): 1682-1698. doi: 10.1097/HJH.0000000000002508.
89. Bozkurt B., Aguilar D., Deswal A. et al. Contributory Risk and Management of Comorbidities of Hypertension, Obesity, Diabetes Mellitus, Hyperlipidemia, and Metabolic Syndrome in Chronic Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2016; 134(23): e535-e578. doi: 10.1161/CIR.0000000000000450.
90. Saxton S. N., Clark B. J., Withers S. B. et al. Mechanistic Links Between Obesity, Diabetes, and Blood Pressure: Role of Perivascular Adipose Tissue. Physiol Rev. 2019; 99(4): 1701-1763. doi: 10.1152/physrev.00034.2018.
91. Spurr Sh., Bally J., Bullin C. et al. The prevalence of undiagnosed Prediabetes/type 2 diabetes, prehypertension/hypertension and obesity among ethnic groups of adolescents in Western Canada. BMC Pediatr. 2020; 20(1): 31. doi: 10.1186/s12887-020-1924-6.

ORCID and contributionship:
Viktoriia S. Potaskalova: 0000-0002-6255-7513 [A,E]
Nick V. Khaitovych: 0000-0001-6412-3243 [B,F]
Larysa V. Natrus: 0000-0003-1763-0618 [B,C]
Tsira B. Abdriakhimova: 0000-0002-9723-3067 [C,F]
Kateryna I. Kleban: [B,F]
Vitalii Y. Lunov: 0000-0002-7085-8454 [B,E]
Oleg A. Korop: 0000-0002-8833-4296 [B,E]

Conflict of interest:
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Viktoriia S. Potaskalova
Bogomolets National Medical University
13 Taras Shevchenko Boulevard, 01601 Kyiv, Ukraine
e-mail: doktorviktorya@gmail.com

Received: 12.06.2021
Accepted: 28.12.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article