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METABOLIC DISORDERS AND ADIPOCYTOKINES IMBALANCE IN HYPERTENSIVE PATIENTS WITH DIABETES MELLITUS AND OBESITY

Abstract

The combination of essential hypertension (EH) with excess body weight or with abdominal obesity is considered as one of the most common associated pathologies, which lead to significant increase in the frequency of cardiovascular complications.

The **aim** of the work was to study the features of adipocytokine imbalance and metabolic disorders in patients with hypertension in combination with 2 type diabetes mellitus and obesity.

Material and methods. 48 patients with essential hypertension II stage were examined (22 men and 26 women). The average age of patients was 57.6 ± 4.7 years. The patients were divided into 2 groups: the 1st group consisted of 23 patients with isolated hypertension, the 2nd group – of 25 patients with hypertension in combination with diabetes and obesity. The level of chemerin, IL-6 and C-reactive protein (C-RB) was determined by the immune-enzymatic method.

Results. The results of the study show increased IL-6 levels in both groups compared with the control group ($p \leq 0.05$), and the group with combined course of EH with diabetes and obesity had almost twice higher IL-6 level than in control. The level of C-RP in serum also exceeded the value of control values in both groups, the highest level was in patients with a combined course of hypertension with diabetes and obesity and was up to 2.3 higher. The level of serum chemerin increased in patients with essential hypertension with a combined pathology.

Conclusions. It has been established that patients with hypertension with diabetes mellitus have the most distinct imbalance of adipokines, hyperlipoproteinemia, carbohydrate disturbances and systemic inflammation, which should be taken into account in the appointment of pathogenetic therapy in this category of patients. The close pathogenetic relationships between metabolic disorders and increased serum chemerin level have been proven, therefore it must be considered as an unfavorable factor in the combined course of hypertension with diabetes and obesity. The results of the research can be applied to new and more effective methods of individual treatment of such cohort of patients with combined pathology.

Keywords: essential hypertension, diabetes mellitus, obesity, chemerin, inflammation.

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Резюме

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МЕТАБОЛІЧНІ ПОРУШЕННЯ І АДИПОЦИТОКІНОВИЙ ДИСБАЛАНС ПРИ АРТЕРІАЛЬНІЙ ГІПЕРТЕНЗІЇ З ЦУКРОВИМ ДІАБЕТОМ І ОЖИРІННЯМ

Поєднаний перебіг артеріальної гіпертензії (АГ) з надлишковою масою тіла або з абдомінальним ожирінням розглядаються як один з найбільш розповсюджених варіантів коморбідної патології, що приводить до значного підвищення частоти серцево-судинних ускладнень.

Метою роботи було вивчення особливостей адипоцитокінового дисбалансу і метаболічних порушень у хворих на АГ у поєднанні з ЦД 2 типу і ожирінням.

Матеріал і методи. Обстежено 48 хворих з АГ II стадії і 2-ї ступені (22 чоловіків і 26 жінок). Середній вік хворих складав 57,6 ± 4,7 років. Хворі були розподілені на 2 групи: 1-у групу склали 23 пацієнта з ізольованою артеріальною гіпертензією, 2-у групу – 25 хворих на АГ у поєднанні з цукровим діабетом і ожирінням. Рівень хемерину, ІЛ-6 і С-реактивного білка (С-РБ) визначали імуноферментним методом.

Результати. Рівень ІЛ-6 підвищувався в обох групах у порівнянні з контрольною групою ($p \leq 0,05$) і, майже, в 2 рази він був вище при поєднаному перебігу АГ з ЦД і ожирінням. Рівень С-РП в сироватці крові також перевищував в обох групах значення контрольних значень, найбільше (в 2,3 рази) підвищуючись у хворих при поєднаному перебігу АГ з ЦД і ожирінням. Рівень хемерину в сироватці крові підвищувався у хворих на артеріальну гіпертензію з поєднаною патологією.

Висновки. Встановлено, що хворі на АГ з ЦД на фоні підвищеної маси тіла мають найбільш виразний дисбаланс адипокінів, дисліпідемій, вуглеводні порушення і показники системного запалення, що потрібно враховувати при призначенні патогенетичної терапії у даної категорії хворих. Доведені тісні патогенетичні взаємовідносини між метаболічними порушеннями і підвищенням рівня хемерину сироватки крові, що необхідно розглядати як несприятливий фактор поєднаного перебігу АГ з ЦД і ожирінням.

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

Резюме

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МЕТАБОЛИЧЕСКИЕ НАРУШЕНИЯ И АДИПОЦИТОКИНОВЫЙ ДИСБАЛАНС ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ С САХАРНЫМ ДИАБЕТОМ И ОЖИРЕНИЕМ

Сочетанное течение артериальной гипертензии (АГ) с избыточной массой тела или абдоминальным ожирением рассматривается как один из наиболее распространенных вариантов коморбидной патологии, и приводит к значительному повышению частоты сердечно-сосудистых осложнений.

Цель работы – изучение особенностей адипоцитокинового дисбаланса и метаболических нарушений у больных АГ в сочетании с СД 2 типа и ожирением.

Материал и методы. Обследовано 48 больных с АГ II стадии и 2-й степени (22 мужчин и 26 женщин). Средний возраст больных

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составлял 57,6 ± 4,7 лет. Больные были разделены на 2 группы: первую группу составили 23 пациента с изолированной артериальной гипертензией, второй группу – 25 больных АГ в сочетании с сахарным диабетом и ожирением. Уровень хемерина, ИЛ-6 и С-реактивного белка (С-РБ) определяли иммуноферментным методом.

Результаты. Уровень ИЛ-6 повышался в обеих группах по сравнению с контрольной группой ($p \leq 0,05$), почти в 2 раза он был выше при одновременном течении АГ с СД и ожирением. Уровень С-РП в сыворотке крови также превышал в обеих группах значения контрольных значений, больше всего (в 2,3 раза) повышаясь у больных при одновременном течении АГ с СД и ожирением. Уровень хемерина в сыворотке крови значимо повышался у больных АГ с сочетанной патологией.

Выводы. Установлено, что при сочетанной патологии наблюдается наиболее значимый дисбаланс адипокинов, дислипидемий, углеводного обмена и воспаления, что нужно учитывать при назначении патогенетической терапии у данной категории больных. Доказанные тесные патогенетические взаимоотношения между метаболическими нарушениями и повышением уровня хемерина, необходимо рассматривать как неблагоприятный фактор сочетанного течения АГ с СД и ожирением.

Ключевые слова: артериальная гипертензия, сахарный диабет, ожирение, хемерин, воспаления.

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Introduction

The most rapid development of complications from the cardiovascular system is due to arterial hypertension and diabetes mellitus. The one third of patients with type 2 diabetes mellitus (DM) has diagnosed arterial hypertension (AH) [1]. In case of combined course of hypertension with diabetes, the risk of ischemic heart disease (IHD) developing rises up to 2-4 times, stroke - 2-3 times, loss of vision 10–25 times, uremia – 15–20 times, gangrenes of the lower extremities – 20 times more (6 – 2005). These two diseases are more common when increased body mass or obesity present and are manifestations of metabolic syndrome [2].

In people with obesity, the risk of hypertension developing is 50% higher, than among people with normal body weight [3]. The Framingham Study demonstrated that, systolic blood pressure increases by 4.2 mm Hg. accordingly to every excessive 4.5 kg in women [4]. Obesity, which is a modifying risk factor for diabetes, is present among almost 90% of patients with diabetes [5]. In concordance with body weight increasing, aggravation of the degree and duration of obesity, the risk of diabetes developing becomes more important and significant. Direct proportional dependence was found between the body mass and the total mortality. To a greater extent, increased mortality was due to cardiovascular pathology [6].

At present, there is no consensus on the mechanisms of pathological accumulation of adipose tissue. However, it has been shown that fatty tissue plays a role not only as energy material but also as an endocrine organ whose functional activity is closely interwoven with the immune system. Adipocytokines` imbalance is known to be associated with an increased risk of cardiovascular complications. Accordingly, it remains relevant to study the features of this balance and metabolic disorders in patients with hypertension associated with diabetes and obesity.

In the last decade, new adipokines have been described, the role of which in the processes of metabolism is being studied in detail. Among such factors are omentin, visfatin, nisfatin, vaspin, chemerin and others. Adipokines are able to influence not only on the processes of insulin resistance formation, but also have vasomotor effects and influence on the course of the inflammatory process and organ remodeling [7].

The purpose of the study: to study the features of adipocytokine imbalance and metabolic disor-

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ders in patients with hypertension in combination with diabetes and obesity.

Materials and methods. There were 48 patients under observation, with AH II stage and 2nd degree of risk (22 men and 26 women). The average age of patients was 57.6 ± 4.7 years. The patients were divided into groups: the first group consisted of 23 patients with isolated hypertension (just hypertension, without DM2 and obesity), the second group – 25 with AH in combination with 2 type diabetes mellitus and obesity. The control group (n = 20) was matched according to age and sex with the examined patients.

The diagnosis of hypertension was established in accordance with the recommendations of the European Society for Agents and the European Community of Cardiologists (ESH/ESC, 2013), as well as the Ukrainian Association of Cardiologists (2013). To determine abdominal obesity, anthropometric measurements were performed to measure body mass index (BMI) and obesity rates according to IDF criteria (2015). The diagnosis of diabetes was based on the general recommendations of the EASD (2015).

Criteria for inclusion in the study were subcompensated 2 type diabetes: fasting glycemia was not higher than 8.5 mmol/l, postprandial hyperglycemia not higher than 11 mmol/L and HbA1c levels not higher than 9%.

The level of chemerin was determined by RayBiotech (USA) kits, an enzyme-linked immunoassay method, and the contents of serum IL-6 and C-reactive protein (C-RP) were investigated using the "DRG" (USA) reagent kits by immunoenzymatic method.

Biochemical studies of lipids included the determination of plasma total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL) cholesterol by enzymatic method using “Humana” company's kits (Germany).

Cholesterol content of VLDL was calculated according to the formula: LDL cholesterol (mmol/l) = TG: 2.2. Cholesterol level of LDL cholesterol – on the difference between TC and cholesterol in the remaining fractions of LP: LDL cholesterol (mmol/l) = TC – (TG: 2.2 + HDL). Cholesterol atherogenic index (AI) was calculated according to the formula: AI = (TC – HDL): HDL. The limits of the norm were selected by the criteria most often used in clinical and epidemiological studies [8].

The level of HbA1c in the blood was determined using the test systems of the company "Reagent" (Ukraine). The index of insulin resistance (HOMA-IR) was calculated according to the formula: HOMA-IR index was measured according to the formula: fasting insulin (microU/L) x fasting glucose (nmol/l)/22.5. At the index HOMA-IR ≥ 2.77 – patients were assigned to insulin-resistant. The level of glucose onset and insulin in serum was determined by the immune enzyme method using "DRG" (USA) kits. An oral glucose tolerance test was used to determine glucose tolerance.

The statistical processing of the research results was carried out using the Statistica-8.0 software package using Student's t-criterion and non-parametric statistics methods.

Results and discussion.

When analyzing the trophological status of patients, study found that the large proportion of patients with isolated and combined course of arterial hypertension (78.3% and 66.5% respectively) were with BMI in the range of 30–34.9 kg/m2. While also, only few patients had BMI in the range of 25–29.9 kg/m2 (7 patients) and 35–39.9 kg/m2 (4 patients).

More distinct violations of lipid exchange of blood serum were diagnosed (67.8% and 36.4% respectively, $p \leq 0.05$) in patients with a combined course of hypertension with diabetes and obesity. The level of triglycerides in blood serum in these patients was 1.4 times higher ($p \leq 0.05$) than those in the 1st group and 2.5 times with the control group ($p \leq 0.05$).

In patients with hypertension with diabetes and obesity, there was more often a decrease in the level of HDL in the group than in the comparison group (63.2% and 28.3%, respectively, $p \leq 0.05$). Patients in the 2nd group who had BMI 30–34.9 kg/m2 showed lower HDL cholesterol levels compared to the first group ($p \leq 0.05$). The progression of lipid spectrum disorders with the combined course of the disease also depended on BMI: the maximal values of TC and TG were observed at BMI 35–39.9 kg/m2, and the concentration of HDL cholesterol in these patients had the smallest values.

The study showed maximal values of the HOMA-IR index, insulin and C-RB occurred in patients from the 2nd group in comparison with the indicators of the 1st group ($p \leq 0.05$), and such results are indicators of the progression of insulin resistance in conditions of hyperinsulinemia associated with diabetes mellitus. The HOMA-IR index exceeded the control factors by 1.7 times in an isolated course of hypertension and by 2.4 times higher in the combined course of hypertension with diabetes and obesity.

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Disturbances of glucose tolerance in patients with hypertension were observed in 7.5% of cases, whereas in patients with hypertension in combination with diabetes and obesity in 96.3% of cases. The probable increase in HbA1c in patients with the 2nd group compared with the control ($p \leq 0.05$) indicates a negative effect of the increased body weight on unsatisfactory compensation for carbohydrate metabolism

Table 1 – Character of carbohydrate metabolism and chemerin in patients with hypertension and in combination with diabetes and obesity

Parameters	Control (n = 20)	Hypertension only (n = 23)	AH+DM+Obesity (n = 25)
Glucose, mmol/l	4,56 ± 0,53	5,72 ± 0,64	7,36 ± 0,71*#
Insulin, microU/l	5,62 ± 1,14	10,3 ± 1,27*	13,6 ± 1,43*#
HbA1c, %	4,6 ± 1,2	5,7 ± 1,36	8,17 ± 1,52*
GTT, mmol/l	4,97 ± 1,43	8,44 ± 1,64*	11,5 ± 1,73*
HOMA-IR	1,46 ± 0,61	3,76 ± 1,3*	4,48 ± 1,47*
Chemerin, ng/ml	95,4 ± 12,3	134,6 ± 23,5*	247,4 ± 26,3*#

Notes: * – the difference with control is significant, $p \leq 0.05$;
– the difference is significant between the AG group and AG + DM group, $p \leq 0.05$

7.5% of patients had statistically significant increased fasting glucose test compared to the control group, which is explained by the presence of abdominal obesity, since overweight is one of the causes of the development of the IR. The maximum values of fasting glucose test reached in patients with a combined course of hypertension with diabetes and obesity ($p \leq 0.05$).

The level of IL-6 increased in both groups in comparison with the control group ($p \leq 0.05$), but patients with combined hypertension with diabetes and obesity had almost twice higher. The level of C-RP in serum also exceeded the values of control values in both groups, but the most was in patients with a combined course of hypertension with diabetes and obesity up to 2.3 times more. C-RP in the fourth group correlated with BMI ($r = 0.45$, $p \leq 0.05$), TG level ($r = 43$, $p \leq 0.05$), the index HOMA – IR ($r = 047$, $p \leq 0.05$).

The level of chemerin in the control group was 95.4 ± 12.3 ng/ml, rising in patients with hypertension to 134.6 ± 23.5 ng/ml and in patients with hypertension in combination with diabetes and obesity to 247.4 ± 26.3 ng/ml. In human studies, it has been shown that plasma concentrations of chemerin are associated with such indicators as body mass index (BMI), blood pressure, and blood triglyceride concentration [9]. The growth of chemerin level accordingly to BMI has been shown in studies in both adults and children [10]. In addition, the chemerin blood level increases according to glucose concentration rising at 120 minutes glucose tolerant test, increased level of fasting and peak blood insulin, growth of the HOMA-index, blood pressure elevating [10]. Thereafter, an development and progression of the metabolic syndrome is associated with an increase in chemerin plasma concentrations.

Conclusions

1. It has been established that hypertensive patients with 2 type diabetes mellitus and obesity have the most distinct imbalance of adipokines (chemerine was 1,8 times higher than only hypertensive patients, $p < 0.05$), dyslipoproteinemia (HDL-C decreased in 63.2%, $p \leq 0.05$), and systemic inflammation (IL-6 almost twice higher, CR-P up to 2.3 times increased comparing with only hypertension, $p < 0.05$) , which should be taken into account when appointment of pathogenetic therapy in this category of patients.

2. The close pathogenetic relationship between metabolic disorders and increased serum chemerin level have been proven, which should be considered as an adverse factor in the combined flow of hypertension with diabetes and obesity.

3. The results of the research can be applied to new and more effective methods of individual treatment of such cohort of patients with combined pathology.

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