ORIGINAL ARTICLE

CONTENTS

Changes in lipid profile parameters depending on the a1166c polymorphism of the angiotensin II type I receptor gene as a predictor of arterial hypertension

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ABSTRACT

Aim: To investigate lipid profile parameters depending the polymorphism of the A1166C I type gene receptor of the angiotensin II as a predictor of arterial hypertension.

Materials and Methods: The study involved 86 patients with arterial hypertension. The control group consisted of 30 practically healthy individuals. Indicators of lipid metabolism in the blood serum of patients were determined using "Lachema" kits on an analyzer. The the polymorphism of the A1166C I type gene receptor of the angiotensin II was studied by polymerase chain reaction with electrophoretic detection of the results.

Results: Higher levels of total cholesterol were found in patients with CC genotype compared to AA genotype carriers ((8.94±0.09) vs (5.18±0.02) mmol/L). The level of low-density lipoprotein in CC-genotype carriers was (7.43±0.03) versus (3.66±0.02) mmol/L in A-allele homozygotes. Triglycerides and very low density lipoproteins were also significantly higher in CC genotype carriers compared to patients with AA genotype. The level of high-density lipoprotein was lower in homozygotes with C-allele than in patients with the AA genotype, and was (0.59±0.12) versus (0.99±0.03) mmol/L.

Conclusions: The presence in the CC genotype the I type gene receptor of the angiotensin II type is a predictor of dyslipidemia. In patients with arterial hypertension, the presence in the C-allele of the I type gene of the angiotensin II type contributes to a significant increase in serum adipokines and a decrease in ghrelin levels.

KEY WORDS: arterial hypertension, polymorphism of the A1166C gene, lipidogram, predictor, lipid profile, ghrelin

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INTRODUCTION

The clinical and pathogenetic heterogeneity of arterial hypertension (AH) and insufficient study of the mechanisms of blood pressure regulation and, as a result, the improvement of the schematics of complex therapy of AH, stipulates further study of the pathogenetic mechanisms of persistent high blood pressure. A unique feature of AH is the dominance of disorders of functional mechanisms of blood pressure regulation (nervous and humoral), which cover the main homeostatic systems of the body, the formation of vicious circles and the so-called cardiovascular continuum [1, 2].

Functionally, blood pressure regulatory systems are genetically determined. In view of this, the combination of genetic predisposition with living conditions and environmental factors allowed us to classify hypertension as a multifactorial pathology. The stratification of risk factors for hypertension has led to the most significant mutational changes in the genes responsible for the balance of the pressor (tissue and renal renin-aldosterone-angiotensin system (RAAS) vasoconstrictors-endothelin 1, 2, 3, vasopressin, aldosterone, leukotrienes C and D, prostaglandin-E2) and depressor (NO, Na-urethic peptides, kallikrein-kinin system, prostacyclin) long-acting circuits [3, 4].

The realization of pathophysiological effects of these «mediators» of hypertension is possible only in cases of expression of the corresponding receptors on target cells and organs. In addition, non-peptide components of the

Table 1. Characteristics of the examined patients (n=86)

Indicator	Meaning
Average age, years	61,35±13,3
Men, % (n)	45 (39)
Women, % (n)	55 (47)
Duration of the disease, years	12,6±1,8
BMI, kg/m^2	32,6±1,1
Obesity (BMI > 30 kg/m2), % (n)	34,9 (30)
Smoking	31,4 (27)
Alcohol abuse	12,8 (11)
Burdened heredity for early development of CVD (for men age < 55 years, for women < 65 years), % (n)	54,7 (47)
Grade 1 hypertension, % (n)	24,4 (21)
Grade 2 hypertension, % (n)	54,6 (47)
Grade 3 hypertension, % (n)	21 (18)

pressor and depressor circuits realize their physiological and pathophysiological effects only in the case of the activity of the corresponding enzymes. Mutational processes affecting the synthesis, production, and reception of these mediators of hypertension are an important component of this disease. The identification of specific polymorphisms associated with hypertension and their involvement in pathogenetic patterns of blood pressure dysregulation gave rise to the definition of these genes as candidate genes for hypertension. The most relevant polymorphisms in hypertension are the polymorphisms of the angiotensin-converting enzyme (ACE) gene, the angiotensin (AGT) gene polymorphism, the angiotensin II receptor (AGTR) gene polymorphism, and the NO-synthase gene polymorphism [5, 6, 7].

There are many gene-candidates, whose SNP-mutations are associated with a predisposition to cardiovascular disease, and one of the most common is undoubtedly arterial hypertension (AH). Despite some progress in the study of the pathogenesis and diagnosis of arterial hypertension, most patients fail to achieve adequate control of high blood pressure, which leads to an increased risk of developing complications of AH [8, 9].

The results of numerous studies confirm the relationship between arterial hypertension and genes of the renin-angiotensin-aldosterone system, namely the polymorphism of the A1166C I type gene receptor of the angiotensin II (AGTR1) in patients with hypertension and the evaluation of the relationship between polymorphism, high blood pressure and dyslipidemia [10, 11].

Given the material we have accumulated, we considered it appropriate to conduct additional research to help understand the interaction of genes with the environment to obtain a complete picture of the complex genetic architecture of AH.

AIM

The aim of the work is to investigate lipid profile parameters depending on the polymorphism of the A1166C I type gene receptor of the angiotensin II (AGTR1) as a predictor of arterial hypertension.

MATERIALS AND METHODS

86 patients (47 (55 %) women and 39 (45 %) men) with arterial hypertension, who were treated and examined in the therapeutic department of Koziv Central District Hospital were examined. Their age ranged from 45 to 76 years, with a mean age of (61.35 ± 13.30) years. The control group consisted of 30 people without signs of arterial hypertension. The criteria for inclusion in the study was the presence of arterial hypertension of 1-3 degrees. The diagnosis of hypertension was established in accordance with the orders of the Ministry of Health of Ukraine No. 54 and 436 and the Recommendations of the Ukrainian Association of Cardiologists on the prevention and treatment of hypertension on the basis of anamnestic data, complaints, physical and clinical examination data.

The study was conducted in accordance with the principles of bioethics, which are set out in the Declaration of Helsinki «Ethical Principles for Medical Research Involving Human Subjects», the Universal Declaration on Bioethics and Human Rights (UNESCO), and the Order of the Ministry of Health of Ukraine «On Approval of the Procedure for Conducting Clinical Trials of Medicines and Examination of Clinical Trial Materials and the Model Regulations on Ethics Commissions» No. 690 of 23.09.2009. Written informed consent for the study was obtained from all patients (Conclusion of the Biomedical Ethics Committee of the Ternopil National Medical University No. 69 dated 12.04.2022).

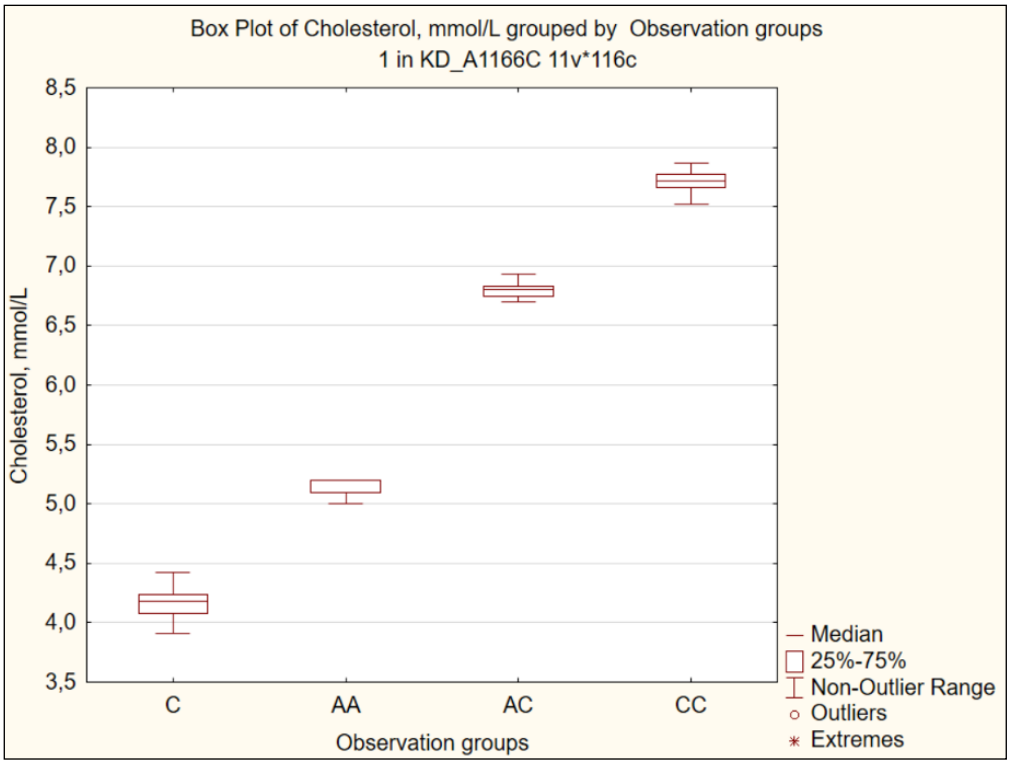

Fig. 1. Changes in general cholesterol level in patients with arterial hypertension depending on the polymorphism of the A1166C gene receptor of the of AA, AC and CC type carriers.

The study did not include patients with a history of myocardial infarction and stroke, secondary arterial hypertension, congenital or acquired heart disease, rhythm and conduction disorders, functional class III-IV heart failure by NYHA, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease, cancer, and mental illness. The clinical and anamnestic characteristics of the patients are shown in Table 1.

All patients underwent the following studies: measurement of body weight and height, office blood pressure, electrocardiography (ECG), lipid profile, and the polymorphism of the A1166C I type gene receptor of the angiotensin II was determined.

The lipid profile in the blood serum of the studied patients was measured in the laboratory of the Koziv Central District Hospital of the CEB. Concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and high-density lipoprotein (HDL) were determined using commercially available kits on a Biochem FC-200 analyzer (HTI, USA).

The allelic polymorphism of the A1166C I type gene receptor of the angiotensin II was studied by polymerase chain reaction with electrophoretic detection of the results using SNP-EXPRESS reagent kits (Litex Ltd.).

Statistical processing of the study materials was performed using biostatistical analysis methods implemented in the licensed software packages Microsoft Office 2010 Professional Plus (Microsoft Access 2010, Microsoft Excel 2010) - registration number 49521210; software product STATISTICA 6.1 (StatSoftInc., serial number AGAR909E415822FA).

The following basic statistical characteristics were calculated: number of observations (n), arithmetic mean (M), relative values (P), mean error of the mean (mM), mean error of the relative value (mr), standard deviation (SD), 95% confidence interval (95% CI); median (Me) with interquartile range (25% and 75% percentile) in case of asymmetric data distribution. These values are presented in the figures and text.

RESULTS

The state of lipid metabolism in patients with arterial hypertension depended on the A1166C polymorphism.

Analyzing the lipid status, we found the presence of pathological changes in lipid metabolism in all patients with AH, but in patients with the CC genotype compared with carriers of the AA genotype of the A1166C gene, lipid homeostasis disorders were more profound, as evidenced by a statistically significant increase in the levels of GCL, TG, VLDL, LDL. There was a tendency to a greater increase in all atherogenic blood fractions in the group of patients carrying the CC genotype compared with carriers of the AA genotype of the AGTR1 gene.

When analyzing the lipid profile of patients with arterial hypertension, higher cholesterol values were noted in all groups compared to controls.

All indicators were distributed according to a non-normal distribution law, so all their numerical values

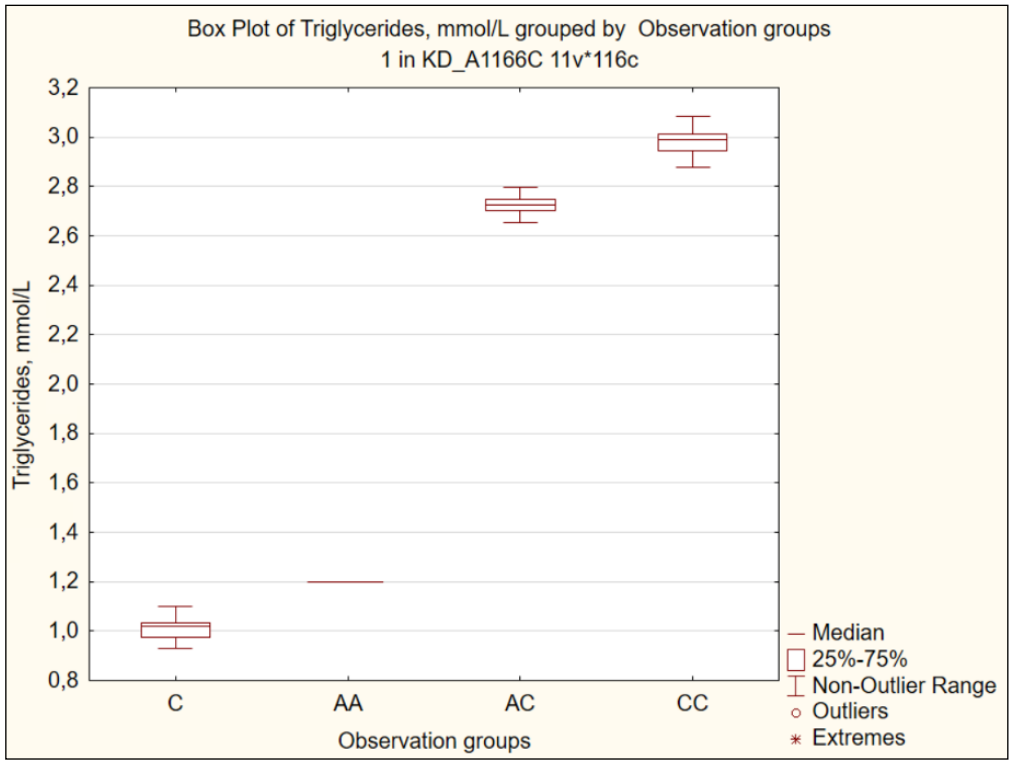

Fig. 2. Changes in triglycerol content in patients with hypertension depending on the polymorphism of the A1166C gene receptor of AA, AC and CC type carriers.

are presented in the form of medians and quartiles in the form of Me (IQR). Based on the results of the comparative analysis presented in Fig. 1, it can be concluded that a statistically significant difference for total cholesterol is observed when comparing the control group (C) (Me (IQR) 4.1 (4.1; 4.2)) and the groups of patients with arterial hypertension of AA carriers (Me (IQR) 5.1 (5.1; 5.2)), AC (Me (IQR) 6.8 (6.7; 6.8)) and CC genotype Me (IQR) 7.7 (7.7; 7.8)) of the A1166C gene, statistically significant differences were found with significance levels of $p<0.001$.

Our studies have shown that the level of general cholesterol in carriers of the homozygous AA genotype (n=18) is 1.23 times higher than in the control group (n=30). In patients with the AC genotype (n=38), the general cholesterol level was 1.68 times higher than in the control group. The most significant increase in the study index was recorded in patients with the CC genotype (n=30). In these patients, the level of general cholesterol was 2.14 times higher than in the control group.

Our next task was to analyze the value of triglycerols. TG had a similar trend to general cholesterol in the group of carriers of the CC genotype of the AGTR1 gene and was statistically significantly higher than in the group of carriers of the AA genotype.

According to the results of the comparative analysis shown in Fig. 2, it can be concluded that a statistically significant difference for triglycerols is observed when comparing the control group (C) (Me (IQR) 1.0 (0.9; 1.0)) and groups of patients with hypertension with AA (Me (IQR) 1.2 (0; 0)), AC (Me (IQR) 2.7 (2.7; 2.7)) and CC genotype Me (IQR) 3.0 (2.9; 3.0)) of the A1166C gene, statistically significant differences were found with significance levels of $p<0.001$.

According to the results of the comparative analysis shown in Fig. 3, it can be concluded that a statistically significant difference for LDL was observed when comparing the control group (C) (Me (IQR) 2.7 (2.6; 2.7)) and the groups of patients with hypertension of AA carriers (Me (IQR) 3.6 (0; 0)), AC (Me (IQR) 5.1 (5.1; 5.2)) and CC genotype Me (IQR) 5.4 (5.4; 5.5)) of the A1166C gene, statistically significant differences were found with significance levels of $p<0.001$.

The level of low-density lipoprotein (LDL) in patients with arterial hypertension with the CC genotype was 5.43 ± 0.03 mmol/L versus 3.66 ± 0.02 mmol/L in the group with AA genotype carriers.

We observed a similar trend in changes in VLDL content in patients with the CC genotype.

According to the results of the comparative analysis shown in Fig. 4, it can be concluded that a statistically significant difference for VLDL is observed when comparing the control group (C) (Me (IQR) 0.2 (0.2; 0.3)) and the groups of patients with hypertension of AA carriers (Me (IQR) 0.5 (0; 0)), AC (Me (IQR) 0.8 (0.8; 0.9)) and CC genotype Me (IQR) 1.7 (1.6; 1.8)) of the A1166C gene, statistically significant differences were found with significance levels of $p<0.001$.

Our studies have shown that the VLDL content in carriers of the homozygous AA genotype (n=18)

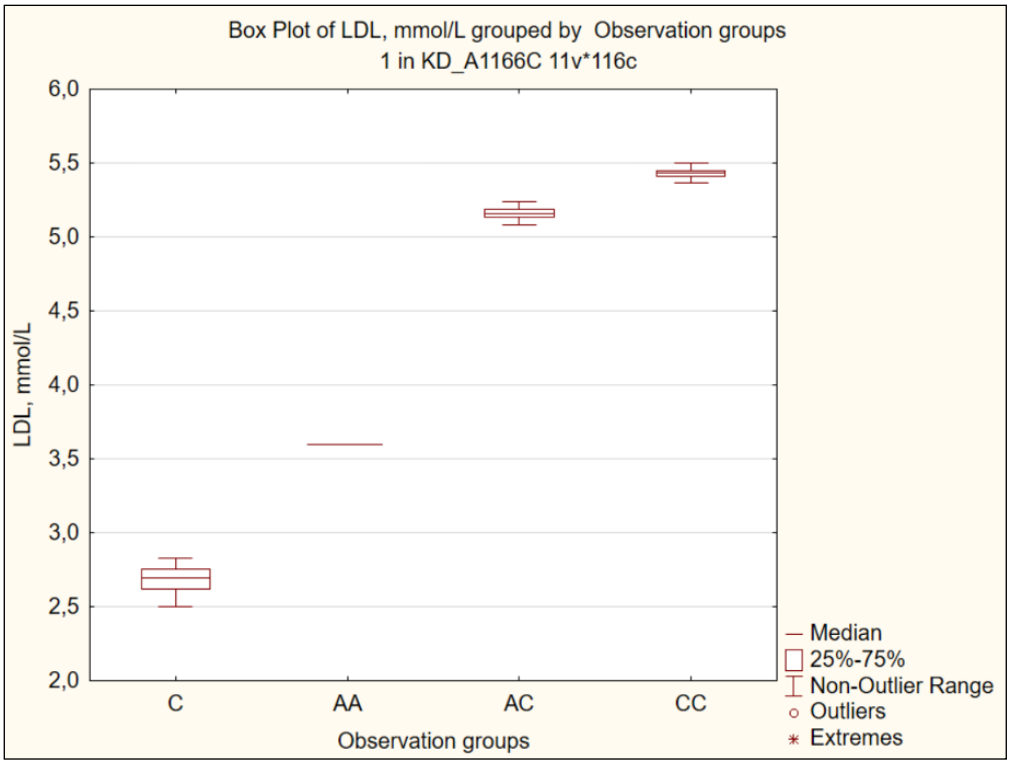

Fig. 3. Changes in low-density lipoprotein (LDL) content in patients with arterial hypertension depending on the polymorphism of the A1166C gene receptor of AA, AC and CC type carriers.

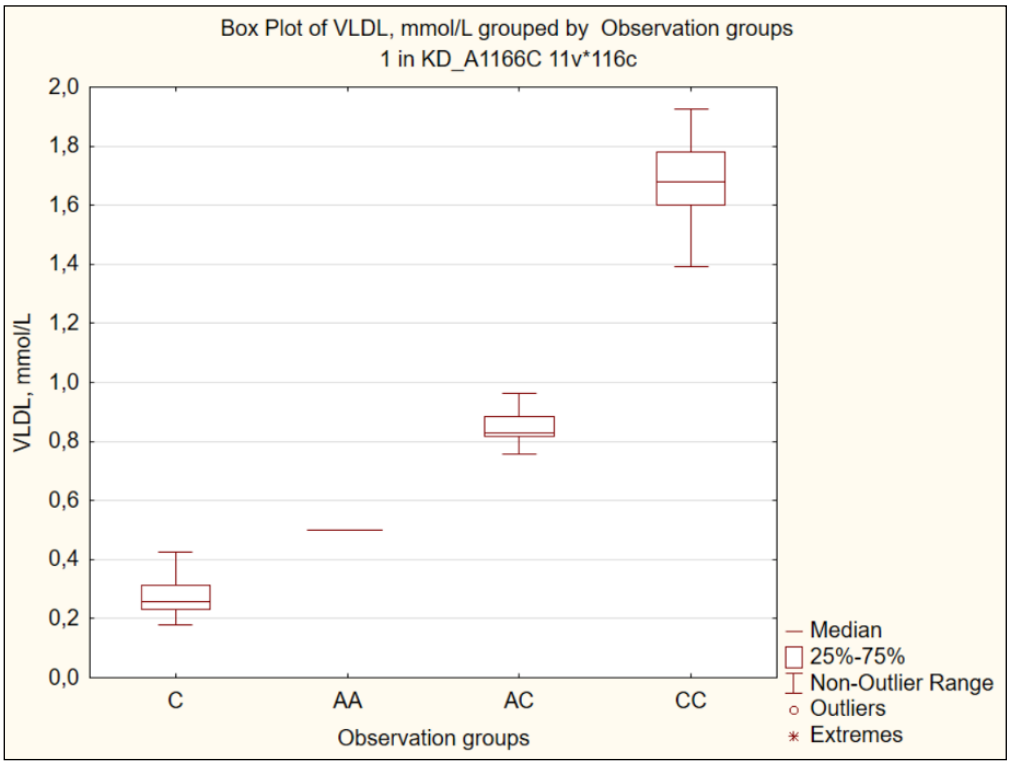

Fig. 4. Changes in the content of very low-density lipoprotein (VLDL) in patients with hypertension depending on the polymorphism of the A1166C gene receptor of AA, AC and CC type carriers.

differed from the patients of the control group and was 1.96 times higher. In patients with the AC genotype (n=38), the VLDL content was 3.14 times higher than in the control group (n=30). The most significant increase in the studied index was recorded in patients with the CC genotype (n=30). In these patients, VLDL content was 6.29 times higher than in the control group. A statistically significant increase in this indicator by 3.2 times in patients with CC genotype was observed relative to AA genotype carriers.

Regarding the level of HDL as an antiatherogenic factor, in the group of carriers of the CC genotype of the A1166C gene, this indicator was statistically significantly lower and amounted to 0.59 ± 0.12 mmol/l compared to the group with carriers of the AA genotype of 0.99 ± 0.03 mmol/l (Fig. 5). The decrease in HDL against the

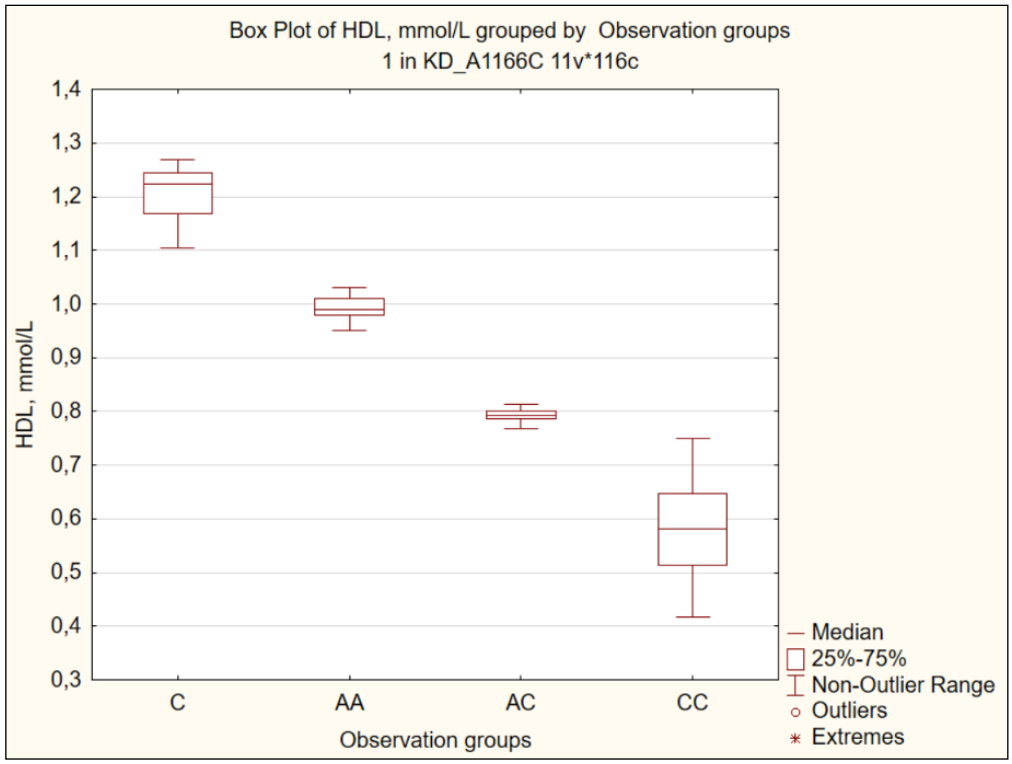

Fig. 5. Changes in the content of high-density lipoprotein (HDL) in patients with hypertension depending on the polymorphism of the A1166C gene receptor of AA, AC and CC type carriers.

background of increased LDL and VLDL in patients with arterial hypertension contributes to the formation of secondary IV type dyslipidemia according to the classification of D.S. Fredrickson [12].

According to the results of the comparative analysis presented in Fig. 5, it can be concluded that a statistically significant difference for HDL is observed when comparing the control group (C) (Me (IQR) 1.2 (1.1; 1.2)) and the groups of patients with hypertension with AA (Me (IQR) 0.9 (0.9; 1.0)), AC (Me (IQR) 0.7 (0.7; 0.8)) and CC genotype Me (IQR) 0.5 (0.5; 0.7)) of the A1166C gene, statistically significant differences were found with significance levels of $p<0.001$.

DISCUSSION

Many of the direct effects of angiotensin II (e.g., vasoconstriction) are realized through AGTR1. Stimulation of AGTR1 also activates membrane-binding H oxidase, which leads to the formation of reactive oxygen species. A number of authors describe that in almost all organ systems, activation of RAAS is associated with regeneration, remodeling, and tissue dysfunction, which are probably secondary to reactive oxygen species. All of this, when chronically activated, will contribute to inflammation, atherosclerosis, thrombosis and fibrogenesis in the vessels [13]. According to Lastra-Lastra G., the role of RAAS in the development of cardiovascular pathology is probably mediated by activation of I type receptor of angiotensin II and increased production of aldosterone, which is involved in the development of hypertension, endothelial dysfunction and fibrosis of cardiovascular tissue, remodeling, inflammation and oxidative stress [14, 15, 16].

Abdollahi M. (2007) described a new approach to the quantitative evaluation of transcriptional haplotypes of the AGTR1 gene [8]. According to his data, there were no significant differences in mRNA levels for rs5182: C > T alleles, but allele haplotypes and mRNA carrying A1166C showed a reduced widespreadness. The effect was much greater in CC homozygotes than in heterozygotes. It was also confirmed that the promoter region is located in a separate haplotype block from the 3'-region of AGTR1 containing rs5182: C > T and rs5186: A > C. The associations with metabolic syndrome symptoms were strongest for the 3'-block in general and for the C allele of rs5186: A > C allele, specifically [17]. All effects were expressed in homozygotes, possibly reproducing the mutual interaction through mRNA regulation feedback loops.

P. Palatini and colleagues (2009) studied the polymorphism of the A1166C gene AGTR1 for the frequency of arterial hypertension and metabolic syndrome in young patients with hypertension and found that this polymorphism is a predictor of hypertension and metabolic syndrome in the European population. Carriers of the C allele were more likely to develop resistant hypertension, and patients with the CC genotype had a 60 % increased risk compared with

patients with the AA genotype. At the beginning of the study, the authors noted higher fasting glucose levels, a significant increase in triglycerides, overweight, and other clinical signs of insulin resistance and hypertension in patients with the CC genotype. These results provide insight into the mechanisms that link obesity, arterial hypertension, and other features, and indicate that the polymorphism of the AGTR1 gene is involved in the pathogenesis of these clinical conditions. The authors propose to consider the polymorphism of the A1166C gene AGTR1 as a possible marker of the severity and development of arterial hypertension [18, 19]. Carriers of the C-allele also had an increased risk of MS, which is partly explained by a tendency to weight gain, but the occurrence of arterial hypertension was associated not only with the development of MS. The authors note that patients with the CC genotype at the beginning of the study had higher fasting glucose, significantly higher triglycerides, and were overweight. Their findings provide insight into the mechanisms linking obesity, hypertension, and MS, indicating that the polymorphism of the AGTR1 gene is involved in the pathogenesis of these conditions. It is likely that activation of RAAS in adipose tissue may be a link between obesity, AH and MS [20, 21]. The authors propose to consider the AGTR1 gene polymorphism (A1166C) as a possible marker of the severity and development of arterial hypertension. Our data match with those of these researchers. We have found a significant increase in all atherogenic lipid parameters (general cholesterol, trislycerides, LDL and VLDL) against the background of a decrease in HDL in patients with AH.

CONCLUSIONS

A statistically significant increase in all atherogenic lipid parameters of the lipidogram of patients with arterial hypertension and a worsening of dyslipidemia in carriers of the CC genotype compared with carriers of the AA genotype of the AGTR1 gene were found, which suggests that carriers of the CC genotype are predictors of dyslipidemia.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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