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Adipokine levels and T786C polymorphism of eNOS gene promoter correlation in patients with arterial hypertension

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Objective. Genetic factors contribute to the development of metabolic syndrome and subsequent arterial hypertension (AH). The study of the T786C polymorphism of the endothelial nitric oxide synthase (eNOS) gene in arterial hypertension is important as its correlation with adipokine imbalance is a novelty area to find associations between hypertension development, obesity, and heredity. The purpose of the current study was to investigate serum adipokines levels, depending on the T786C polymorphism of the eNOS in patients with arterial hypertension.

Methods. We examined 86 patients with arterial hypertension who underwent the determination of the T786C-gene promoter eNOS allelic polymorphism by PCR with electrophoretic detection. Additionally, the serum adipokines (resistin, leptin, adipoleptin, and ghrelin) levels were determined using enzyme-linked immunosorbent assay.

Results. In the patients with arterial hypertension, a significant increase in resistin level was found only in TC and CC genotype carriers of T786C, while adiponectin and leptin levels were significantly higher in all three genotypes (TT, TC, CC) compared to control healthy group. The most severe increase in the adipokine levels was observed in CC genotype, followed by TC genotype. The antianorexic hormone ghrelin had an opposite trend, with the lowest levels found in CC, followed by TC, and TT genotypes of T786C promoter eNOS gene. Interestingly, ghrelin level in TT genotype patients was not statistically different from control healthy group.

Conclusions. We demonstrated that CC and TC, compared with TT genotype carriers of the T786C polymorphism of the promoter eNOS gene, had significantly higher levels of all adipokines, except ghrelin, where an opposite trend was observed, which suggests their higher risk in development of more severe arterial hypertension with concomitant obesity, and other associated disorders.

Keywords: arterial hypertension, eNOS gene T786C polymorphism, resistin, adiponectin, leptin, ghrelin.

In the structure of non-fatal and fatal complications of cardiovascular diseases, arterial hypertension occupies one of the main positions (Krynytska et al. 2021). It remains not only an independent and disabling disease, but also one of the leading risk factors that leads to mortality from major cardiovascular complications, such as myocardial infarction, cerebral stroke, etc. (Marushchak et al. 2022). For many years, when studying the triggering mechanisms of arterial hypertension, the interest of researchers and physicians has been focused on modifiable risk factors, as it was widely believed that

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by influencing lifestyle, a positive result could be obtained. A detailed analysis of such unmodifiable risk factors as genetic predisposition was not relevant, primarily due to a number of methodological limitations. At present, the situation has changed and the study of genetic mechanisms associated with the formation of arterial hypertension with comorbidities is quite promising both from the point of view of predicting the risk of developing the disease in certain categories of individuals and from the perspective of the possibility of developing a sound strategy for the management of patients with clinically manifested arterial hypertension (Pidruchna et al. 2024a, b; Hnizdyukh et al. 2024).

One of the arterial hypertension predictors is endothelial dysfunction, which is manifested by imbalance in the production of vasoconstrictors and vasodilators, primarily nitric oxide (NO) and endothelin (Yaremchuk et al. 2020). A decrease in endothelial NO synthase (eNOS) production leads to a decrease in the concentration of NO in the bloodstream, as a result of which vasodilation decreases, which can be an important mechanism for the arterial hypertension development. The protective influence of eNOS on the cardiovascular system is also emphasized by Tran et al. (2022) in their recent review article. They concluded that dysfunction of the eNOS enzyme correlates well with the pathogenesis of cardiovascular diseases such as arteriosclerosis, arterial hypertension, myocardial infarction, as well as stroke.

eNOS syntheses NO in the endothelial cells, and as of today, a total of 11 polymorphisms in the gene encoding eNOS, are known. The most studied is the 786T>C polymorphism in the promoter region of eNOS gene (Pidruchna et al. 2024a; Hnizdyukh et al. 2024). However, Niu and Qi (2011) suggested that a total of three polymorphisms in the eNOS gene, including T786C, are associated with arterial hypertension.

Metabolic syndrome, as a cluster of risk factors for the development of cardiovascular disease, includes abdominal obesity and high blood pressure, which often go concomitantly and may be interdependent. The risk markers for obesity include decreased blood levels of ghrelin, which was shown to reduce fat utilization, stimulate lipogenesis, inhibit lipolysis, and activate lipid synthesis in the liver, thus influencing obesity.

One of the adipokines, leptin, plays a role in inflammation response as an adipose tissue damage marker (Korda et al. 2010), and hyperleptinemia is correlated well with cardiovascular diseases complications and the amount of visceral fat in patients with arterial hypertension (Galletti et al. 2012). Adiponectin, on the other hand, is an antagonist of leptin, and its low concentrations are associated with atherosclerosis, coronary artery disease, arterial hypertension (Jiang et al. 2016). Another adipokine, resistin, inhibits endothelial NO and induces prothrombotic endothelial dysfunction, and it is assumed that one of the mechanisms in arterial hypertension formation is dominated by resistin-mediated reduction of eNOS expression and increased expression and release of endothelin-1 in endothelial cells (Colombo et al. 2003; Gomma et al. 2002.

Therefore, the study of the T786C polymorphism of the gene promoter of the eNOS in arterial hypertension is a promising area for assessing the relationship between heredity, hypertension and adipokine imbalance.

Thus, the aim of our study was to investigate serum adipokines (resistin, leptin, adiponectin, and ghrelin) levels depending on the T786C polymorphism of the eNOS in patients with arterial hypertension.

Materials and Methods

Study population. We examined 86 patients with arterial hypertension aged from 45 to 76 years with average age 61.35±13.3 years (mean±SD), of which 47 were women (55%) and 39 were men (45%). Thirty individuals without signs of arterial hypertension and obesity formed the control group. The inclusion criterion in the study was the presence of arterial hypertension from the 1st to the 3rd stage. The diagnosis of arterial hypertension and its stage were 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 arterial hypertension on the basis of anamnesis, complaints, physical and clinical examination.

Genotyping of the T786C polymorphism of the eNOS. The allelic T786C polymorphism of the eNOS was studied in patients with arterial hypertension by polymerase chain reaction with electrophoretic detection of the results using SNP-EXPRESS reagent kits (Litex Ltd.).

Laboratory data. The levels of adipokines in the blood serum were determined by enzyme-linked immunosorbent assay (ELISA) using Human Resistin ELISA Kit (Thermo Fisher Scientific, USA), Leptin ELISA Kit (LDN Labor Diagnostica Nord GmbH&Co,KG, Germany), Human Adiponectin ELISA Kit (Thermo Fisher Scientific, USA), and

Human Ghrelin ELISA Kit (Thermo Fisher Scientific, USA) on a Multiscan FC analyzer.

Additional data were collected from patients, including the following information: body weight and height, blood pressure, electrocardiography (ECG), besides determination of the T786C polymorphism and blood laboratory data.

Ethical details. The principles of bioethics were strictly followed, as described in the Universal Declaration on Bioethics and Human Rights (UNESCO), Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", as well as 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 dated September 23, 2009. All patients provided written informed consent for the study and the study itself was approved by the conclusion of the Biomedical Ethics Committee of Ternopil National Medical University, No. 69 dated April 12, 2022.

Statistical analysis. Statistical analysis was done using the Statistica 10.0 software package (Statsoft, USA) and Microsoft Office Excel 2016 (Microsoft Corp., USA). The arithmetic mean and standard deviation (SD) were determined. The distribution of samples was checked for normality by the Kruskal-Wallis test. Reliability of changes in the mean values of the study results between groups was calculated by Student's t-test considering the observed normal distribution of independent samples. Differences at $p<0.05$ were considered statistically significant.

Results

The characteristics of the study groups are provided in Table 1. The genotype distribution regarding T786C polymorphism in the promoter region of the eNOS gene among healthy participants of the control group (N=30) was 11 for TT, 14 for TC, and 5 for CC genotype. On the contrary, the genotype distribution among patients with arterial hypertension was 31 for CC, 31 for TC, and 24 for TT genotype, emphasizing the possible role of CC genotype in arterial hypertension pathology. The overall average body mass index (BMI) of the patients with arterial hypertension was 32.6±1.1 kg/m^2 (mean±SD), while the mean BMI for the TT, TC, CC subgroups were not significantly different compared to each other ($p>0.05$, Table 1), ensuring homogeneity of data regarding obesity and their influence on serum adipokines results. On the contrary, control group individuals were generally non-obese with no arterial hypertension detected (Table 1).

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

The comparative analysis revealed that resistin levels were significantly ($p<0.05$) increased in the patients with arterial hypertension with TC (1.55 times) [Me (IQR) 12.8 (12.4; 14.1)] and CC (1.93 times) [Me (IQR) 16.1 (14.5; 18.8)], but not TT [Me (IQR) 8. 6 (7.9; 9.9)] genotype carriers of the T786C polymorphism of eNOS compared to

Table 1
Investigated groups of patients with arterial hypertension and their characteristics

Parameter	Control group	AH group	AH group		
			TT subgroup	TC subgroup	CC subgroup
Number of patients	30 (11, 14, 5)	86	24	31	31
Males [% (n)]	50 (15)	45 (39)	–	–	–
Females [% (n)]	50 (15)	55 (47)	–	–	–
Age (years)	30.0±10.3	61.4±13.3	–	–	–
BMI (kg/m^2)	23.1±1.2	32.6±1.1	n.d.	n.d.	n.d.
AH duration (years)	n/a	12.6±1.8	n.d.	n.d.	n.d.
AH stage	n/a	2.0±0.7^a	2.0±0.7^a	2.0±0.7^a	2.1±0.6^a
Daily average systolic BP (mmHg)	122.6±2.4^d	150.3±2.0^b	141.0±1.9^c	147.3±2.1^b	162.5±1.9^a
Daily average diastolic BP (mmHg)	75.9±1.5^d	96.8±2.3^b	90.0±1.7^c	93.3±2.3^c	107.3±2.8^a

Data are presented as mean ± S.D. Different superscripts indicate statistically significant differences between the groups within the same row ($p<0.05$); n.d. – not significant difference between any of the TT, TC, CC subgroup pairs within the same row ($p>0.05$).
Abbreviations: AH – arterial hypertension; BMI – body mass index; BP – blood pressure; n/a – not applicable.

the control healthy group [Me (IQR) 8.4 (7.5; 9.3)] (Figure 1).

We detected significantly ($p<0.05$) increased leptin levels in the patients with arterial hypertension with all genotypes of the T786C polymorphism of eNOS: TT [Me (IQR) 8.5 (7.8; 9.5)], TC [Me (IQR) 13.3 (11.3; 14.3)] and CC genotype (1.69 times) [Me (IQR) 15.3 (13.2; 16.5)] compared to the control group [Me (IQR) 6.0 (5.4; 6.4)] based on the comparative analysis. The highest leptin levels were found in the patients with CC genotype (Figure 2).

Based on the results of the comparative analysis we found a significant increase ($p<0.05$) in adiponectin levels in the patients with arterial hypertension carrying TT [Me (IQR) 11.0 (10.4; 12.1)], TC [Me (IQR) 22.7 (21.1; 23.5)] and CC genotype [Me (IQR) 30.3 (29.3; 30.9)] of the T786C polymorphism of eNOS compared to the control group [Me (IQR) 7.5 (7.0; 8. 0)] (Figure 3). In particular, adiponectin levels in the group of patients carrying CC genotype of the T786C polymorphism of eNOS were significantly higher by 2.7 and 1.4 times, respectively ($p<0.05$) compared to the groups of carriers of TT and TC genotypes (Figure 3).

Finally, we detected a significant decrease ($p<0.05$) in ghrelin levels in the groups of patients with arterial hypertension carrying TC [Me (IQR) 843.6 (605.4; 932.4)] and CC [Me (IQR) 471.7 (394.3; 536.7)] genotypes of the T786C polymorphism of eNOS, but not TT genotype [Me (IQR) 1243.4 (968.1; 1437.2)], compared to the control group [Me (IQR) 1365.7 (1101.5; 1640.2)] (Figure 4).

Discussion

Previously, a statistically significant increase in all atherogenic lipid parameters of the lipid profile in patients with arterial hypertension and a deepening of dyslipidemia in carriers of the TC and CC genotype compared with carriers of the TT genotype of the T786C polymorphism of the eNOS gene was found (Pidruchna et al. 2024a). However, TT carriers also had significantly higher atherogenic lipid values compared to the healthy control group (Pidruchna et al. 2024a). These findings suggested that the TC and CC genotypes of the T786C polymorphism of the eNOS gene may be predictors in the development of arterial hypertension accompanied by severe dyslipidemia.

In this paper, a significant decrease in ghrelin levels ($p<0.05$) was shown in patients with arterial hypertension, as well as a statistically significant increase in serum adipokine levels resistin ($p<0.05$), adiponectin ($p<0.05$), and leptin ($p<0.05$), especially in carriers of the CC genotype, followed by the TC genotype, of T786C polymorphism of the eNOS gene.

In 2001, a polypeptide resistin was isolated, which consisted of 114 amino acid residues and belonged to the family of cysteine-containing proteins called resistin-like molecules, which are involved in inflammation and may link obesity to diabetes (Steppan et al. 2001). Resistin is primarily secreted by macrophages, monocytes, preadipocytes, and mature adipocytes of visceral adipose tissue. Expression of resistin is induced by various inflammatory stimuli, including

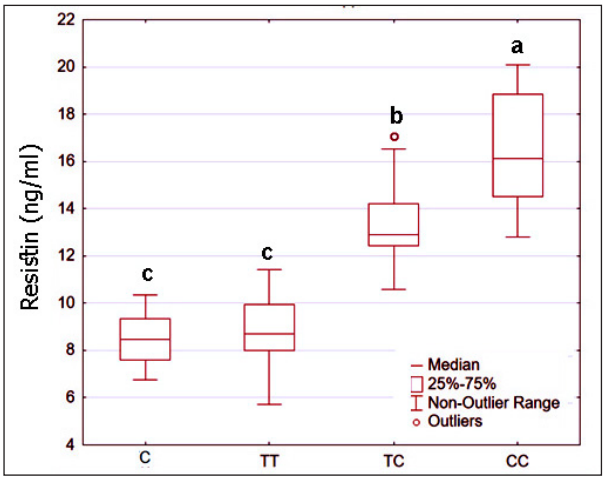

Figure 1. Resistin levels (ng/ml) in patients with arterial hypertension depending on the T786C polymorphism of the endothelial nitric oxide synthase (eNOS) of the TT, TC and CC genotype compared to healthy control group (C). Different superscripts indicate statistically significant differences ($p>0.05$).

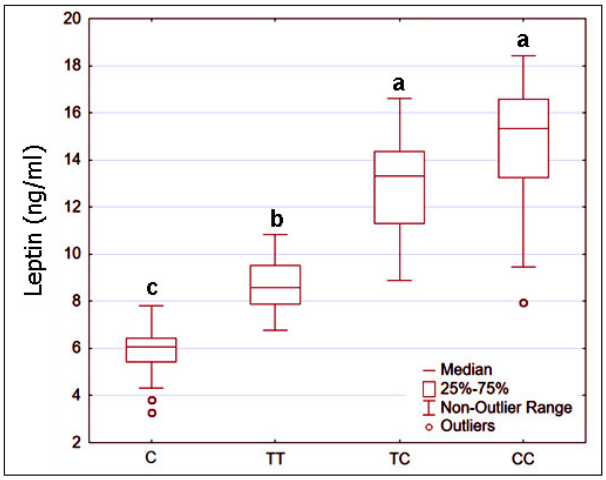

Figure 2. Leptin levels (ng/ml) in patients with arterial hypertension depending on the T786C polymorphism of the endothelial nitric oxide synthase (eNOS) of the TT, TC and CC genotype compared to healthy control group (C). Different superscripts indicate statistically significant differences ($p>0.05$).

tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), while resistin itself increases macrophage expression of proinflammatory cytokines (Milan et al. 2002). Resistin inhibits endothelial NO, induces prothrombotic endothelial dysfunction and platelet activation by increasing P-selectin expression. Taken together, these data show that resistin plays an important regulatory role in modulating the interactions between endothelial cells and monocytes/macrophages in the pathogenesis and progression of atherosclerosis (Khera et al. 2015). Circulating resistin levels correlate with inflammatory and fibrinolytic markers such as C-reactive protein, IL-6, TNF-α in general population, as well as in people with type 2 diabetes, coronary atherosclerosis, and rheumatoid arthritis (Park and Ahima 2013). It is assumed that the potential mechanism in the formation of arterial hypertension is dominated by resistin-mediated reduction of eNOS expression and increased expression and release of endothelin-1 in endothelial cells (Colombo et al. 2003; Gomma et al. 2002). In the present study, elevated levels of resistin were found in all arterial hypertension patients - carriers of CC and TC, but not TT genotype, of the eNOS (T786) polymorphism compared to control.

Elevated levels of leptin lead to inflammation and damage to adipose tissue, provoking malfunctioning of the body antioxidant system (Korda et al. 2010). High leptin levels are associated with increased insulin resistance, myocardial hypertrophy, chronic heart failure, and angiopathy associated with inflammation. Galletti et al. (2012) have shown that leptin levels correlated well with the risk of cardiovascular disease in patients with arterial hypertension, complicated by obesity.

The antagonist of leptin is adiponectin. Adiponectin has major anti-atherogenic and anti-inflammatory properties, it is inversely correlated with BMI. The concentration of both total adiponectin and bound adiponectin significantly decreases in case of obesity and increases during weight loss. Low serum adiponectin levels can lead to atherosclerosis, coronary artery disease, and arterial hypertension (Jiang et al. 2016). In addition, adiponectin reduces the expression of adhesive molecules on endothelial cells, promoting the regression of cell proliferation and oxidative stress, by activating NOS, which ultimately contributes to the recovery of endothelial cells. Recent studies have shown that adiponectin reduces inflammation in endothelial, muscle, epithelial cells and macrophages, and is involved in the regulation of cancer cell growth and apoptosis (Rojas et al. 2014).

Interestingly, in our research, we found an increase in serum leptin levels in patients with arterial hypertension, which was more severe in case of CC genotype, followed by TC genotype of T786 polymorphism of the eNOS, on the background of increasing adiponectin levels. Therefore, one can suggest a presence of compensatory mechanisms, where the negative influence of elevated leptin is compensated by the positive influence of elevated adiponectin. Similarly, Fang and Judd (2018) used the leptin/adiponectin index as a more precise predictor for the development of cardiovascular disease, metabolic

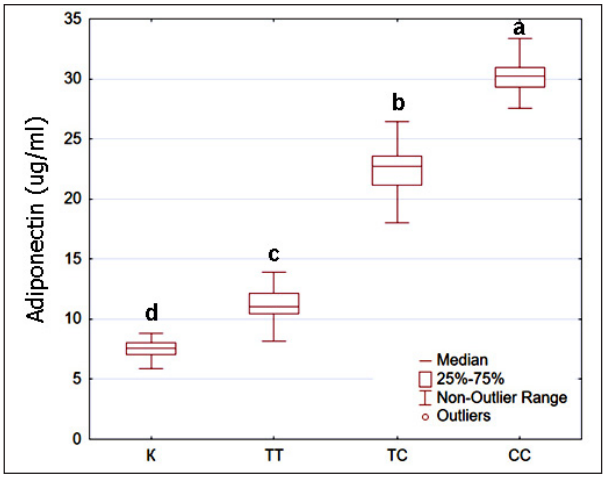

Figure 3. Adiponectin levels (μg/ml) in patients with arterial hypertension depending on the T786C polymorphism of the endothelial nitric oxide synthase (eNOS) of the TT, TC and CC genotype compared to healthy control group (C). Different superscripts indicate statistically significant differences (p>0.05).

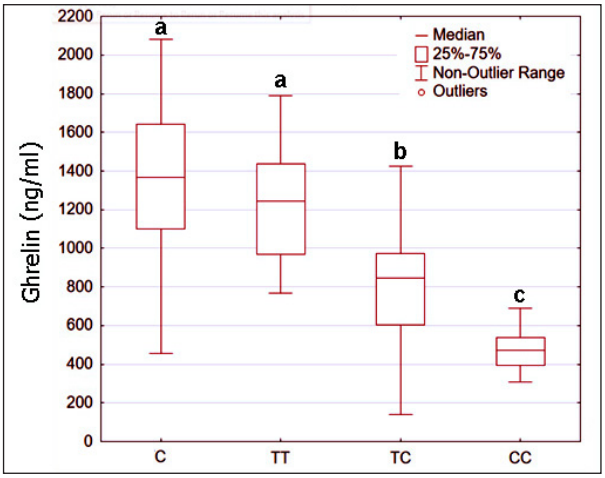

Figure 4. Ghrelin levels (ng/ml) in patients with arterial hypertension depending on the T786C polymorphism the endothelial nitric oxide synthase (eNOS) of the TT, TC and CC genotype compared to healthy control group (C). Different superscripts indicate statistically significant differences (p>0.05).

syndrome, and resulting arterial hypertension compared to the leptin or adiponectin levels alone.

Regarding ghrelin, it has been shown to reduce the fat utilization and contribute to the development of obesity, as it stimulates lipogenesis and inhibits lipolysis, as well as promotes lipid synthesis in liver (Poykko et al. 2003). The analysis of the results of this study regarding ghrelin levels showed a significant decrease in patients with arterial hypertension carrying TC and CC genotypes, but not TT genotype, of eNOS gene polymorphism alleles, compared to control. Thus, in the group of CC carriers of the T786C polymorphism of the eNOS gene, this index was significantly lower than in the group of TT genotype carriers by 2.54 times and by 2.9 times compared to the control levels. It has been previously shown that low ghrelin levels are associated with arterial hypertension and type 2 diabetes (Davenport et al. 2005). It is also assumed that ghrelin can affect blood pressure. As a result, low ghrelin levels are considered as a risk factor for arterial hypertension and type 2 diabetes (Tritos and Kokkotou 2006), also supported by current findings.

To summarize above-mentioned findings, the CC genotype of T786C polymorphism of the eNOS can be considered as a genetic predictor of the formation of several hemodynamic factors of cardiovascular risk for the development of arterial hypertension in patients, including obesity and inflammation.

Conclusions

We found a statistically significant decrease in serum ghrelin levels ($p<0.05$) and an increase in serum resistin levels ($p<0.01$) in carriers of the CC and TC genotypes of the T786C polymorphism of eNOS compared to carriers of the TT genotype, what suggests that carriers of the TC and CC genotype are predictors of the development of arterial hypertension associated with other comorbidities in our patients, such as obesity and inflammation. Simultaneous increase in both leptin and adiponectin levels may indicate compensatory mechanism to diminish negative influence of leptin.

However, there is no single polymorphism or even a single gene that is the only causal agent for arterial hypertension or related comorbidities such as obesity or dyslipidemia; it may be many genes affected, small changes in expression of which cause such interrelated pathologies as arterial hypertension, dyslipidemia, and obesity.

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

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