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HYPERTENSION GRADE INFLUENCE ON INFLAMMATION AND ADROPIN LEVEL IN DIABETIC PATIENTS WITH OBESITY

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The article deals with the question of the arterial hypertension grade influence on the levels of pro-inflammatory interleukin-6 and adropin in hypertensive patients. Considering the relationship between hypertension and obesity and diabetes mellitus type 2, it was important to determine the levels of inflammatory markers in patients with isolated hypertension and in patients with concomitant hypertension, obesity and diabetes, depending on the degree of blood pressure.

The purpose of the work was to reveal an influence of the grade of arterial hypertension on inflammation indicators depending on the presence of concomitant pathologists.

Material and methods. The study involved 127 patients with hypertension of stage II, 1-2nd degree, 42% men, the average age was 61.9 ± 6.1 years. Patients were divided into groups depending on the degree of hypertension: the first consisted of 68 patients with grade 1 arterial hypertension; the second, 59 patients with grade II hypertension, each group being divided into 3 subgroups: the 1st – with isolated course of hypertension, the 2nd – combination of hypertension with obesity, and the 3rd – polymorbid hypertensive patients with obesity and type 2 diabetes.

Results and discussion. The study results showed that there is a general pattern for all groups in the form of elevated levels of pro-inflammatory interleukin-6 in patients with hypertension compared to control. At the same time, the difference when comparing control and isolated course of hypertension of I grade was unreliable ($p>0.05$). In the group of patients with isolated arterial hypertension, the level of adropin in patients with II grade of hypertension was significantly lower than the control group, but was not significant in case of comparison I grade with control group ($p>0.05$). In patients with both grades I and II hypertension when combined with diabetes mellitus and obesity, difference of adropin levels achieved the values of reliability compared to control group ($p<0.01$). There were no statistically significant differences in the levels of interleukin-6 and adropin between grade I and II of arterial hypertension, except for the group of patients with isolated hypertension, where this difference turned out to be significant ($p <0.05$).

Conclusions. The degree of increase in hypertension affects the concentrations of adropin and interleukin-6, and this effect is more pronounced in an isolated course of hypertension, while in patients with arterial hypertension in combination with diabetes and obesity, this effect is not so significant. This difference may be determined by the additional potentiation effect of obesity and diabetes on inflammatory markers.

Keywords: inflammation, arterial hypertension, obesity, diabetes mellitus, adropin.

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Inroduction. A variety of modern data confirms links of inflammation with hypertension [3, 15]. The relationship between obesity and arterial hypertension is considered to be causal relationships, due to the potential two-way relationship between high blood pressure and obesity [6].

Nowadays studies confirm the fact that obesity is considered highly associated with low-grade inflammation. Fatty tissue plays an important role as an endocrine organ, expressing cytokines: IL-1, IL-6, TNFα, leptin, resistin. Adipocytes by producing these peptides lead to the chronic inflammation, which diverges from usual type of inflammation due to the absence of typical signs of inflammation, but it is similar due to the same disorders caused by typical inflammation mediators [2].

Obesity can be the reason of a pro-inflammatory condition through the rising levels of inflammatory peptides: interleukins, and diminishing of adiponectin. Obese patients have increased IL-6 that effect the liver to produce CRP. At the same time, obesity reduces adiponectin concentration. Moreover, the inflammation causes vascular and endothelial dysfunction through depression nitric oxide and increased oxidative stress. Moreover, oxidative stress together with inflammation instigates hypertension, atherosclerosis, and metabolic disorders [7].

Interleukin-10 is considered to be a major anti-inflammatory cytokine synthesized by activated T-helper type 2 (Th2), basophils, oversaturated cells, and switching B-lymphocytes to IgE production. It inhibits the synthesis of activated monocytes of proinflammatory cytokines - TNF-α, IL-1β, IL-6, IL-8, suppresses IL-2, and therethrough enhances anti-inflammatory response. The genes of these ILs are located in one cluster on the chromosomal site 5q24-31, which is adhered with atopic inflammation that was repeatedly shown [8].

Recent studies of insulin resistance suggest that some peptides (e.g. irisin, vaspin, vsfatin, adropin) are secreted by several tissues (muscle, liver, and adipose tissue) regulating lipid and carbohydrate metabolism in key insulin-targeting tissues. [5,11,16]. Adropin is important for energy homeostasis, lipid metabolism and maintains insulin sensitivity [12]. Kumar et al. showed that adropin protected from obesity-related hyperinsulinemia and hepatostathosis by regulating lipids and glucose metabolism [12].

Actually, recent investigations expanded our knowledge of the mechanisms supporting the energy homeostasis by adropin, but many issues remain unresolved. This situation makes us review traditional diagnosis considering the new information, in particular on adropin, due to accumulated data about the last one.

The purpose of the study was to compare the levels of inflammatory interleukin-6 and adropin in hypertensive obese patients with diabetes mellitus 2 type according to the grade of hypertension.

Material and methods. 127 patients with arterial hypertension were examined, which were divided into 2 groups according to the level of blood pressure level. The first group consisted of 68 patients with arterial hypertension II stage 1 degree (less than 160 mm Hg.), which included patients with isolated AH – 24 patients, with hypertension and obesity – 21 patients and with hypertension, diabetes and obesity – 23 patients. The second group (SBP over 160 mm Hg.) included 59 patients who were diagnosed with arterial hypertension of II stage 2 degree, which also were divided into 3 subgroups: the first subgroup had 23 patients with isolated hypertension, the 2nd subgroup included 19 patients with obesity, and the 3rd one encompassed 17 patients with hypertension and with diabetes and obesity. The average age of the subjects was 61.9 ± 6.1 years, males were 42%. The mean values of systolic blood pressure (SBP) in the examined patients were 163.5 ± 7.9 mm Hg, and the mean diastolic blood pressure (DBP) was 95.3 ± 4.9 mm Hg. The heart rate (HR) was 85.9 ± 7.9 beats per minute. Chronic heart failure was not severe than II class NYHA. The study also included 20 people without signs of hypertension, diabetes and obesity (heart rate was not beyond the norm) as a control group (their average age was 51.5 years, 40 to 59 years, men were 12, women – 8). All enrolled patients signed patient informed consent, the study conducted in accordance to the Helsinki Declaration of the World Medical Association, the Statute of the Ukrainian Bioethics Association, the standard provisions on ethics of the Ministry of Health of Ukraine No. 66 dated February 13, 2006.

The groups were matched by sex, age, severity of the clinical condition, concomitant pathology. A statistical analysis was done with help of Statistica 8.0 software, as the distribution was close to the normal parametric methods were used, and results are presented as M±m.

Results and discussion. There is a general pattern for all groups in the form of increased levels of proinflammatory IL-6 in all hypertensive patients compared with the control. At the same time, this difference did not reach reliability when comparing the control and the isolated course of hypertension of I grade ($p>0.05$). Analysis of the interleukins concentrations showed significant increasing its levels in patients with isolated arterial hypertension II grade and in the groups when combined with obesity and the group with combination of obesity and diabetes mellitus 2 type compared with the control group ($p>0.05$).

In a combined course of hypertension with obesity and in a group with comorbidity of hypertension with obesity and diabetes, there was the most marked increasing of IL-6 compared to control ($p<0.01$). Significant differences between I grade and II grade of hypertension were not found, except the group of patients with only hypertension where this difference reached the value of statistical significance ($p<0.05$).

This indicates a subclinical course of inflammation in patients with arterial hypertension combined with obesity. When combined with both obesity and diabetes, inflammation became more valuable.

Obviously, such a process can be considered as a consequence of obesity, accompanied by the action of intermediate toxic substances, products of metabolism of fatty acids and proliferation of cells of the macrophage type in adipose tissue [10] (**Figure**).

In the group of patients with isolated arterial hypertension, the level of adropin in patients with II grade of hypertension was significantly lower than the control group, but did not reach the values of reliability in case of 1 grade compared with controls ($p>0.05$). Adropin decreased significantly in the group of patients with combination of hypertension I and II grades and obesity in comparison with controls ($p<0.05$). In patients with both grades I and II of hypertension when combined with diabetes mellitus and obesity,

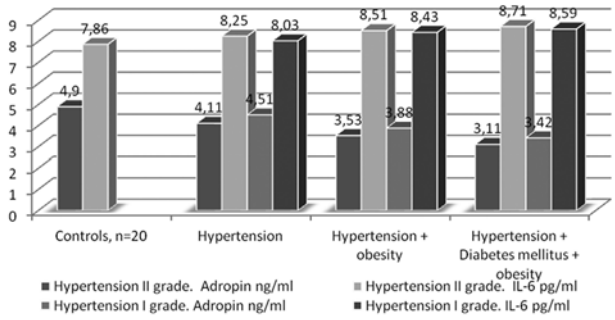

Fig. Levels of adropin and interleykin-6 in dependance of hypertension grade

difference of adropin levels also achieved the values of reliability compared to control group ($p<0.01$).

In the group of patients with isolated hypertension diminished adropin level in II grade compared to I grade was significant ($p<0.05$), but in the rest of groups with comorbidity – combined with obesity and in combination with both obesity and diabetes mellitus 2 type – significant differences between the grades of hypertension was not noted ($p>0.05$).

To some extent, our findings correlate with the Gulen's investigation. Gulen showed that the adropin levels did not differ significantly between the patients with or without target organ damage, and at the same time adropin was reliably increased in normotensive patients compared to hypertensive ones ($p<0.001$) [9].

The work of Bolayir found a significant link between night-time blood pressure and adropin, hsCRP levels. They suggested that low adropin level in non-dipper hypertensive patients correlates with elongated influence of increased blood pressure [1].

Adoprin, by increasing the level of eNOS, is involved in endothelial function and inhibition of atherosclerosis [14]. This peptide may be an important, unfavorable component of cardiometabolic disease. This thesis was confirmed by Yu et al. clinical studies [17]. They found that patients with stable ischemic heart disease had lower serum adropin concentrations compared with the corresponding control group, and patients with myocardial infarction had lower adropin concentrations than those with persistent coronary heart disease.

Demircelik et al. [4] showed that serum adropine had lower levels in patients with late SVG occlusion compared to the control group with SVG patent. They concluded that circulating levels of adropin might be the new marker of occlusion of SVG. CAD is often associated with insulin resistance and T2DM. However, it is unclear whether there is a coexistence of CAD and T2DM, which are potentially reducing the levels of adropin.

Adipose tissue secretes matter adipokines, which lead to a variety of metabolic effects. They affect the functions and system of the organism in the brain, liver, muscle, endothelium, immune system. Inflammatory disorders in hypertension can be considered to be an important factor determining the origin and course of the disease, and the cause of its deterioration, development and progression of hypertension. Mechanisms of inflammatory effects can have immunological and hemodynamic, intoxicative and genetic basis.

Mechanisms of immunological disorders that damage the tissue are hypercoagulation due to the violation of the regulatory function of procoagulants, the activation of β-lipidocytes and complement, therefore leads to the formation of immune complexes, as well as the formation of proinflammatory cytokines [13].

Conclusions. Levels of interleukins 6 in patients with isolated arterial hypertension were elevated compared to the control group, meanwhile when hypertension was combined with obesity and in comorbidity with diabetes and obesity, such difference was more perceivable.

The degree of hypertension influence on the adropin and interleukin concentrations, and this influence was more pronounced in case of isolated course of hypertension, but in hypertensive patients combined with diabetes and obesity this influence was not so considerable. Such difference is possibly determined by additional potentiating action of obesity and diabetes on the inflammatory markers. The changes of inflammatory agents and novel signaling peptides are important in understanding of progressing of hypertension course and can help to find new diagnostic and therapeutic approaches in patients with comorbidity, but further investigations are needed.

Prospects for further research reside in a deeper study of various new and well-studied pro-inflammatory and anti-inflammatory agents in hypertensive patients with comorbidity.

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ВПЛИВ СТУПЕНЯ ГІПЕРТОНІЇ НА ЗАПАЛЕННЯ І РІВЕНЬ АДРОПІНУ У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ З ОЖИРІННЯМ

Шелест Б. О.

Резюме. В роботі розглядається оцінка впливу ступеня артеріальної гіпертензії на рівні прозапального інтерлейкіну-6 і адропіну. Виходячи з даннях про взаємозв'язок гіпертензії з ожирінням і цукровим діабетом 2 типу, уявлялося важливим визначити рівні запальних маркерів у хворих з ізольованим перебігом гіпертензією і у пацієнтів з поєднаним перебігом гіпертонії, ожиріння та цукрового діабету в залежності від підвищення артеріального тиску. Дана робота дозволила виявити відмінність в рівні впливу гіпертензії на показники запалення в залежності від наявності супутньої патології.

У дослідженні взяли участь 127 хворих з артеріальною гіпертензією II стадії, 1-2-го ступеня, 42% чоловіків, середній вік склав 61.9 ± 6.1 років. Хворі були розділені на групи в залежності від ступеня АГ: першу склали 68 пацієнтів з артеріальною гіпертензією 1 ступеня; другу – 59 хворих з II ступенем АГ, при цьому кожна група розбивалася на 3 підгрупи: 1 – з ізольованим перебігом АГ, 2 поєднання АГ з ожирінням і 3 поліморбідних гіпертензивні пацієнти з ожирінням і цукровим діабетом 2 типу.

У дослідженні показано, що існує загальна тенденція у гіпертензивних пацієнтів з усіх груп у вигляді підвищених рівнів прозапального інтерлейкіна-6 порівняно з контролем. У групі пацієнтів з ізольованим

перебігом артеріальної гіпертензії II-го ступеня рівень адропіну виявився значно нижчим значень контрольної групи, але при порівнянні гіпертензії I ступеня з контролем різниця в концентрації адропіну не досягнула статистичної значущості (p> 0,05). Було встановлено, що статистично значущих відмінностей в рівнях інтерлейкіну-6 і адропіна між I і II ступенем артеріальної гіпертонії виявлено не було, за винятком групи пацієнтів з ізольованою АГ, де ця різниця досягла статистичної значущості (p<0,05).

Ступінь гіпертонії впливає на концентрації адропіна і інтерлейкіну-6, причому цей вплив більш виражений при ізольованому перебігу гіпертонії, при цьому у пацієнтів з артеріальною гіпертонією в поєднанні з діабетом і ожирінням цей вплив стає менш значним.

Ключові слова: запалення, артеріальна гіпертензія, ожиріння, цукровий діабет, адропін.

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ВЛИЯНИЕ СТЕПЕНИ ГИПЕРТОНИИ НА ВОСПАЛЕНИЕ И УРОВЕНЬ АДРОПИНА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ С ОЖИРЕНИЕМ

Шелест Б. А.

Резюме. Современные данные свидетельствуют о взаимосвязи гипертензии с ожирением и сахарным диабетом 2 типа. *Целью работы* было определить различие в уровне влияния артериальной гипертензии на показатели воспаления в зависимости от наличия сопутствующей патологии.

В исследовании приняли участие 127 больных с артериальной гипертензией II стадии, 1-2-й степени, 42% мужчин средний возраст составил 61,9 ± 6,1 лет. Больные были разделены на группы в зависимости от степени АГ: первую составили 68 пациентов с артериальной гипертензией 1 степени; вторую – 59 больных со II степенью АГ, при этом каждая группа разбивалась на 3 подгруппы:1 – с изолированным течением АГ, 2 – сочетание АГ с ожирением и 3 – полиморбидные гипертензивные пациенты с ожирением и сахарным диабетом 2 типа.

В исследовании показано, что существует общая тенденция для гипертензивных пациентов из всех групп в виде повышенных уровней провоспалительного интерлейкина-6 по сравнению с контролем. В группе пациентов с изолированной артериальной гипертензией II степени уровень адропина был значительно ниже, чем в контрольной группе, при этом разница не достигала статистической значимости в случае сравнения I степени гипертензии с контролем (p>0,05). Было установлено что статистически значимых различий в уровнях интерлейкина-6 и адропина между I и II степенью артериальной гипертонии обнаружено не было, за исключением группы пациентов с изолированной АГ, где эта разница оказалась значимой (p<0,05). Степень повышения артериальной гипертензии оказывает воздействие на концентрации адропина и интерлейкина-6, причем это влияние более выражено при изолированном течении гипертонии, при этом у пациентов с артериальной гипертонией в сочетании с диабетом и ожирением это влияние не столь значительно.

Ключевые слова: воспаление, артериальная гипертензия, ожирение, сахарный диабет, адропин.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of coauthors of the article.

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