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Changes in adipokine indicators depending on A1166C polymorphism of the angiotensin II type 1 receptor gene as a predictor of the arterial hypertension

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Objective. Genetic factors substantially contribute to the development and duration of arterial hypertension. The study of the A1166C polymorphism of the angiotensin II type 1 receptor gene (*AGTR1*) in arterial hypertension is an auspicious area for assessing the relationship between heredity, hypertension development, and adipokines, but it still remains debatable. The purpose of the current study was to investigate serum adipokines levels depending on the *AGTR1* A1166C polymorphism.

Methods. A total of 86 patients with arterial hypertension were examined, who underwent the evaluation of the allelic A1166C polymorphism of *AGTR1* by polymerase chain reaction with electrophoretic detection and determination of serum adipokines levels using enzyme-linked immunosorbent assay.

Results. In the group of patients with arterial hypertension, a significant increase in serum adipokines (resistin, adiponectin, and leptin) levels was found against the background of a decrease in the antianorexic hormone ghrelin with a predominance of CC genotype carriers compared with AA genotype carriers of the *AGTR1*. A statistically significant decrease in ghrelin and an increase in serum adipokines (resistin, adiponectin, and leptin) in CC genotype carriers compared with AA genotype carriers of the *AGTR1* were found suggesting that CC genotype carriers may be predictors of the development of arterial hypertension in our patients.

Conclusions. Statistically significant decrease in ghrelin and increase in serum adipokines (resistin, adiponectin, and leptin) were found in CC genotype carriers compared with AA genotype carriers of the *AGTR1*, which suggests that carriers of the CC genotype are predictors of the arterial hypertension development in our patients.

Keywords: arterial hypertension, A1166C polymorphism, angiotensin II type 1 receptor gene, adipokines

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Adipokines (leptin, resistin, and adiponectin) may play a specific role in the development of arterial hypertension (Sabbatini et al. 2015; Pidruchna et al. 2024).

A number of studies have shown an association of arterial hypertension with hyperleptinemia. The authors have explained the pathophysiological mechanisms of high blood pressure by the sympathoadrenal reaction caused by the effect of leptin on the hypothalamus and an increase in peripheral vascular resistance due to the smooth muscle cell proliferation initiated by hyperleptinemia (Kamareddine et al. 2021; Prodan et al. 2023).

According to the results of the recent studies, genetic factors usually play an important role in the arterial hypertension development and course (Krynytska et al. 2021; Marushchak et al. 2022). The study on the A1166C polymorphism of the angiotensin II type 1 receptor gene (*AGTR1*) in arterial hypertension is a promising area for assessing the relationship between heredity, hypertension, and adipokines, but it may remain controversial. Therefore, it is interesting to investigate the role of leptin, resistin, and adiponectin in patients with arterial hypertension, since no studies of adiponectins and ghrelin taking into account *AGTR1* A1166C polymorphism and arterial hypertension have been found in the available literature to the best of our knowledge.

The aim of the present study was to investigate the serum adipokines levels depending on the A1166C polymorphism of *AGTR1* as a predictor of arterial hypertension.

Materials and Methods

Study population. A total of 86 patients with arterial hypertension who attended and were examined at the therapeutic department of Kozivska CDH participated in this study. All participants underwent the following examinations: body weight and height determination, blood pressure measurements, daily blood pressure monitoring, electrocardiography (ECG), cardiac ultrasound, and A1166C polymorphism of *AGTR1* and determination of serum adipokines levels.

Genotyping of the *AGTR1* A1166C polymorphism region. The allelic A1166C polymorphism of *AGTR1* was studied by polymerase chain reaction (PCR) with electrophoretic detection using SNP-EXPRESS reagent kits ("Litex", RF). The frequency of distribution of polymorphic genes in the population was checked according to the Hardy-Weinberg law of genetic equilibrium.

Laboratory data. Determination of the serum adipokines levels was performed by enzyme-linked immunosorbent assay (ELISA) using reagent kits: Human Resistin ELISA Kit (Thermo Fisher Scientific, USA) for resistin analysis, Leptin ELISA (LDN Labor Diagnostica Nord GmbH&Co,KG, Germany) for leptin analysis, Human Adiponectin ELISA Kit (Thermo Fisher Scientific, USA) for adiponectin analysis, and Human Ghrelin ELISA Kit (Thermo Fisher Scientific, USA) for ghrelin analysis using a Multiscan FC analyzer at 620 nm.

Ethical details. While conducting this research project, we followed the principles of bioethics 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. 69 of 23.09.2009. Written informed consent for the study was obtained from all patients (Conclusion of the Biomedical Ethics Committee of the I. Horbachevsky Ternopil National Medical University of the Ministry of Health of Ukraine No. 69 dated from 12.04.2022).

Statistical analysis. The statistical analysis of the research data was performed using Statistica 10 (Statsoft, USA, serial number CDDR415X254504GVZ7) and the statistical functions of Microsoft Office Excel 2016 (Microsoft Corp., USA). The arithmetic mean (M) and its error (m) were determined. The distribution of samples was checked for normality by the Shapiro-Wilk test. Authenticity of changes in the mean values of the study results between groups was calculated by Student's t-test with a normal distribution of independent samples and the nonparametric Kruskal-Wallis test in the absence of a normal distribution. Differences were considered statistically significant at a significance level of $p<0.05$.

Results

In the group of patients with arterial hypertension, we found a significant increase in serum adipokines – resistin ($p<0.05$), adiponectin ($p<0.05$), and leptin ($p<0.05$) – against the background of a decrease in the antianorexic hormone ghrelin.

An excessive resistin production in all studied groups of patients with arterial hypertension was recorded (Figure 1). However, in patients with the CC genotype compared with carriers of the AA genotype of the *AGTR1*, the serum resistin content

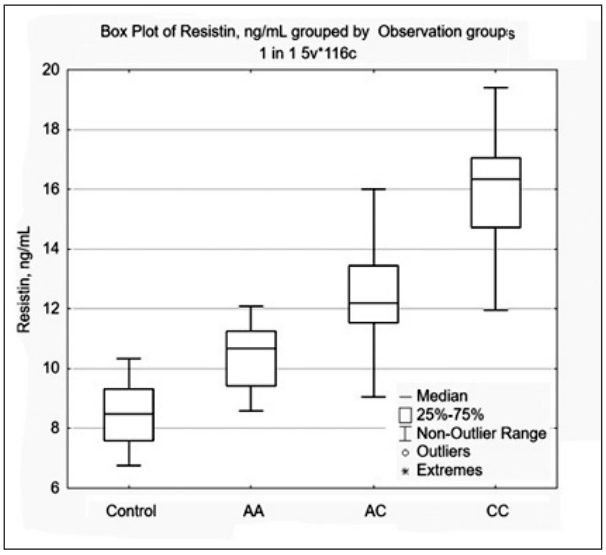

Figure 1. Changes in resistin content in patients with arterial hypertension depending on the AA, AC, and CC genotypes of angiotensin II type 1 receptor gene (*AGTR1*) A1166C polymorphism.

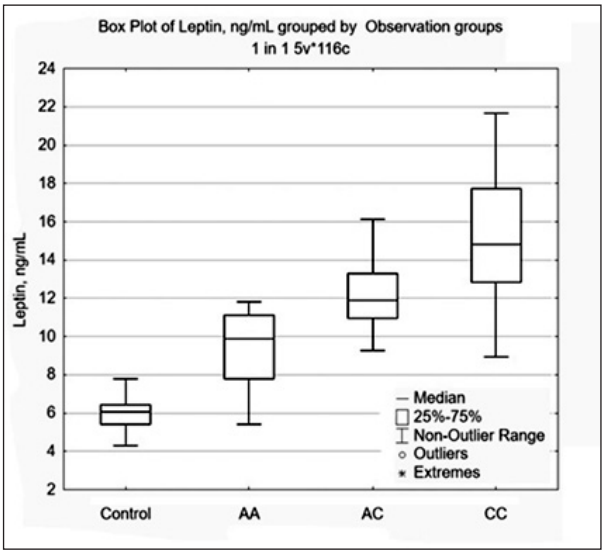

Figure 2. Changes in leptin content in patients with arterial hypertension depending on the AA, AC, and CC genotypes of angiotensin II type 1 receptor gene (*AGTR1*) A1166C polymorphism.

was significantly higher ($p<0.05$) and amounted to 15.7±2.10 ng/ml vs. 10.4±1.01 ng/ml, respectively.

According to the results of the comparative analysis presented in Figure 1, it can be concluded a statistically significant difference for resistin when comparing the control group (C) [(Me (IQR) 8.4 (7.5; 9.3)] with the groups of arterial hypertension patients with AA [(Me (IQR) 10.6 (9.4; 11.2)], AC [(Me (IQR) 12.2 (11.5; 13.6)] and CC genotype [Me (IQR) 16.2 (14.6; 17.0)] of the *AGTR1*. Our data are consistent with the results of other researchers (Jiang et al. 2016), who have shown that resistin induces both insulin resistance and hypertension in mice and these effects are dependent on the toll-like receptor 4 (TLR4).

We also recorded an excessive leptin production in all study groups of patients with arterial hypertension (Figure 2). However, in patients with the CC genotype compared to the carriers of the AA genotype of the *AGTR1*, the serum leptin content was significantly higher by 2.4 times.

According to the results of the comparative analysis shown in Figure 2, it can be concluded a statistically significant difference for leptin when comparing the control group (C) [(Me (IQR) 6.0 (5.4; 6.4)] and the groups of patients with hypertension of AA carriers [(Me (IQR) 9.8 (7.8, 11.1)], AC [(Me (IQR) 12.0 (10.9, 13.9)], and CC genotype Me [(IQR) 15.1 (12.8, 17.7)] of the *AGTR1*.

A similar change tendency was observed in the adiponectin content in patients with the CC genotype

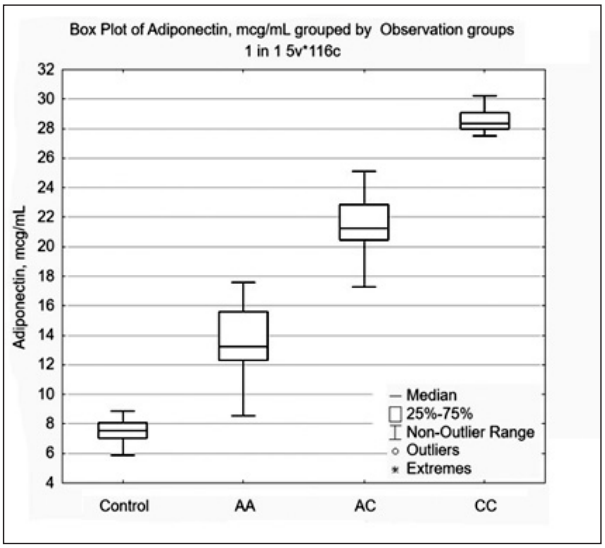

Figure 3. Changes in adiponectin content in patients with arterial hypertension depending on the AA, AC, and CC genotypes of angiotensin II type 1 receptor gene (*AGTR1*) A1166C polymorphism.

of *AGTR1*. As shown in Figure 3, the adiponectin content in carriers of the homozygous AA genotype (n=18) differed from the control group of patients and was 1.82 times higher. In patients with the AC genotype (n=38), the adiponectin content was 2.86 times higher than in the control group (n=30). Highest significant increase in the studied index was

recorded in patients with the CC genotype (n=30). In these patients, the adiponectin content was 3.75 times higher than in the control group.

According to the results of the comparative analysis shown in Figure 3, it can be concluded a statistically significant difference for adiponectin when comparing the control group (C) [(Me (IQR) 7.5 (7.0; 8.0)] and the groups of patients with hypertension of AA carriers [(Me (IQR) 13.2 (12.2; 15.5)], AC [(Me (IQR) 21.1 (20.4; 22.7)], and CC genotype [Me (IQR) 28.3 (27.9; 29.0)] of the *AGTR1.*

According to the results of the comparative analysis shown in Figure 4, it can be concluded a statistically significant difference for ghrelin when comparing the control group (C) [(Me (IQR) 1365.7 (1101.4; 1640.2)] with groups of patients with arterial hypertension of AA carriers [(Me (IQR) 1014.6 (999.3, 1181.8)], AC [(Me (IQR) 784.7 (567.2, 901.3)], and CC genotype [Me (IQR) 497.6 (419.0, 885.1)] of the *AGTR1.*

Discussion

The study of ghrelin levels showed a tendency to decrease in all studied groups of *AGTR1* A1166C polymorphism alleles. In the group of carriers of the CC genotype of the *AGTR1*, this indicator was statistically significantly lower than in the group with carriers of the AA genotype and amounted to 613.35±289.30 ng/ml vs. 1153.86±324.05 ng/ml with a value of 1380.48±0.50 ng/ml in the control group of subjects. Our data are aligned with other researchers who have found a low plasma ghrelin concentration in patients with arterial hypertension with concomitant obesity compared with lean Europeans (Shiiya et al. 2002). Low ghrelin concentrations are characterized by patients with type 2 diabetes mellitus (T2DM), indicating a possible genetic component in the regulation of plasma ghrelin levels. Some authors have shown that low ghrelin concentrations are independently associated with T2DM and insulin resistance (Poykko et al. 2003).

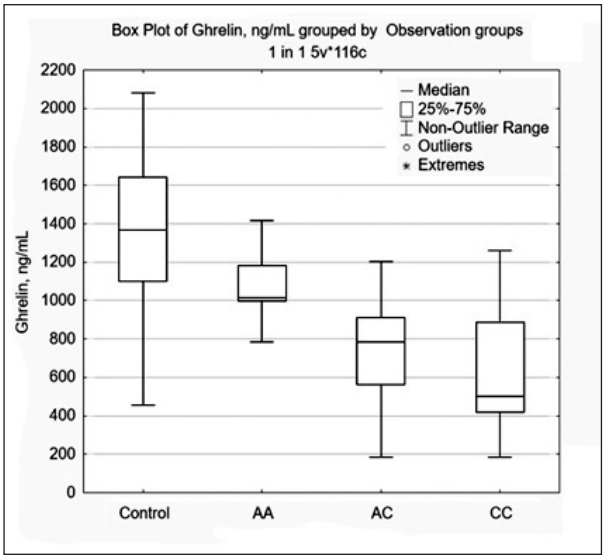

Figure 4. Changes in ghrelin content in patients with arterial hypertension depending on the AA, AC, and CC genotypes of angiotensin II type 1 receptor gene (*AGTR1*) A1166C polymorphism.

Excessive production of leptin serves as a marker of inflammation and adipose tissue damage contributing to the weakening of antioxidant processes in the body (Korda et al. 2010; Hutor et al. 2020). Hyperleptinemia is associated with activation of the sympathoadrenal system, increased insulin resistance, the pathogenesis of the myocardial hypertrophy, chronic heart failure, and angiopathy conditions associated with subclinical inflammation. In patients with arterial hypertension, leptin levels correlate with the risk of cardiovascular disease complications and are associated with the amount of visceral fat (Galletti et al. 2012).

Adiponectin plays a key role in energy metabolism; the concentration of both total adiponectin and bound adiponectin decreases with obesity and increases after weight loss. Adiponectin has antiatherogenic and anti-inflammatory properties and is inversely correlated with body mass index and the amount of visceral fat. Low serum adiponectin levels are associated with the development of atherosclerosis, coronary artery disease, arterial hypertension, and left ventricular hypertrophy (Jiang et al. 2016). In recent years, the leptin/adiponectin index has been shown to be more predictive of the development of cardiovascular disease, vascular disease, T2DM, metabolic syndrome, and arterial hypertension than leptin or adiponectin levels alone (Fang and Judd 2018). The data on the role of ghrelin in the pathogenesis of arterial hypertension have been obtained. More than 80% of circulating ghrelin is synthesized and secreted into the blood by endocrine cells of the gastrointestinal tract (Dziubanovskyi et al. 2022).

Ghrelin has been shown to reduce the fat utilization and contribute to the development of obesity (stimulates lipogenesis and inhibits lipolysis) and activates the lipid synthesis in the liver. Hypersecretion of ghrelin causes obesity. There is an inverse relationship between ghrelinaemia and insulin resistance, i.e. low levels of ghrelin induce more distinct insulin resistance.

Conclusion. We found a statistically significant decrease in ghrelin and an increase in the serum adipokines (resistin, adiponectin, and leptin) in carriers of the CC genotype compared with carriers of the AA genotype of the *AGTR1*, which suggests that carriers of the CC genotype are predictors of the development of arterial hypertension in our patients.

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Conflict of interest: *The authors declare no conflict of interest.*

References

Dziubanovskyi IY, Prodan AM, Pidruchna SR, Melnyk NA, Dzhyvak VG, Nikitina IM. Pathogenetic aspects of metabolic syndrome in experimental animals. Wiad lek 75, 514–519, 2022.

Fang H, Judd RL. Adiponectin regulation and function. Compr Physiol 8, 1031–1063, 2018.

Galletti F, D'Elia L, De Palma D, Russo O, Barba G, Siani A, Miller MA, Cappuccio FP, Rossi G, Zampa G, Strazzullo P. Hyperleptinemia is associated with hypertension, systemic inflammation and insulin resistance in overweight but not in normal weight men. Nutr Metab Cardiovasc Dis 22, 300–306, 2012.

Hutor NS, Pidruchna SR, Melnyk NA, Avdeev OV, Boykiv AB, Kovtun, NY, Skochylo OV, Tverdokhlib NO, Goncharuk-Khomyn MY. The role of prooxidant-antioxidant system in the development of alveolitis after teeth extraction. J Int Dent Med Res 13, 561–565, 2020.

Jiang Y, Lu L, Hu Y, Li Q, An C, Yu X, Shu L, Chen A, Niu C, Zhou L, Yang Z. Resistin induces hypertension and insulin resistance in mice via a TLR4-dependent pathway. Sci Rep 6, 22193, 2016.

Kamareddine L, Ghantous CM, Allouch S, Al-Ashmar SA, Anlar G, Kannan S, Djouhri L, Korashy HM, Agouni A, Zeidan A. Between inflammation and autophagy: the role of leptin-adiponectin axis in cardiac remodeling. J Inflamm Res 5349–5365, 2021.

Korda M, Yavorska S, Yaroshenko T, Ostrivka O, Pidruchna S, Suslova N, Kuzmak I. The role of leptin in obesity induced nitrooxidative stress and endothelial dysfunction-nanomedical approach. Pharmacia 23, 215–220, 2010.

Krynytska I, Kucher S, Tokarskyy O, Koval M, Marushchak, M. The association of angiotensin-converting enzyme gene insertion/deletion polymorphism with bronchial asthma. Pol Merkur Lek 49, 442–444, 2021.

Marushchak M, Krynytska I, Tokarskyy O, Koval M, Demianchuk M. Genetic polymorphism of the angiotensin-converting enzyme in bronchial asthma. Bangladesh J Med Sci 21, 492, 2022.

Pidruchna S, Shmanko V, Hnizdyukh R, Sverstiuk A, Lykhatskyy P, Kuzmak I, Yaroshenko T, Bandas I, Vasylyshyn N, Ostrivka O, Mudra M, Palytsia L, Letnyak N, Tokarskyy O. Statistically verified methods for determining predictors of development of arterial hypertension depending on endothelial nitric oxide synthase T786C gene promoter polymorphism using lipid profile indicators Endocr Regul 58, 138–143, 2024.

Poykko SM, Kellokoski E, Horkko S, Kauma H, Kesaniemi YA, Ukkola O. Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes 52, 2546–2553, 2003.

Prodan A, Dzubanovsky I, Kamyshnyi O, Melnyk N, Pidruchna S, Voloshyn S. GHRL, LEP, LEPR genes polymorphism and their association with the metabolic syndrome in the Ukrainian population. Endocr Regul 57, 269–278, 2023.

Sabbatini AR, Fontana V, Laurent S, Moreno H. An update on the role of adipokines in arterial stiffness and hypertension. J Hypertens 33, 435–444, 2015.

Shiiya T, Nakazato M, Mizuta M, Date Y, Mondal M, Tanaka M, Nozoe S, Hosoda H, Kangawa K, Matsukura S. Plasma ghrelin levels in lean and obese humans and the effect of glucose on ghrelin secretion. J Clin Endocrinol Metab 87, 240–244, 2002.