

THE LEVELS OF VISFATIN AND TOLL-LIKE RECEPTORS IN ARTERIAL HYPERTENSION AND TYPE 2 DIABETES MELLITUS

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Hypertension and type 2 diabetes mellitus (DM) remain widespread diseases that are becoming more prevalent. The role of visfatin and toll-like receptor (TLR) molecules in the pathogenesis of these diseases requires further research. Our aim was to study changes in visfatin and TLR levels in patients with hypertension and type 2 diabetes. Fifty-one patients were examined and divided into two groups: group 1 included 27 patients with hypertension and group 2 included 24 people with hypertension and type 2 DM. The control group included 18 practically healthy people. All individuals underwent general blood test, coagulogram, biochemical blood test, enzyme immunoassay to determine the level of visfatin and TLR in the blood serum and echocardiography. Hypertrophy of the walls of the left ventricle (LV) was observed in patients of two observed groups. The most common type of LV geometry was concentric hypertrophy (41.2%). The level of visfatin was significantly higher in patients of group 1, while in patients of group 2 it was decreased ($P < 0.05$) and the level of TLR was increased ($P < 0.05$). The elevated level of TLR in the serum of patients with hypertension can be considered a factor of low-grade inflammation, especially in combination with type 2 DM. The increase in the concentration of visfatin in hypertension serves as a more sensitive marker compared to TLR regarding the risk of developing comorbid cardiovascular pathology. The therapeutic treatments of patients with type 2 DM cause a reduction in the concentration of visfatin induced by hypertension.

Key words: hypertension, type 2 diabetes mellitus, visfatin, toll-like receptors.

Hypertension remains the main cause of cardiovascular pathology with an increasing trend worldwide. In particular, hypertension affects 30 to 45% of adults and may cause disability and premature death due to severe complications (stroke, myocardial infarction, heart failure, chronic kidney failure). Therefore, at present, the relationship between hypertension and cardiovascular diseases requires close attention from the point of view of public health and requires timely prevention and effective treatment [1-5].

The prevalence of type 2 diabetes mellitus (DM) is progressively increasing throughout the world. Despite numerous studies, treatment options are still limited. Type 2 DM often occurs in patients with metabolic disorders and especially in obesity due to the development of insulin resistance and an

imbalance of pro- and anti-inflammatory factors [6-9].

The danger of elevated blood glucose levels in type 2 DM in patients with hypertension is associated with the occurrence of neuropathy, damage to the glomeruli of the kidneys with the development of nephropathy and retinopathy. The presence of type 2 DM is associated with atherosclerosis and cardiovascular diseases, as well as cognitive impairment, Alzheimer's disease and vascular dementia [9, 10].

Adipose tissue is an organ that is responsible for the synthesis of adipocytokines, which participate in metabolic homeostasis and are the link between obesity and comorbid pathologies. An important pro-inflammatory adipokine that attracts attention is visfatin, which performs a regulatory function in many physiological and pathological processes, and

exhibits an insulin-mimetic effect through binding to the insulin receptor-1 and affects the development of insulin resistance [6, 11, 12].

In the context of metabolic diseases, more evidence is accumulating about the influence of low-grade inflammation, excessive expression of pro-inflammatory cytokines, cellular infiltration and oxidative stress on the course of hypertension and type 2 DM [13]. These conditions are accompanied by an increase in the level of visfatin [14]. Currently, the association between circulating visfatin and cardiovascular pathology is being intensively investigated [15].

Visfatin is pre-B cell colony-enhancing factor (PBEF), nicotinamide phosphoribosyltransferase (NAMPT), NAmPRTase, EC = 2.4.2.12, PBEF1. Nowadays the terms visfatin, PBEF and NAMPT are used interchangeably. Visfatin has been proposed as an insulin-mimicking adipocytokine predominantly secreted from visceral adipose tissue and correlated with obesity. Visfatin is actively produced by visceral adipose tissue and its level correlates with body mass index (BMI) and is associated with the progression of obesity. Visfatin is a proinflammatory marker of adipose tissue associated with systemic insulin resistance and hyperlipidemia [11, 12]. In addition, synthesis of visfatin occurs in cardiomyocytes, skeletal muscles, liver and brain cells. Visfatin acts as a PBEF, which also participates in the regulation of the synthesis of interleukins (IL-1 β , IL-6 and tumor necrosis factor - α). Visfatin exhibits pleiotropic effects (being a cytokine, hormone and enzyme), has both intracellular and extracellular functions and is involved in the synthesis of nicotinamide [12].

A progressive decrease in the level of visfatin leads to severe multiorgan insulin resistance [6]. In the context of metabolic diseases, elevated levels of visfatin are considered a marker of endothelial dysfunction, inflammation and destabilization of atherosclerotic plaques. At the same time, visfatin exhibits an insulin-mimetic effect, which leads to a decrease in the level of glucose and stimulates its utilization in adipocytes and myocytes [6]. An increased level of visfatin reflects a higher activity of the inflammatory process, which is associated with the formation of carotid atherosclerotic plaques in patients with type 2 DM. Among the biochemical effects of visfatin, which leads to endothelial dysfunction, the effect on the activity of nitric oxide synthase and the activation of oxidative stress due to the increase in the formation of superoxide anion is shown [16]. The increased serum level of visfatin can be considered a

potential risk marker for the development of comorbid cardiovascular pathology [17, 18].

Toll-like receptors (TLR) belong to integral membrane glycoproteins that are involved in response to pathogens and damage, as well as stimulating the production of antimicrobial peptides, cytokines and chemokines that neutralize pathogens and initiate inflammation [9]. The expression and activation of epithelial TLR depend on their location. In vascular endothelial cells, TLR activation is a link in the inflammatory response of the microcirculation [9]. It is believed that TLR may be involved in the pathogenesis and development of type 2 DM, as well as its complications. TLR regulates the creation of vasoactive lipids and reactive oxygen species, which leads to the release of proinflammatory cytokines, such as tumor necrosis factor- α and interleukin-1 β [9]. Recent studies have shown that visfatin induces TLR4-mediated-NF- κ B signaling activation [19, 21].

The insulin-like effect of visfatin leads to a decrease in glucose levels. However, research results are contradictory with both positive and negative effects found. Relationships and changes in visfatin and TLR levels in patients with hypertension and type 2 DM require further research. The aim of this research is to study changes in the levels of visfatin and TLR in patients with hypertension and type 2 DM.

Material and Methods

Patient selection. Fifty-one inpatients at the Lviv St. Panteleimon Clinical Hospital were examined. They were divided into two groups, group 1 included 27 patients with hypertension and group 2 included 24 people with hypertension and type 2 DM. The control group included 18 practically healthy people. All patients were urgently hospitalized and provided with appropriate treatment to stabilize their condition. Patients were treated according to the existing pathologies, namely, with antihypertensive drugs (ACE inhibitors, sartans) and hypoglycemic drugs (insulin, metformin) for the immediate stabilization of each patient's condition.

Ethical approval. Before the examination, all patients signed a voluntary consent to participate in the study, which was approved by the committee on the ethics of scientific research, experimental developments and scientific works of the Danylo Halytsky Lviv National Medical University (protocol No 8 dated 09.26.2022).

Inclusion and exclusion criteria. The inclusion criteria in the study were age of patients 40–75 years with a diagnosis of hypertension, type 2 DM. Patients with decompensated concomitant diseases, existing mental disorder, alcohol and drug addiction were excluded from the study.

Patients' examination. All study participants underwent a general physical examination with measurement of blood pressure (BP), anthropometric measurements with calculation of BMI, complete blood count (erythrocytes, hemoglobin, leukocytes, platelets using *Convergys® X5 Main Unit* reagents on automatic hematological analyzer *Convergys X5 Convergent Technologies GmbH Co. KG* (Germany)), coagulogram (prothrombin time, prothrombin index, fibrinogen, international normalized ratio, using *Human* reagents on automatic coagulometer *HumaClot Pro Human GmbH* (Germany)), biochemical blood test (glucose, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, urea, glomerular filtration rate (GFR), total bilirubin, total protein), as well as enzyme immunoassay to determine the level of visfatin and TLR in blood serum using *Human Visfatin Intracellular (CLOUD-CLONE CORP., Houston, USA)* and *Human TLR4 (ab277392, Abcam, Cambridge, UK)* ELISA Kits. GFR was calculated according to the formula CKD-EPI Creatinine Equation (2021). In addition, an echocardiographic examination was performed to determine the thickness of the interventricular septum (IVS), the posterior wall of the left ventricle (PWT), the size of the chambers of the left atrium (LA), right ventricle (RV), left ventricle (LV), calculation of the myocardial mass index of the left ventricle (LVMMI) and relative LV wall thickness (RWT), as well as establishing the left ventricular ejection fraction (LVEF) and the type of LV geometry, taking into account indicators of RWT and LVMMI.

Diagnosis establishment. The diagnosis of hypertension was established in patients with BP greater than 140/90 mm Hg, as well as in persons with a previously established diagnosis who received antihypertensive drugs. Type 2 DM confirmation is based on the determination of the glucose level of capillary blood, the results of the glucose tolerance test as well as in patients with a previously established diagnosis following current protocols.

Statistical analysis. Statistical analysis of the obtained results was carried out using *Microsoft Excel* (2010) and *GraphPad Prism 8.01.1* licensed software. All data are presented as mean values with standard deviation and as median and percen-

tiles according to the normality of the distribution, which was determined by the three-sigma rule. Student's *t*-test, chi-square and ANOVA test were used to determine the reliability of intergroup differences. Mann-Whitney-Wilcoxon test was used to assess the difference between two groups with non-Gaussian distribution of parameters. Correlations were studied with the calculation of the Pearson correlation coefficient. Significance was considered at $P < 0.05$.

Results and Discussion

During the patients' examination, no difference was found in gender, age and anthropometric parameters, which indicates the homogeneity of the examined groups. It was established that systolic BP was significantly higher in individuals of group 1 ($P < 0.05$), while diastolic BP did not show a difference ($P > 0.05$) (Table 1). Heart rate (HR) as well as systolic and diastolic BP were significantly higher in patients of the two main groups compared with practically healthy individuals of the control group ($P < 0.05$). There was no statistically significant difference in the duration of anamnesis of hypertension in patients of the observed groups (group 1 – 14.1 ± 4.2 years, group 2 – 14.8 ± 5.0 years, $P > 0.05$, Student's *t*-test).

The prothrombin index and hemoglobin were significantly lower ($P < 0.05$), the blood glucose level ($P < 0.01$) and the fibrinogen level was higher ($P < 0.01$) in patients of group 2 (Table 2).

Glucose level was significantly higher in the group with hypertension and type 2 DM ($P < 0.01$) as well as increased urea level (Table 3). The GFR was significantly lower in groups 1 and 2 ($P < 0.05$), as well as a decrease in its level in patients of the two groups, which is probably associated with the development of hypertensive and diabetic nephropathy [10].

Structural and functional changes of the myocardium are characteristic of the long course of hypertension, characterized by myocardial hypertrophy [21]. There was an increase in the thickness of the IVS ($P < 0.01$), the size of the LA ($P < 0.01$), an increase in the LVMMI in patients of two experimental groups and an increase in the size of the LV in patients of groups 1 and 2 ($P < 0.01$) (Table 4). The most common type of LV geometry was concentric hypertrophy (41.2%). These changes were caused by long-term pressure overload of the LV, which is typical for hypertension.

Table 1. Comparison of gender, age and physical parameters of patients of the examined groups with hypertension and type 2 diabetes mellitus

Parameters	Control group, <i>n</i> = 18	Group 1, patients with hypertension, <i>n</i> = 27	Group 2, patients with hypertension and type 2 DM, <i>n</i> = 24	<i>P</i> -value
Gender*:				
Male %	66.6	55.6	58.3	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Female %	33.4	44.4	41.7	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Age, years	38.4 ± 6.5	62.0 ± 7.6	61.5 ± 10.3	$P_{C-1} < 0.05$ $P_{C-2} < 0.01$ $P_{1-2} > 0.05$
BMI, kg/m ²	24.0 ± 3.5	24.0 ± 2.6	25.4 ± 4.4	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
HR, beats/min	73.5 ± 7.9	81.8 ± 12.1	87.0 ± 21.8	$P_{C-1} > 0.05$ $P_{C-2} < 0.05$ $P_{1-2} > 0.05$
Systolic BP, mm Hg	121.4 ± 8.4	157.0 ± 23.8	142.1 ± 26.5	$P_{C-1} < 0.01$ $P_{C-2} < 0.05$ $P_{1-2} < 0.05$
Diastolic BP, mm Hg	77.4 ± 6.6	90.4 ± 10.4	85.4 ± 15.3	$P_{C-1} < 0.01$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$

Notes: BP – blood pressure; BMI – body mass index; DM – diabetes mellitus; P_{C-1} – *P*-value when comparing the control group with group 1; P_{C-2} – *P*-value when comparing the control group with group 2; P_{1-2} – *P*-value when comparing group 1 with group 2, using ANOVA test; *chi-square test

The level of visfatin was significantly highest in patients with hypertension, while it was decreased in patients with hypertension and type 2 DM compared to group 1 ($P < 0.05$), which could be due to the effect of drug treatment with insulin and metformin aimed at correcting carbohydrate metabolism (Fig. 1). The existing results are contradictory because according to the researchers, the level of visfatin was increased in individuals with type 2 DM [22]. Taking into account the data of other studies, it is known that antihypertensive, hypolipidemic and hypoglycemic drugs can both decrease and increase the content of the studied protein [8, 23].

The insulin-mimetic effect of visfatin has attracted attention since it became possible to identify an adipokine that allows the lowering of the blood

glucose level; however, numerous studies indicate ambiguous relationships between the level of visfatin and blood glucose [6]. In an in vivo study by Haider and colleagues, it was established that intravenous infusion of glucose increased the level of visfatin in healthy individuals, while infusion of insulin and somatostatin, on the contrary, decreased the level of this enzyme [6]. Inhibition of visfatin synthesis in plasma by oral administration was greater in overweight and female patients, whereas intravenous glucose infusion, induction of osmotic stress (by mannitol administration) and use of sex steroids (estradiol and testosterone) did not promote visfatin synthesis in this group of persons [12].

Intracellular enzymatic effects of visfatin affect the synthesis of NAD⁺, which makes it an important

Table 2. Comparison of the results of general blood test and coagulogram of patients of the examined groups

Parameters	Control group, <i>n</i> = 18	Group 1, patients with hypertension, <i>n</i> = 27	Group 2, patients with hypertension and type 2 DM, <i>n</i> = 24	<i>P</i> -value
Erythrocytes, $\times 10^{12}/l$	4.6 ± 0.4	4.6 ± 0.8	4.3 ± 0.6	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Hemoglobin, g/l	139.6 ± 8.4	134.5 ± 24.7	122.8 ± 20.7	$P_{C-1} > 0.05$ $P_{C-2} < 0.05$ $P_{1-2} > 0.05$
Leukocytes, $\times 10^9/l^*$	8.6 ± 2.4	6.4 (5.2; 8.6)	7.7 ± 2.3	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Platelets, $\times 10^9/l^*$	213.0 (186.0; 302.0)	232.5 (175.5; 282.5)	227.0 (178.0; 307.0)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Prothrombin time, sec	13.8 ± 4.1	12.4 ± 1.3	13.3 ± 3.4	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Prothrombin index, %	96.0 ± 17.2	104.6 ± 19.7	91.9 ± 16.3	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} < 0.05$
Fibrinogen, g/l*	3.7 ± 0.4	3.8 (3.0; 4.2)	5.4 (4.4; 6.2)	$P_{C-1} > 0.05$ $P_{C-2} < 0.01$ $P_{1-2} < 0.01$
INR*	1.1 ± 0.2	1.0 ± 0.1	1.1 (1.0; 1.2)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$

Notes: DM – diabetes mellitus; INR – international normalized ratio; P_{C-1} – *P*-value when comparing the control group with group 1; P_{C-2} – *P*-value when comparing the control group with group 2; P_{1-2} – *P*-value when comparing group 1 with group 2, using ANOVA test; *Mann-Whitney-Wilcoxon test

regulator particularly of sirtuins, poly-ADP-ribose polymerases and proteins [24]. Sirtuins are a class of NAD-dependent proteins that have the properties of histone deacetylases and monoribosyltransferases. Visfatin, in turn, possessing ribosyltransferase activity, catalyzes the formation of NAD⁺ from nicotinamide, i.e., serves as the main enzyme of its reutilization reactions (salvage) [19]. Because the activity of sirtuins depends on the content of NAD⁺, NADH and nicotinamide or a combination of these parameters, it is visfatin that can serve as a decisive factor in their production. Analyzing the results, it can be as-

sumed that the increased level of visfatin in patients with hypertension has both a direct effect on metabolic processes and possibly mediates its metabolic effects through the formation of sirtuins. Visfatin, regulating the level of NAD⁺, also affects the functioning of poly-ADP-ribose polymerases (enzymes that participate in the post-translational modification of proteins using NAD⁺), regulate cell division, DNA repair and RNA transcription [25, 26].

The extracellular effects of visfatin are associated with the modulation of the immune response. Visfatin has been shown to regulate about 50

Table 3. Comparison of the results of general blood test and coagulogram of patients of the examined groups

Parameters	Control group, <i>n</i> = 18	Group 1, Patients with hypertension, <i>n</i> = 27	Group 2, Patients with hypertension and type 2 DM, <i>n</i> = 24	<i>P</i> -value
Glucose, mmol/l	4.9 ± 0.5	4.6 ± 0.8	9.8 ± 2.5	$P_{C-1} > 0.05$ $P_{C-2} < 0.01$ $P_{1-2} < 0.01$
ALT, U/l*	17.6 (14.4; 26.3)	17.6 (13.0; 33.6)	22.7 (14.4; 32.1)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
AST, U/l*	21.5 (16.3; 31.0)	18. (15.2; 33.6)	24.1 (18.7; 35.2)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Creatinine, μmol/l*	96.2 ± 10.1	113.3 (58.8; 11.8)	116.4 ± 23.3	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Urea, mmol/l*	6.1 ± 1.5	7.1 (5.9; 8.5)	7.3 (5.4; 9.2)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
GFR, ml/ min/1.73m ²	83.2 ± 11.1	64.3 ± 17.7	70.4 ± 19.0	$P_{C-1} < 0.01$ $P_{C-2} < 0.05$ $P_{1-2} > 0.05$
Total bilirubin, mmol/l*	13.3 (9.1; 15.4)	10.0 (8.1; 11.8)	10.1 (7.0; 16.6)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
Total protein, g/l	66.9 ± 7.4	66.8 ± 6.9	66.1 ± 8.1	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$

Notes: ALT – alanine aminotransferase; AST – aspartate aminotransferase; DM – diabetes mellitus; GFR – glomerular filtration rate; P_{C-1} – *P*-value when comparing the control group with group 1; P_{C-2} – *P*-value when comparing the control group with group 2; P_{1-2} – *P*-value when comparing group 1 with group 2, using ANOVA test; *Mann-Whitney-Wilcoxon test

different inflammatory genes in peripheral blood mononuclear cells [19]. In addition, it was established that visfatin induces the production of monocyte chemoattractant protein 1 (MCP-1) [27] and the expression of matrix metalloproteinases [28]. Visfatin is associated with the activation of many inflammatory pathways, in particular NF-κB – the activated intracellular pathway [29]. Inflammasome activation is an important factor in the pathogenesis of adipose tissue inflammation, insulin resistance and metabolic diseases associated with obesity and impaired visfatin synthesis [30]. Visfatin has been shown to

induce endothelial dysfunction in the early stages of obesity via the NLRP3 inflammasome [31]. Visfatin-induced vascular dysfunction in mice was also found to involve the NLRP3 inflammasome and IL-1β through a toll-like receptor 4 (TLR4)-dependent NAMPT signaling pathway [14]. However, in our study no correlation was found between the level of visfatin and the concentration of TLR in the blood serum of patients with hypertension and type 2 DM.

A significant increase in the level of TLR in patients of group 2 ($P < 0.05$) can be explained by an increase in the activity of the inflammatory process,

Table 4. Comparison of the results of the morpho-functional characteristics of the myocardium in patients with hypertension and type 2 DM

Parameters	Control group, <i>n</i> = 18	Group 1, Patients with hypertension, <i>n</i> = 27	Group 2, Patients with hypertension and type 2 DM, <i>n</i> = 24	<i>P</i> -value
LA, cm	3.8 ± 0.1	4.2 ± 0.5	4.5 ± 0.4	$P_{C-1} < 0.01$ $P_{C-2} < 0.01$ $P_{1-2} < 0.05$
LV, cm	5.1 ± 0.8	4.9 ± 0.7	5.5 ± 0.6	$P_{C-1} < 0.01$ $P_{C-2} < 0.01$ $P_{1-2} < 0.05$
IVS, cm	1.0 ± 0.1	1.2 ± 0.2	1.2 ± 0.2	$P_{C-1} < 0.01$ $P_{C-2} < 0.01$ $P_{1-2} > 0.05$
PWT, cm	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.2	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
RV, cm	2.4 ± 0.3	2.7 ± 0.3	2.5 ± 0.3	$P_{C-1} < 0.01$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
LVEF, %*	58.3 ± 3.5	56.0 (25.0; 65.0)	55.0 (27.0; 60.0)	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$
LVMM, g	193.3 ± 46.4	225.9 ± 45.9	263.4 ± 65.8	$P_{C-1} > 0.05$ $P_{C-2} < 0.01$ $P_{1-2} < 0.05$
LVMMI	98.3 ± 29.0	117.2 ± 21.8	135.2 ± 32.6	$P_{C-1} > 0.05$ $P_{C-2} < 0.01$ $P_{1-2} > 0.05$
RWT	0.41 ± 0.1	0.44 ± 0.1	0.42 ± 0.1	$P_{C-1} > 0.05$ $P_{C-2} > 0.05$ $P_{1-2} > 0.05$

Notes: DM – diabetes mellitus; IVS – interventricular septum, LA – left atrium; LV – left ventricle; LVEF – left ventricular ejection fraction; LVMM – myocardial mass index of the left ventricle; LVMMI – myocardial mass index of the left ventricle; PWT – posterior wall thickness; RWT – relative wall thickness; P_{C-1} – *P*-value when comparing the control group with group 1; P_{C-2} – *P*-value when comparing the control group with group 2; P_{1-2} – *P*-value when comparing group 1 with group 2, using ANOVA test; *Mann-Whitney-Wilcoxon test

which is confirmed by established positive correlations between the level of TLR and leukocytes in the blood ($r = 0.480$; $P < 0.05$) and BMI ($r = 0.428$; $P < 0.05$) (Fig. 2).

An increase in the level of TLR was also associated with an increase in the size of the LA ($r = 0.795$; $P < 0.01$). It is known that TLR activation

is enhanced under conditions of hyperglycemia, and can be a trigger for the release of pro-inflammatory cytokines [32].

There is some data about the relation between the increasing level of visfatin and obesity, low-grade inflammation and insulin resistance [33]. However, it is known that insulin can affect the level

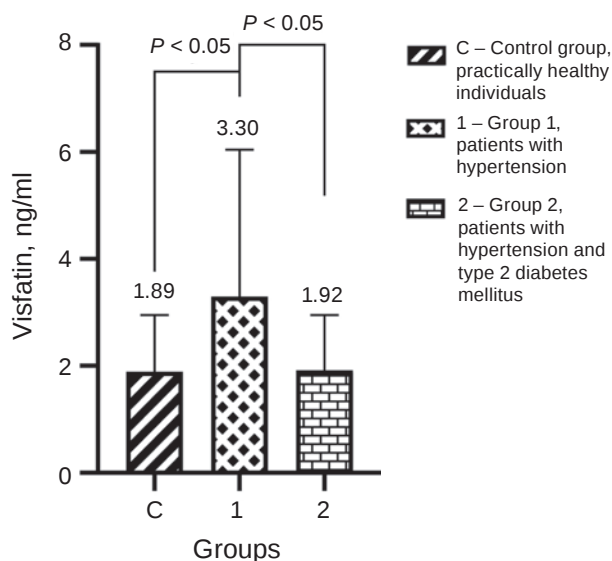


Fig. 1. Comparison of visfatin levels in patients of the examined groups (Mann-Whitney-Wilcoxon test)

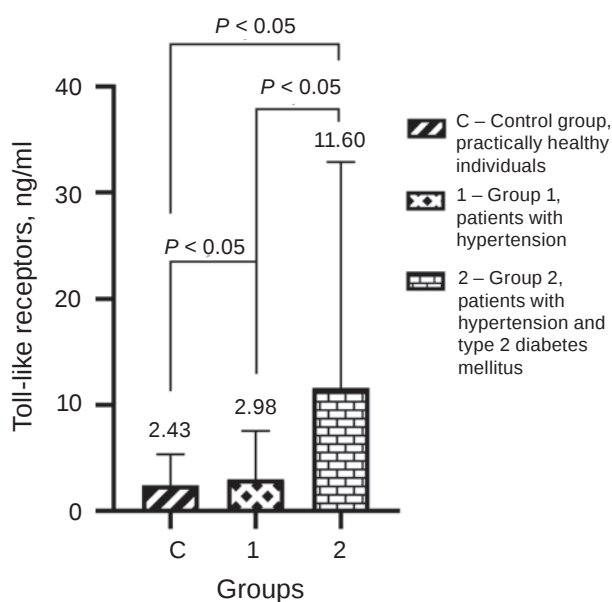


Fig. 2. Comparison of the levels of toll-like receptors in patients of the examined groups (Mann-Whitney-Wilcoxon test)

of visfatin causing its decrease. The patients received therapy with insulin to lower their blood glucose levels. Insulin may promote the anti-inflammatory effect and suppress the generation of O_2 radicals and oxidative stress [33]. Nevertheless, no difference was found in visfatin concentration in patients with type 2 DM and healthy individuals [19]. At the same time, one more study shows the association between the GFR and level of visfatin. It was shown that

in patients with GFR more than 75 ml/min/1.73m² the level of visfatin was lower, while in individuals with decreased GFR visfatin concentration tended to increase. In our study, the group of patients with hypertension showed a significantly lower level of GFR and a higher level of visfatin [34]. However, the level of TLR was increased and its concentration was not affected despite the treatment. All blood samples were taken 3–5 days after hospitalization and receiving therapy. We consider that visfatin is a more sensitive marker that immediately tends to decrease after using insulin for diabetes treatment compared to TLR concentration that remained increased. Further research is needed to establish more precise mechanisms.

To summarize, hypertension and type 2 DM affect the concentration of visfatin and TLR. The highest level of visfatin in blood serum was found in patients with hypertension ($P < 0.05$), while a lower level of this marker was observed in people with a comorbid course of hypertension and type 2 DM, which is probably related to the peculiarities of drug treatment of the main pathologies using metformin and insulin. The TLR level is significantly higher in patients with a combined course of hypertension and type 2 DM ($P < 0.05$) as well as established correlations with the level of blood leukocytes ($r = 0.480$; $P < 0.05$) and BMI ($r = 0.428$; $P < 0.05$) due to possible consequence of the synthesis of pro-inflammatory cytokines and activation of the inflammatory process in conditions of hyperglycemia.

The long-term course of hypertension in patients of two groups led to the occurrence of morpho-functional changes in the myocardium, namely, hypertrophy of the walls of the LV myocardium and an increase in the size of the LV. Under conditions of chronic LV pressure overload, concentric hypertrophy was the most frequently determined type of LV geometry. It was observed in 41.2% of all patients, due to the anamnesis of hypertension.

Conclusions. The elevated level of TLR in the serum of patients with hypertension can be considered a factor of low-grade inflammation, especially in combination with type 2 DM. The increase of visfatin concentration in hypertension serves as a more sensitive marker compared to TLR regarding the risk of developing comorbid cardiovascular pathology. The therapeutic approaches for treating patients with type 2 DM cause the reduction of visfatin concentration induced by hypertension.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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РІВНІ ВІСФАТИНУ ТА TOLL-ПОДІБНИХ РЕЦЕПТОРІВ ПРИ АРТЕРІАЛЬНІЙ ГІПЕРТЕНЗІЇ ТА ЦУКРОВИМУ ДІАБЕТІ 2 ТИПУ

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Актуальність. Гіпертензія та цукровий діабет (ЦД) 2 типу залишаються широко розповсюдженими захворюваннями, кількість яких прогресивно зростає. Особливу увагу виділяють вісфатину та Toll-подібним рецепторам (TLR), роль яких у патогенезі гіпертензії та ЦД 2 типу залишається не до кінця з'ясованою та потребує подальших досліджень. Мета роботи. Вивчити зміни рівнів вісфатину і TLR у пацієнтів із гіпертензією та ЦД 2 типу. Методи. Обстежено 51 пацієнта, яких було розділено на дві групи: 1 група – 27 пацієнтів із гіпертензією та 2 група – 24 особи з гіпертензією та ЦД 2 типу. До контрольної

групи ввійшло 18 практично здорових осіб. Усім особам проводили загальний аналіз крові, коагулограму, біохімічний аналіз крові, а також імуноензимний аналіз для визначення рівня вісфатину і Toll-подібних рецепторів у сироватці крові, ЕХоКГ. Результати. У пацієнтів двох груп спостерігали гіпертрофію стінок лівого шлуночка (ЛШ). Найбільш поширеним типом геометрії ЛШ була концентрична гіпертрофія (41,2%). Рівень вісфатину був достовірно найвищим у пацієнтів із гіпертензією, тоді як у пацієнтів із гіпертензією та ЦД 2 типу був зниженим ($P < 0,05$), а рівень TLR навпаки підвищеним ($P < 0,05$). Висновки. Підвищений рівень TLR у сироватці крові пацієнтів із гіпертензією можна розглядати як чинник запалення низької інтенсивності, особливо в поєднанні з ЦД 2 типу. Збільшення концентрації вісфатину при гіпертензії є більш чутливим маркером порівняно з TLR щодо ризику розвитку коморбідної серцево-судинної патології. Проте, особливості терапевтичних підходів у лікуванні пацієнтів із ЦД 2 типу спричиняють зниження концентрації вісфатину, зумовленого гіпертензією.

Ключові слова: гіпертензія, цукровий діабет 2 типу, вісфатин, toll-подібні рецептори.

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