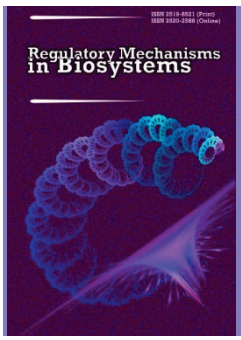

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Adipokines in patients with hypertensive disease with obesity in the dynamics of combined antihypertensive therapy

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Hypertensive disease today is one of the most common cardiovascular diseases, as well as the most common disease associated with obesity. Evaluation of the level of adipokines, namely adiponutrin and galanin, depending on the degree and duration of hypertension, the degree of obesity and their correction against the background of combined antihypertensive therapy is relevant for further understanding of this comorbidity and improvement of the early diagnostics. 127 people were examined, including 107 patients with hypertension of degree 1–3 and 20 healthy persons. Of the patients included in the study, the adiponutrin and the galanin levels were determined in 58 patients, out of which 22 were prescribed different regimens of combined antihypertensive therapy. To determine the level of adiponutrin and galanin, an enzyme-linked immunosorbent assay was used. A significant increase was found in the blood serum of the examined adipokines in comparison with the control group: the galanin level was 4.8 times higher than in the control group, the adiponutrin level in patients with this comorbid pathology was 3.3 times higher than that in the control group. The galanin level is most pronounced in patients with hypertension of degree 3 and obesity of degree 3, which is confirmed by the presence of a direct correlation with systolic, diastolic and pulse blood pressure, very low density lipoprotein cholesterol. The adiponutrin level in the blood serum increased correspondingly to the increase in body mass index: in patients with obesity of degree 3 it was 15.8 times higher than this indicator in patients with normal body weight, 8.8 times higher than in patients with overweight, 6.1 times higher than in patients with obesity of degree 1 and 2.5 times higher than in patients with obesity of degree 2. The levels of the studied adipokines in patients differed also relative to the duration of hypertension. There was a 1.8-, 5.1-, 5.2-fold increase (respectively, ≤5, 6–10, >10 years) of the galanin content in the blood serum compared to the control group. Also an increase of the serum adiponutrin level was noted in comparison with the control group. Against the background of combined antihypertensive therapy, we observed favourable dynamics of galanin and adiponutrin. It is important to conduct further studies to assess the activity of galanin and adiponutrin with a longer follow-up period in wider populations.

Keywords: adiponutrin; galanin; blood pressure; body mass index; enalapril; valsartan.

Introduction

Today, human pathology can be characterized by such features as the prevalence of chronic diseases, the genesis of which is predominantly of multifactorial nature, the prevalence of diseases characterized by systemic damage, as well as the progressive growth of comorbid conditions, which are among the main problems of modern medicine.

The term comorbidity, introduced by A. Feinstein in 1970 (Nobili et al., 2011) implies individual diseases that exist or develop against the background of the underlying disease and are of a secondary, "subordinate" nature, while their influence on the course and treatment of the underlying pathology is not excluded. At the same time, it is proposed to evaluate clinical symptoms as a holistic, overall result of combined pathology (Valderas et al., 2011).

A clear example of the relevance and importance of the problem of comorbid conditions is hypertension (HD), which today is one of the most common cardiovascular diseases (CVD). Moreover, high blood pressure (BP) becomes the main factor in the development of cardiovascular complications and premature death (Williams & Mancia, 2018). Thus, based on office BP values, it was found that the number of patients in the world with hypertension in 2015 was 1.13 billion people. Moreover it caused about 10 million deaths and more than 200 million cases of disability (Forouzanfar et al., 2017). According to official statistics, over 12 million patients with hypertension have been registered in Ukraine, which is about 31.5% of the adult population (Kovalenko & Kornac'kyj, 2017). HD is also the most common disease associated with obesity, which acts both as a risk factor for its development, and as a factor, determining the global cardiovascular risk in patients with HD (Williams & Mancia, 2018). And the further prevalence of HD is only increasing – it is predicted that by 2030, 1/2 (57.8%) of the total adult population of the world will have a body mass index (BMI) of 25 kg/m^2 or higher (Ogden et al., 2016).

The world leaders in the prevalence of obesity are traditionally considered the countries of Western Europe and the United States, while its increase is also observed in developing countries. Every year the number of obese people in the population increases by at least 1%. The most alarming indicator in the epidemiology of obesity is the percentage of children and adolescents with increased body weight: in developed countries in 2013 it was 23.8% among boys and 22.6% among girls. The study by Ogden et al. (2016) which analyzed the data of 40,780 American children and adolescents aged 2 to 19 years old showed that the prevalence of obesity was 17%, and children with severe obesity – 5.8%. The prevalence of obesity is growing steadily in Ukraine too. According to the results of the first nationwide study on the prevalence of the main risk factors for non-communicable diseases in Ukraine, which corresponds to the WHO-approved Staged Approach to Epidemiologic Surveillance (STEPS), only 2/5 (39.6%) of Ukrainians were of normal weight in 2019, while almost 3/5 (59.1%) of the population were overweight, among them a quarter of the population (24.8%) – were obese (World Health Organization, 2020). In most countries of the world, obesity is now becoming one of the main risk factors for the development and progression of chro-

nic non-communicable diseases (Lim et al., 2012), which is largely due to the constantly growing rates of its prevalence. At the same time, in the structure of nosologic units associated with overweight and obesity, cardiovascular pathology is in the lead: of the annual four million deaths in the world associated with high BMI, more than two thirds are cases of cardiovascular death (The GBD 2015 Obesity Collaborators, 2017).

Numerous studies in various populations have shown an almost linear relationship between BMI and levels of systolic and diastolic blood pressure (Hall et al., 2015), and the prevalence of HD among obese patients exceeds 60% (DeMarco et al., 2014). At the same time, the association of obesity and HD is characterized by two main consequences: higher morbidity and mortality from CVD, as well as an increase in the number of cases of treatment-resistant HD (Reisin et al., 2014).

There are a large number of hypothetical pathogenetic mechanisms through which obesity can lead to HD (Landsberg et al., 2012). They include the activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, metabolic disorders (including hyperinsulinemia, adipokine imbalance and an increase in the number of cytokines). The influence of adipokines in conditions of overweight and obesity, perhaps, is one of the key processes in the development of hypertension. When analyzing numerous studies, it was concluded that the nature of the distribution of adipose tissue, consisting in the predominance of abdominal visceral adipose tissue, is the most important factor in increasing blood pressure in overweight and obese individuals (Chandra et al., 2014; Sullivan et al., 2015; Bhaskar et al., 2017).

The cellular composition of white adipose tissue, which consists of both subcutaneous adipose tissue and visceral adipose tissue, includes preadipocytes, adipocytes and the stromal vascular complex, represented by fibroblasts, endothelial and smooth muscle cells, as well as immune cells – resident macrophages. The extracellular matrix of white adipose tissue consists of structural proteins, mainly collagen and fibronectin, which provide its normal architectonics (Sun et al., 2011). Currently, the perception of adipose tissue as a store of fatty acids and an energy accumulator has been replaced by the concept of adipose tissue as an active endocrine organ that produces hormones – adipokines (originally called "adipocytokines"), biologically active low molecular weight proteins. It is visceral fat that has the highest metabolic activity, and according to a recent study, it is the only significant predictor of the development of insulin resistance (Hsieh et al., 2014). Adipokines are one of the regulators of insulin sensitivity (Saleem et al., 2009), oxidative stress (Tsimikas et al., 2008), energy metabolism, blood clotting, inflammatory reactions (Jacobs et al., 2009), and are involved in thrombus formation and atherogenesis, regulation of blood pressure and the function of various organs and tissues (Nakamura et al., 2014). In overweight and obese patients the production and regulation of adipokine secretion is disrupted: the secretion of certain adipokines decreases, while that of the others increases. With an increase in the mass of visceral fat and hypertrophy of adipocytes, the processes of blood supply to fat cells are disrupted, which causes their hypoxia (Cinti et al., 2005). In response to ischemia, foci of necrosis and infiltration of adipose tissue by macrophages appear, which leads to excessive formation of proinflammatory cytokines and adipokines, free fatty acids, tumour necrosis factor alpha, interleukin-6, plasminogen activator inhibitor-1, C-reactive protein (Lau et al., 2005). As a result, local foci of chronic inflammation in adipose tissue are formed and maintained, which leads to systemic inflammation and the occurrence of diseases associated with obesity. Persons with visceral obesity are constantly in a state of systemic inflammation (Hsieh et al., 2014). Endothelial dysfunction arises and is maintained, and atherosclerosis develops (Trayhurn et al., 2004).

The discovery of new adipokines could define new tools for diagnosing cardiovascular diseases and contribute to the development of new strategies for their treatment. Among adipokines, galanin (GAL) and adiponutrin (ADPN) are noteworthy. Galanin is a 29 amino acid peptide (30 in humans) that was discovered in 1983 in the intestines of pigs as an orexigenic neuropeptide that increases food intake. It is mainly synthesized in the nervous system, both in the central and peripheral and gastrointestinal tract, as well as in adipose tissue, endocrine organs, skeletal system, and also in immune and hematopoietic cells (Fang et al., 2012; Fang et al., 2015). Adiponutrin is a protein encoded by the gene PNPLA3 (patatin-like domain containing 3 phospholipase), it consists of 481 amino acids responsible for endoplasmic reticulum function, structure and function of mitochondrial membranes and lipid inclusions in hepatocytes and adipocyte membranes (Huang et al., 2010). Despite numerous clinical and experimental studies of involvement of the above mentioned adipokines in energy metabolism and other metabolic processes, the evidence of the role of GAL and ADPN in the association of hypertension and visceral obesity, as well as the mechanisms of the formation of the pathophysiological consequences of this comorbidity remain insufficiently defined, which in turn make makes this issue relevant.

The objective of the study is to assess the level of adipokines, namely ADPN and GAL, in relation to the indices of carbohydrate and lipid metabolism in the blood serum of patients with this comorbid pathology, to assess the ADPN and GAL level depending on the degree and duration of hypertension, the degree of obesity and their correction against the background of combined antihypertensive therapy.

Materials and methods

The study was conducted in accordance with current ethical requirements. The research protocol was approved at the meeting of the Bioethics Committee of the Kharkiv National Medical University, the Department of Internal Medicine Propedeutics No. 2 and Nursing (Protocol No. 7 of September 11, 2018). All patients participating in the study signed a voluntary informed consent to participate. In the conditions of the hospital, 127 people were examined, including 107 patients with hypertension of degree 1–3 and 20 healthy persons. The age of patients in the surveyed sample ranged from 32 to 79 years old (mean age 58.6 ± 9.88 years old) and did not differ significantly from that in the control group 45.6 ± 13.2 years old. Among the patients there were 51 men and 56 women who had not previously received regular antihypertensive therapy. The patients underwent in patient treatment in the cardiology department of the PUC "Kharkiv City Clinical Hospital No. 27" Kharkiv City Council.

Of the patients included in the study, 22 were diagnosed with hypertension of degree 1, 26 – of degree 2 and 59 – of degree 3. The ADPN and GAL levels were determined in 58 patients with hypertension of degree 1–3, aged from 32 to 79 years old (mean age 57.5 ± 10.1 years old), of whom 32 were women and 26 were men. At the same time, HD of degree 1 was diagnosed in 12 patients, HD of degree 2 – in 16, and HD of degree 3 – in 30 examined patients. Anamnesis of an increase in blood pressure up to 5 years was observed in 27% of patients, from 6 to 10 years – in 33%, more than 10 years – in 40%. A survey of the examined patients revealed the presence of astheno-neurotic complaints in 98.3%, cerebral complaints were detected in 84.5%, cardiac complaints – in 84.5%. It should be noted that in patients with hypertension associated with overweight and obesity, the symptoms were more pronounced.

The diagnosis was verified on the basis of clinical, laboratory and instrumental research methods. The exclusion criteria from this study, in addition to patients with symptomatic hypertension, were patients with cancer, acute and chronic inflammatory processes, concomitant thyroid diseases and diabetes mellitus. Blood pressure was measured in all patients in a sitting position after a 5-minute rest according to the method of N. S. Korotkov. Verification of the diagnosis and assessment of the degree of hypertension were carried out in accordance with the clinical guidelines of the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) (2018) (Williams & Mancia, 2018), criteria of the Ukrainian Association of Cardiology. The diagnosis of obesity was established in accordance with the classification based on the definition of BMI. This classification was developed by the National Health Institute of the United States of America and endorsed by the World Health Organization. Anthropometric measurements included height (cm), weight (kg), waist circumference (WC, cm) and hip circumference (HC, cm), as well as calculation of WC/HC ratio. Then BMI (kg/m^2) was calculated using the formula BMI = body weight (kg)/square of height (m^2). WC/HC value > 0.90 for men and > 0.85 for women indicates the presence of an abdominal (visceral) type of adipose tissue distribution. Blood for biochemical study was taken in the morning the next day after the patient was admitted to the hospital after 12–18 hours of fasting. Blood sampling was performed fasting from the cubital vein in the morning, the day after the patient was admitted to the hospital, 12–18 hours after a meal, and at the

end of the course of in patient treatment (n = 22) against the background of combined antihypertensive therapy. Treatment of patients with hypertension was carried out individually in accordance with the protocols for the provision of medical care of the Ministry of Health of Ukraine (order of the Ministry of Health of Ukraine No. 384 of 24.05.2012, "Unified clinical protocol for primary, emergency and secondary (specialized) medical care. Arterial hypertension"), as well as based on the evidence that the combination of the two drugs as initial therapy is safe and well tolerated with little or no episodes of hypotension, even when administered to patients with hypertension of degree 1. Moreover, all patients were in conditions of the same physical activity.

To determine the level of adiponutrin (pkg/mL) and galanin (pkg/mL), an enzyme-linked immunosorbent assay was used using the TheRayBio® Adiponutrin Enzyme Immunoassay (EIA) Kit, (USA) and Elabscience® Human GAL (Galanin) ELISA Kit reagents (USA), respectively.

In order to control carbohydrate metabolism, the level of fasting glucose was determined by the glucose oxidase method, the determination of the content of glycosylated hemoglobin (Hba1c) in the blood serum was carried out by the photometric method by reaction with thiobarbituric acid using a commercial test system from Reagent (Ukraine) in accordance with the attached instructions. The level of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) was determined by the enzymatic method according to the standard biochemical method. The level of very low density lipoprotein cholesterol (VLDL cholesterol) was calculated by the formula: VLDL cholesterol = TG/2.2. Low density lipoprotein cholesterol (LDL cholesterol) was determined by the Friedewald formula LDL cholesterol = cholesterol – (HDL cholesterol + TG/2.2). The atherogenic coefficient (CA) was calculated using the Klimov formula: CA = (CS – HDL cholesterol) / HDL cholesterol.

Mathematical processing of the results was carried out using the software package Statistica 10 (StatSoft Inc., USA). The mean value (Mean) and standard deviation (SD) were determined. The bulk of the obtained data had a distribution that was different from the normal (Shapiro – Wilk test); therefore, the data were analyzed by methods of nonparametric statistics. Quantitative data are presented as Me (LQ – UQ), where Me is the median of traits, LQ is the lower quartile, UQ is the upper quartile. To compare the results between groups, Kruskal – Wallis H test (Kruskal – Wallis ANOVA test & Median test) and Mann – Whitney U-test were used. Spearman's rank correlation coefficient (r_s) was used to assess the degree of correlation between the samples. A qualitative assessment of the connection tightness was made using the Chaddock scale (Junkerov & Grigor'ev, 2002). To compare the indicators against the background of combined antihypertensive therapy, the Wilcoxon test was used. The null hypothesis was rejected at the confidence level ($P < 0.05$).

Results

When comparing the parameters of the lipid and carbohydrate spectrum, anthropometric and hemodynamic data, both in the control group (group I) and in patients with hypertension and overweight and obesity (group II), statistically significant differences were found, with the exception of blood glucose (Table 1).

The analysis of adipokine level, namely GAL and ADPN, showed a significant increase in the level of the latter in the blood serum of the examined patients in comparison with the control group. In patients with hypertension and overweight and obesity, the GAL level was 4.8 times higher than in the control group: 146.49 (53.86–164.72) versus 30.58 (28.07–31.90) pkg/mL ($P < 0.001$). As we noted before the ADPN level in patients with this comorbid pathology was 3.3 times higher than that in the control group: 5.16 (2.78–11.33) versus 1.55 (1.37–1.68) pkg/mL ($P < 0.001$). In order to elucidate not only the effect of the presence of HD, but also the effect of degree of blood pressure increase on the level of GAL and ADPN, the patients were divided into three groups depending on the severity of HD. To identify differences when comparing these groups for each indicator statistically significant differences were revealed by using the Kruskal – Wallis H test (for GAL $H = 68.43$; $P < 0.001$, for ADPN $H = 36.58$; $P < 0.001$). For a more accurate description of the differences in the groups, they were compared in pairs, taking into account the median.

Table 1
Comparative characteristics of the control and main patient groups (Me (LQ – UQ)

Parameters	I group, n = 20		II group, n = 107		P
	Me	LQ – UQ	Me	LQ – UQ	
Triglycerides, mmol/L	0.73	0.61–1.25	1.35	1.03–2.01	1.5×10^{-5}
Glucose, mmol/L	4.60	4.15–5.30	5.00	4.30–5.80	0.120
Glycosylated hemoglobin, %	4.13	3.94–4.52	5.09	4.08–6.19	2.2×10^{-6}
Total cholesterol, mmol/L	4.10	3.90–4.20	5.35	4.49–6.23	7.0×10^{-6}
High-density lipoprotein cholesterol, mmol/L	1.350	1.225–1.450	1.250	1.160–1.360	0.011
Low density lipoprotein cholesterol, mmol/L	2.32	2.20–2.45	3.40	2.40–4.10	5.2×10^{-5}
Very low density lipoprotein cholesterol, mmol/L	0.325	0.275–0.565	0.581	0.463–0.901	3.7×10^{-5}
Atherogenic coefficient	2.04	1.89–2.19	3.30	2.50–3.80	1.0×10^{-7}
Body mass index	22.0	20.2–24.0	31.1	26.5–35.6	1.0×10^{-7}
Waist circumference, cm	76.0	72.0–82.5	103.0	85.0–116.0	1.0×10^{-6}
Hip circumference, cm	100.0	92.5–109.0	105.0	99.0–114.0	0.024
Waist circumference / Hip circumference	0.775	0.722–0.801	0.901	0.832–0.991	4.0×10^{-6}
Systolic blood pressure, mmHg	125	120–130	170	150–180	1.0×10^{-7}
Diastolic blood pressure, mmHg	70	67–75	100	90–100	1.0×10^{-7}
Heart rate, beats per minute	68	62–72	72	64–82	0.033
Pulse, beats per minute	68	62–72	72	64–82	0.044
Pulse arterial pressure, mmHg	53	50–58	70	60–80	1.0×10^{-6}

Table 2
Galanin and adiponutrin levels depending on the degree of hypertensive disease (Me (LQ; UQ)

Parameter	Control group, n = 20		Patients with hypertensive disease, n= 58					
			degree 1, n = 12		degree 2, n = 16		degree 3, n = 30	
	Me	LQ – UQ	Me	LQ – UQ	Me	LQ – UQ	Me	LQ – UQ
Galanin, pkg/mL	30.58	28.07–31.90	50.22***	40.19–53.55	61.83***$^{\bullet}$	52.12–66.45	164.47***$^{\bullet\bullet\bullet}$	156.82–170.72
Adiponutrin, pkg/mL	1.55	1.37–1.68	8.64***	2.94–10.60	3.81***	1.72–7.85	8.14***	3.12–12.0

Note: * – $P < 0.05$, ** – $P < 0.01$, *** – $P < 0.001$ in comparison with the control group; $^{\bullet}$ – $P < 0.05$, $^{\bullet\bullet}$ – $P < 0.01$, $^{\bullet\bullet\bullet}$ – $P < 0.001$ in comparison with the group of patients with hypertensive disease of degree 1; $^{\bullet}$ – $P < 0.05$, $^{\bullet\bullet}$ – $P < 0.01$, $^{\bullet\bullet\bullet}$ – $P < 0.001$ in comparison with the group of patients with hypertensive disease of degree 2.

As can be seen from Table 2, when comparing the GAL levels in patients with hypertension, a 1.6-, 2.0-, and 5.4-fold increase (1, 2 and 3 degrees, respectively) of the GAL content in the blood serum was observed depending on the blood pressure level compared to the control group. Concentration of GAL in the blood serum increased as the BP numbers increased: in patients with HD of degree 3, it exceeded this indi-

cator by 3.3 times compared to patients with degree 1, and 2.7 times compared to patients with degree 2. With regard to the level of ADPN, in comparison with GAL, there was no dependence of ADPN on the HD degree. There was a 5.6-fold, 2.5-fold, 5.4-fold increase (1, 2 and 3 degrees, respectively) in the content of ADPN in the blood serum compared to the control group.

The levels of the studied parameters, namely GAL and ADPN, in the examined patients differed depending not only on the degree, but also on the duration of hypertension. During the analysis, statistically significant differences were revealed, while the Kruskal – Wallis H test was: for GAL – H = 50.53; P < 0.001, for ADPN – H = 39.86; P < 0.001; with the subsequent comparison of the groups of pairs, taking into account the median for a more accurate description of the differences in these groups (Table 3). As can be seen from Table 3, in patients with hypertension, there was a 1.8-, 5.1-, 5.2-fold increase (respectively, <5, 6–10, >10 years) of the GAL content in the blood serum compared to the control group. Also, patients with this comorbid pathology were characterized by an increase of the serum ADPN level in comparison with the control group: 1.9-, 5.8-, 5.6-fold (respectively, <5, 6–10, >10 years).

With regard to the serum level of the studied parameters depending on BMI, there were identified groups of hypertensive patients without obesity (group I, n = 19) and with obesity (group II, n = 39). When comparing the above groups and the control group using the Kruskal – Wallis H test, statistically significant differences were revealed (for GAL H = 44.20; P < 0.001, for ADPN H = 56.29; P < 0.001). At the same time, in patients of the second group, the serum GAL level was characterized by a significant 4.8-fold increase in comparison with the indicator in the control group: 146.75 (54.55–166.48) versus 30.58 (07.28–31.90) pkg/mL (P < 0.001), and also a significant 4.4-fold increase in the GAL level was observed in patients of the first group in comparison with the control group: 134.25 (52.64–164.72) versus 30.58 (28.07–31.90) pkg/mL (P < 0.001). With regard to the ADPN level, a significant 6.7-fold increase in the latter was observed in patients of the second group compared to the control group: 10.45 (5.08–20.08) versus a 1.55 (1.37–1.68) pkg/mL (P < 0.001) and 1.3-fold increase in patients of the first group in comparison with the control group: 2.03 (1.68–3.09) versus 1.55 (1.37–1.68) pkg/mL (P < 0.001), while the ADPN level of patients in the second group was 5.1 times higher than in patients in the first group (P < 0.001).

For a more detailed analysis of the relationship between the degree of obesity and the serum content of the studied adipokines, subgroups were identified depending on BMI (Table 4). The analysis revealed statistically significant differences, while the Kruskal – Wallis H test was: for GAL – H = 47.93; P < 0.001, for ADPN – H = 68.27; P < 0.001; it was found that the GAL level in all subgroups of patients with different BMIs was significantly increased compared to the control group (P < 0.001), and the maximum GAL level was observed in the group of patients with hypertension and obesity of degree 3 (Me = 166.5 pkg/mL). Our attention is drawn to the GAL level in patients with hypertension with overweight, which was higher than the GAL level in patients with obesity of degrees 1 and 2. It should be noted that the ADPN level in the blood serum increased correspondingly to the increase in BMI: in patients with obesity of degree 3 it was 15.8 times higher than this indicator in patients with normal body weight, 8.8 times higher than in patients with overweight, 6.1 times higher than in patients with obesity of degree 1 and 2.5 times higher than in patients with obesity of degree 2. In the case of GAL, an increase in its level was observed in all groups in comparison with the control group, while the maximum level was observed in the group of patients with hypertension and obesity of degree 3.

Table 3

Galanin and adiponutrin levels depending on the duration of hypertensive disease (Me (LQ; UQ)

Parameter	Control group, n = 20		Patients with duration of hypertension disease (yrs), n = 58					
			≤ 5, n = 16		6–10, n = 19		>10, n = 23	
	Me	LQ – UQ	Me	LQ – UQ	Me	LQ – UQ	Me	LQ – UQ
Galanin, pkg/mL	30.58	28.07–31.90	56.19***	48.31–66.45	155.61***♦♦	70.64–164.22	159.88***♦♦	53.11–170.58
Adiponutrin, pkg/mL	1.55	1.37–1.68	2.96***	1.71–5.16	9.03***♦	3.09–11.72	8.63***♦♦	3.12–21.58

Note: * – P < 0.05, ** – P < 0.01,*** – P < 0.001 in comparison with the control group; ♦ – P < 0.05, ♦♦ – P < 0.01, ♦♦♦ – P < 0.001 in comparison with the group of patients with duration of hypertensive disease < 5 years; • – P < 0.05, •• – P < 0.01, ••• – P < 0.001 in comparison with the group of patients with duration of hypertensive disease 6–10 years.

Table 4

Galanin and adiponutrin levels in patients depending on the presence of obesity and its degree (Me (LQ; UQ)

Examined groups	Galanin, pkg/mL		Adiponutrin, pkg/mL	
	Me	LQ–UQ	Me	LQ–UQ
Control group, n = 20	30.6	28.1–31.9	1.55	1.37–1.68
I group, normal body weight, n = 10	62.3***	46.4–151.3	1.71	1.42–1.94
I group, overweight, n = 9	159.9***	61.6–170.6	3.09***♦♦♦	2.78–3.22
II group, obesity of degree 1, n = 17	65.8***	54.6–159.8	4.42***♦♦♦♦•	3.85–8.63
II group, obesity of degree 2, n = 13	148.9***	67.1–170.1	10.9***♦♦♦♦♦•••###	10.5–11.7
II group, obesity of degree 3, n = 9	166.5***♦	63.5–178.8	27.1***♦♦♦♦♦•••###§§§	24.7–29.1

Note: * – P < 0.05, ** – P < 0.01, *** – P < 0.001 in comparison with the control group; ♦ – P < 0.05, ♦♦ – P < 0.01, ♦♦♦ – P < 0.001 in comparison with the group of patients with normal body weight; • – P < 0.05, •• – P < 0.01, ••• – P < 0.001 in comparison with the group of patients with overweight; # – P < 0.05, ## – P < 0.01, ### – P < 0.001 in comparison with the group of patients with obesity of degree 1; § – P < 0.05, §§ – P < 0.01, §§§ – P < 0.001 in comparison with the group of patients with obesity of degree 2.

Conducting a correlation analysis between adipokines and indicators of lipid, carbohydrate metabolism and anthropometric and hemodynamic indicators made it possible to establish significant direct linear connections. As it can be seen from Table 5, both GAL and ADPN had a statistically significant connection with VLDL cholesterol, at the same time the strength of the connection was moderate. From the indicators of the lipid spectrum, in addition to VLDL cholesterol, moderate connection strength was established between ADPN and TG. ADPN correlated with anthropometric indicators: very high connection strength was observed with BMI, with WC the connection strength was high, as well as noticeable connection strength was with HC and WC/HC. With regard to hemodynamic parameters, statistically significant direct linear connections were found between GAL and diastolic blood pressure (DBP), and of a moderate nature and a noticeable nature – with systolic blood pressure (SBP), pulse arterial pressure (PAP). After the initial examination, all patients received combination antihypertensive therapy. Initial combination therapy is always more effective than monotherapy, even low-dose combinations are better at lowering blood pressure than a single drug at the maximum dose. In addition, the combination of drugs affects various mechanisms, in particular, blocks the RAS and stimulates vasodilation or diuresis, which reduces the heterogeneity of the blood pressure response to treatment and promotes a more pronounced response than in cases of gradual increase in doses of monotherapy. In our study, all patients were prescribed different regimens of combined antihypertensive therapy, depending on which patients were divided into two clinical groups: I clinical group (n = 10; 45.5%) – patients who received angiotensinogen II receptor antagonists (ARA II): valsartan 80 mg/day, in combination with hydrochlorothiazide 12.5 mg/day, II clinical group (n = 12; 54.5%) – patients who received angiotensin-converting enzyme (ACE) inhibitors: enalapril 10 mg/day, in combination with hydrochlorothiazide 12.5 mg/day. If it was impossible to achieve target blood pressure levels in therapy, a beta-blocker (BAB) – bisoprolol 2.5–5.0 mg/day was added to the above fixed

combinations of treatment. The daily dose of bisoprolol was selected by slow continuous titration, starting from low doses – 2.5 mg/day. The dose was gradually increased to achieve a hypotensive effect. In the first group, bisoprolol was added to seven patients, in the second group – to eight patients. Patients had the opportunity to receive drugs: enalapril, hydrochlorothiazide and bisoprolol from the register of the government program "Affordable Drugs", which was important when choosing these drugs. The effectiveness and tolerability of the treatment were assessed on the basis of the subjective symptoms reported by the patients, as well as taking into account the objective observation data and the dynamics of changes in laboratory parameters during the course of treatment in the hospital. Changes in both GAL and ADPN levels were observed (Table 6). Thus, the GAL level during the period of in patient treatment significantly decreased by 30.2% in the first group and by 15.9% – in the second group, the ADPN level – by 25.5% in the first group and by 15.5% – in the second group.

Table 5

Correlation of the main indicators with galanin and adiponutrin
in individuals with hypertensive disease and overweight and obesity (according to Spearman), n = 58

Parameter	Correlation with galanin		Correlation with adiponutrin	
	r_s	P	r_s	P
Triglycerides, mmol/L	0.252	0.057	0.35	0.007
Glucose, mmol/L	0.111	0.412	0.162	0.224
Glycosylated hemoglobin, %	0.054	0.686	0.174	0.193
Total cholesterol, mmol/L	-0.075	0.578	-0.066	0.622
High-density lipoprotein cholesterol, mmol/L	0.163	0.220	-0.029	0.830
Low density lipoprotein cholesterol, mmol/L	-0.177	0.183	-0.09	0.499
Very low density lipoprotein cholesterol, mmol/L	0.30	0.023	0.340	0.009
Atherogenic coefficient	-0.164	0.219	-0.113	0.397
Body mass index	0.227	0.087	0.90	1×10^{-7}
Waist circumference, cm	0.174	0.191	0.790	1×10^{-7}
Hip circumference, cm	0.155	0.245	0.550	8×10^{-6}
Waist circumference / Hip circumference	0.053	0.695	0.650	1×10^{-7}
Systolic blood pressure, mmHg	0.60	1×10^{-6}	0.196	0.140
Diastolic blood pressure, mmHg	0.332	0.011	0.147	0.272
Pulse arterial pressure, mmHg	0.530	18×10^{-6}	0.140	0.286
Heart rate, beats per minute	0.075	0.576	0.094	0.483
Pulse, beats per minute	0.080	0.554	0.073	0.583
Adiponutrin, pkg/mL	0.240	0.066	–	–

Note: r_s – Spearman's correlation coefficient, P < 0.05, P < 0.01, P < 0.001 – the statistical significance of the correlation.

Table 6

Galanin and adiponutrin levels against the background of combination antihypertensive therapy (Me (LQ; UQ), n = 22

Parameter	I group (n = 10)				II group (n = 12)			
	Before treatment		After treatment		Before treatment		After treatment	
	Me	LQ – UQ	Me	LQ – UQ	Me	LQ – UQ	Me	LQ – UQ
Galanin, pkg/mL	153.35	52.64–180.14	107.08**	47.62–159.28	137.55	58.00–170.02	115.70**	55.07–144.60
Adiponutrin, pkg/mL	10.89	4.05–21.58	8.11**	3.72–10.12	3.55	3.09–9.05	3.00**	2.57–6.94

Note: * – P < 0.05, ** – P < 0.01, *** – P < 0.001 vs levels before treatment.

Discussion

In the existing recommendations for the diagnosis and treatment of HD, obesity is assigned the role of a risk factor for HD development, which should also be taken into account in the risk stratification of complications (Williams & Mancia, 2018). Since the etiopathogenetic basis of the formation of HD in case of obesity is represented by a complex of pathophysiological mechanisms, which are a consequence, first of all, of visceral obesity (Seravalle & Grassi, 2017), the indicators of its direct assessment can become an additional predictor of the development of hypertension in patients with high BMI or WC.

The imbalance between energy intake and energy demand leads to a change in metabolism. It is well known that the hypothalamus maintains body weight homeostasis by effectively regulating food intake and energy expenditure, and contains groups of neurons involved in the regulation of energy balance (Liu et al., 2013). The function of the hypothalamic-pituitary-gonadal axis also influences the physiology of nutrition and, therefore, sex differences may contribute to obesity (Asarian & Geary, 2013). GAL is shown to be widespread in the peripheral and central nervous systems of mammals, including the nutrition regulating hypothalamus. Physiological actions mediated by GAL are modulated by receptors GAL 1, 2 and 3, which, like itself, are widespread in the peripheral and central nervous system of mammals, including the nutrition regulating hypothalamus. GAL 1 and 2 receptors mediate signaling cascades leading to adipogenesis, apoptosis and inhibition of cell proliferation (Gopalakrishnan et al., 2020). Thus, the lower level of Galanin concentration obtained by us in this study in patients with obesity of degrees 1 and 2 compared with patients with overweight may be partially due to the binding of GAL to GalR1, which leads to inactivating the activity of this neuropeptide. At the same time, it is possible that GAL triggers the apoptotic cascade, which causes the death of neuropeptide-producing cells. The maximum concentration of Galanin in patients with obesity of degree 3 may indicate that the GalR1 level at a given degree of obesity is insufficient to inactivate GAL. The results obtained for the presence of significantly higher GAL values in the main group and a close connection of this indicator with VLDL cholesterol are consistent with the known literature data on high plasma GAL concentration in women with moderate / severe obesity (Leibowitz, 1998; Baranowska et al., 2000), in patients with abdominal obesity, metabolic syndrome (MS), type 2 diabetes mellitus (DM 2), gestational diabetes mellitus (Fang et al., 2013), as well as in obese children (Acar et al., 2018). Moreover, in obese children, serum GAL levels positively correlate with triglycerides and insulin resistance. Therefore the results show that GAL is associated with lipid metabolism and glucose homeostasis in these children, and the authors suggest that GAL is involved in the development of obesity and associated metabolic disorders The increase in GAL may be associated with the emergence of tissue GAL resistance, or may be a compensatory mechanism against the increase in insulin sensitivity observed in obese individuals with insulin resistance. No allelic differences in the GAL 1 or GAL receptor have been reported in obese children / adolescents compared to healthy individuals, and no association was found between the GAL 2 receptor and obesity phenotypes (Barson et al., 2013). Similar results were presented in another study, which demonstrated that an increase in the expression and circulating GAL level depends on the level of circulating TG, VLDL cholesterol, ratio of esterified and non-esterified fatty acids in the diet (Sternson, 2011).

Correlation with VLDL cholesterol was also noted in ADPN, but unlike GAL, it also correlated with TG, BMI, WC, WC/HC. Little is known yet about the genetic variations in the adiponutrin gene family and their possible effects on metabolic diseases. There are also conflicting data in the literature: some authors have observed an association between PNPLA3I148M and insulin resistance and a decrease in plasma triglyceride levels in obese patients and in persons of Asian origin (Kantartzis et al., 2009; Palmer et al., 2012; Stojkovic et al., 2014). However, the vast majority of studies have shown that PNPLA3I148M does not correlate with manifestations of metabolic syndrome (Romeo et al., 2008; Kantartzis et al., 2009; Speliotes et al., 2010; Tang et al., 2015). Thus, in the study of Speliotes et al. (2010), which included 592 participants of European origin with NAFLD, no associations were found between PNPLA3I148M with body mass index, triglyceride, high-density lipoprotein and low-density lipoprotein levels, and type 2 diabetes mellitus (DM).

As can be seen in our study (Table 5) with regard to hemodynamic parameters, correlations were observed in GAL with SBP, DBP, and PAP. We also identified a relationship between the duration of HD and the serum GAL level, which has not been previously described in other literary sources. As can be seen from our data (Table 2, 3), the ADPN level was significantly higher in patients with HD, in contrast to the control group, but there is no pronounced dependence on both the degree of HD and the duration of HD. Considering that with an increase in both the degree of HD and the duration of HD the activation of oxidative stress (OS) and the progression of endothelial dysfunction occurs, it can be assumed that immuno-inflammatory activation mediated by proinflammatory cytokines triggers an apoptotic cascade leading to the death of adipocytes and a decrease in the production of ADPN by them. There are practically no data on the relationship between ADPN and the degree and duration of HD, which requires more detailed further study. Tracing obtained data on ADPN in persons with the comorbid pathology under consideration, a significant increase in the level of the latter with an increase in BMI is represented by a whole complex of pathophysiological mechanisms, the most significant of which is apparently the dysfunction of the remodeled abdominal and visceral adipose tissue and dysadiponutrinemia.

We have also shown the effect of antihypertensive therapy on the studied adipokines and established significant differences with the indicators before and after treatment. A combination of ARA II (valsartan 80 mg/day) with a diuretic (hydrochlorothiazide 12.5 mg/day) showed better results than an ACE inhibitor (enalapril 10 mg/day) with a diuretic (hydrochlorothiazide 12.5 mg/day), which is explained by the mechanism of their actions. ARBs are one of the classes of drugs recommended as first-line drugs in the treatment of hypertension (Lacourcière et al., 2005). In clinical practice, valsartan has been used as an antihypertensive drug since 1996: then it was first noted that the hypotensive effect of valsartan at a dose of 80 mg/day was not inferior to the effect of enalapril at a dose of 20 mg/day. But at the same time, valsartan is better tolerated, it is less likely to cause dry cough (Black et al., 1997; Benz et al., 1998). According to J. M. Mallionetal, the incidence of dry cough in the valsartan treatment group was 4 times less than in the enalapril group (Black et al., 1997). ARBs are effective in treating hypertension, both as monotherapy and as part of combination therapy. The most rational are combinations of ARBs with diuretics and calcium antagonists (Lacourcière et al., 2005). The synergism of the action of drugs of different classes contributes not only to a more pronounced decrease in blood pressure, but also to a decrease in the number of undesirable reactions (Lacourcière et al., 2005). Thus, the administration of diuretics leads to the activation of the RAAS (Malacco et al., 2003; Abraham et al., 2014). ARBs block this unwanted effect and potentiate the action of diuretics by increasing renal sodium excretion. The combined administration of diuretics and ARBs prevents such undesirable metabolic effects of diuretics as hypokalemia, hyperuricemia, and impaired carbohydrate metabolism (Malacco et al., 2003; Abraham et al., 2014). Along with a decrease in blood pressure, valsartan has a number of additional beneficial effects on CVS, which are not always directly related to a decrease in blood pressure: it has a beneficial effect on the state of all target organs (myocardium, vascular wall, kidneys) and indicators of carbohydrate metabolism.

Conclusions

In the studied group of patients, there was observed a significant increase in galanin and adiponutrin in comparison with the control group. The galanin level is most pronounced in patients with hypertension of degree 3 and obesity of degree 3, which is confirmed by the presence of a direct correlation with systolic, diastolic and pulse blood pressure, very low density lipoprotein cholesterol. The adiponutrin level was directly proportional to the body mass index, which is confirmed by a direct linear correlation. The data obtained during the period of in-patient treatment indicate anti-inflammatory and anti-apoptotic effects of combined antihypertensive therapy. The most pronounced result was observed in individuals receiving the combination of valsartan and hydrochlorothiazide compared with individuals receiving enalapril and hydrochlorothiazide. It is important to conduct further studies to assess the activity of galanin and adiponutrin with a longer follow-up period in wider populations. The results of new studies will help to study the pathogenetic mechanisms of this comorbidity, namely hypertension with overweight and obesity, and to use the studied adipokines in clinical practice as potential biomarkers of metabolic diseases.

The authors declare no conflicts of interest.

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