

КЛІНІЧНА ЕНДОКРИНОЛОГІЯ

**DEPENDENCE OF CARDIOTROPHIN-1
ON BIOCHEMICAL AND HORMONAL FACTORS
IN PATIENTS WITH COMORBID PATHOLOGY:
ARTERIAL HYPERTENSION, TYPE 2 DIABETES MELLITUS
AND OBESITY***

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The prevalence of arterial hypertension (AH), type 2 diabetes mellitus (type 2 DM), and obesity (OB) is constantly increasing worldwide. Today, the complex of factors, which primarily include chronic emotional stress, pandemics of infectious diseases, military conflicts, has led to a significant increase in chronic non-communicable diseases. This is directly related to AH, type 2 DM, and OB, and the increasing prevalence of these diseases among young and middle-aged people is of particular concern. Unfortunately, these comorbid diseases lead to an increased risk of cardiovascular complications, the development of which causes disability and premature death in people of active working age [1–3].

Currently, the search for significant biomarkers, regulators of pathological processes that can be informative in nature regarding

the prediction of the early development of cardiovascular complications in comorbid patients does not lose its relevance.

One of these indicators is Cardiotrophin-1 (CTF-1) — a cytokine from the interleukin-6 family associated with the cardiovascular system pathology. It was found that CTF-1 is involved in energy processes; regulation and metabolism of adipose tissue; carbohydrate, lipid metabolism; myocardium remodeling, the development of atrial fibrillation, etc. [4–8].

Given the urgency of the problem, **the purpose** of our study was to determine the dependence of Cardiotrophin-1 on a number of biochemical and hormonal indicators in patients with arterial hypertension, type 2 diabetes mellitus, and obesity, representatives of the Ukrainian population.

* The work was carried out in accordance with the scientific theme of the Department of Clinical pharmacology and internal medicine of the Kharkiv National Medical University of the Ministry of Health of Ukraine «To determine the features of immunocytokine imbalance in comorbid patients with arterial hypertension and type 2 diabetes and cardiovascular and renal complications» (state registration number 0123U101711).

The institution that finances the study is the Ministry of Health of Ukraine.

The authors assume responsibility for the published work.

The authors guarantee absence of competing interests and their own financial interest when carrying out the research and writing the article.

The manuscript was received by the editorial staff 15.04.2023.

MATERIALS AND METHODS

The complex of studies was carried out in accordance with the ethical and moral-and-legal requirements of the Statute of the Ukrainian Association for Bioethics and GCP (1992), GLP (2002), the principles of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and adopted by the Commission on Ethics and Bioethics of Kharkiv National Medical University.

The study included 211 patients aged 49 to 65 years, who were treated at the clinic of GI «L. T. Malaya Therapy National Institute of the NAMS of Ukraine», and who were divided into groups depending on the pathology: patients with AH — 49 persons, Group I; patients with AH in combination with class 1 OB — 54 persons, Group 2; patients with AH in combination with type 2 DM — 57 persons, Group 3; patients with AH, type 2 DM, class 1 OB — 51 persons, Group 4; as well as 20 persons — the Control group. The study groups of patients were comparable in age and gender.

All patients had body weight, height measured and BMI = body weight/height² (m²) calculated. Body mass index (BMI) was determined to define obesity (BMI > 30 kg/m²), according to WHO criteria. AH verification, its

degree and stage were carried out, according to current European guidelines, DM diagnostics under WHO criteria.

All patients have signed informed consent to participate in the study.

Exclusion criteria for the study were as follows: type I DM, congenital heart diseases and urinary tract defects, the artificial pacemaker, the artificial heart valves, heart failure stages II B and III, acute myocardial infarction, infectious and severe inflammatory processes, hematological diseases.

Determination of the CTF-1, catestatin, leptin, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), N-terminal brain natriuretic peptide (NT-proBNP), 25-OH vitamin D (Vitamin D3) blood levels were carried out by enzyme immunoassay on *Labline-90* analyzer (Austria), using commercial test systems manufactured by *FineTest* (ELISA, China), *BT LAB* (ELISA, China), *DBC* (ELISA, China), *Elabscience* (ELISA, Canada), *Monobind Inc.* (ELISA, USA), according to the instructions included in the kits.

Biochemical studies (the level of creatinine, urea, and lipid spectrum in blood serum) were carried out on *Labline-90* analyzer (Austria). The urea level in blood serum was measured

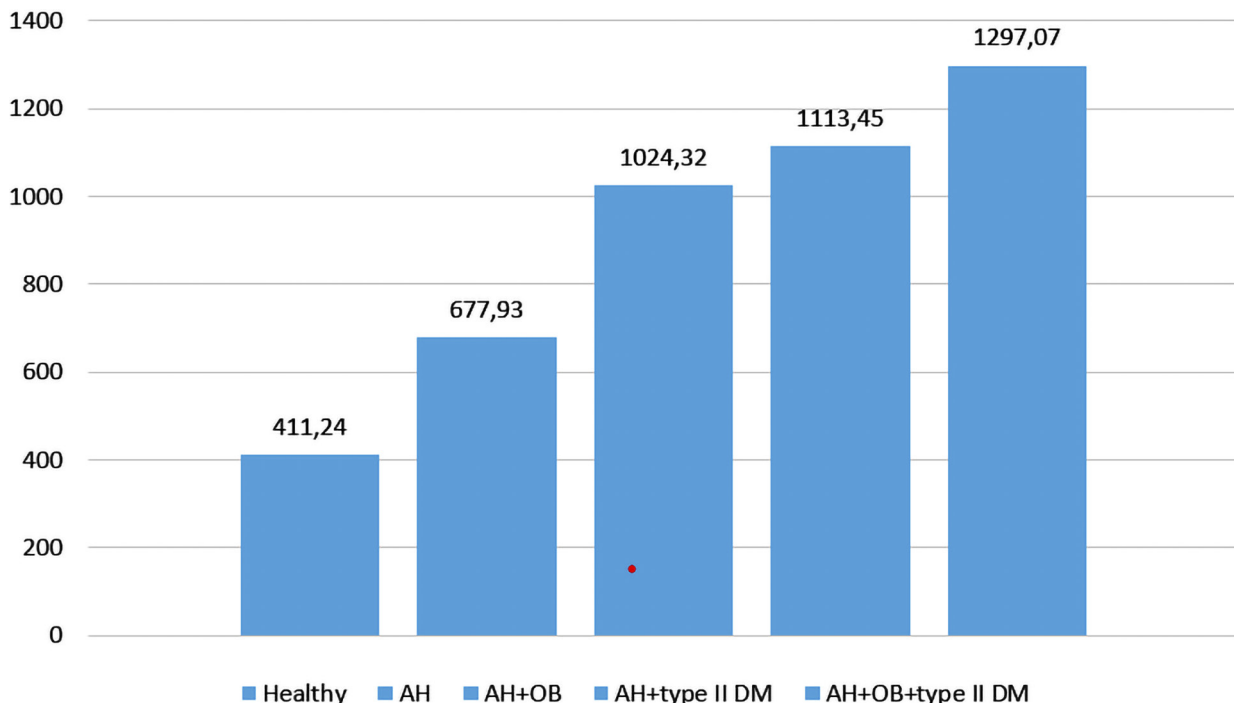


Fig. 1. CTF-1 concentration in all the examined groups

by a kinetic, enzymatic method with urease and glutamate dehydrogenase, using *Liquick Cor-UREA 30* kits (Cormay, Poland), according to the manufacturer's instructions. The creatinine level in blood serum was measured by the modified Jaffe's method without deproteinization, using *LiquickCor-CREATININ 30* reagent kits (Poland), according to the manufacturer's instructions. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined by the enzymatic method, using such reagent kits, as *Cholesterol liquicolor*, *HDL-Cholesterol*, and *Triglycerides liquicolor* (Human, Germany), according to the manufacturer's instructions. The content of very-low-density lipoprotein (VLDL-C) was calculated, according to the formula $TG / 2.22$; the content of low-density lipoprotein choleste-

rol (LDL-C) was calculated by the formula of W. T. Friedewald, 2004:

$$VLDL-C = TC - (HDL-C + TG / 2.22), \text{ mmol/L.}$$

Statistical data analysis was performed, using the statistical software package *Statistica, 12* (Stat Soft Inc, USA), *Microsoft Office Excel 2013*. Data are shown as mean (M) and standard deviations (δ).

Differences between groups of mean values were assessed, using Student's t-test. An error of less than 5% was considered to be significant ($p < 0.05$).

Stepwise regression analysis was used to determine the extent of exposure of the studied indicators to the CTF-1 level, with its effectiveness assessed by one-way analysis of variance (ANOVA).

RESULTS AND THEIR DISCUSSION

According to the study results, it was found that the CTF-1 concentration significantly differed in all the examined groups of patients compared to the controls, as well as among themselves, $p < 0.05$ (Fig. 1).

The data obtained indicate a significant increase in the CTF-1 level in comorbid patients as the aggravation of comorbid pathology and its highest level was observed in patients with AH + type 2 DM + OB. The data obtained are comparable with the results of other researchers [9–11].

In order to determine the exposure of various factors to the CTF-1 level separately in each group of patients, we built mathematical models, using stepwise regression analysis. The inclusion of a number of clinical metabolic and hormonal indicators in the mathematical model makes it possible to expand its information content and significance.

Thus, according to the data obtained, in patients with AH, the CTF-1 level is more clearly influenced by catestatin, the patient's age, and NT-proBNP (Table 1).

Table 1

The impact of various factors on the CTF-1 level in the examined patients with AH (Group 1) (regression analysis) ($R^2 = 0.56$, $F = 4.95$, $p = 0.00004$)

Indicator, n = 49	Beta (δ)	B	Extent of exposure (%)	p-level
Catestatin	-0.484	-63.399	14.04%	0.0004
Age	-0.256	-3.268	7.43%	0.0589
NT-proBNP	0.271	0.306	7.86%	0.0338
Creatinine, $\mu\text{mol/L}$	0.235	2.926	6.82%	0.0911
Leptin	0.262	2.965	7.60%	0.0436
Weight	0.227	3.096	6.59%	0.0766
Atherogenic index (AI)	0.199	17.260	5.77%	0.0992

Note:

R^2 — determination factor;

F — criterion;

p — model statistical significance;

$K_j = ((100 \times \text{BETA}) \times R^2) / \sum (\text{BETA}_j) \text{ in } \%$

Table 2

**The impact of various factors on the CTF-1 level
in the examined patients with AH + OB (Group 2)
(regression analysis) ($R^2 = 0.61$, $F = 4.34$, $p = 0.001$)**

Indicator, n = 54	Beta (δ)	B	Extent of exposure (%)	p-level
Catestatin	- 0.433	- 14.085	13.01 %	0.0012
Age	- 0.354	- 1.193	10.64 %	0.0045
NT-proBNP	0.339	35.292	10.19 %	0.0072
Creatinine, $\mu\text{mol/L}$	- 0.337	- 3.667	10.13 %	0.0120
Leptin	0.303	112.959	9.10 %	0.0193
Weight	- 0.137	- 5.385	4.12 %	0.2682
Atherogenic index (AI)	0.126	50.556	3.79 %	0.3064

Table 3

**The impact of various factors on the CTF-1 level
in the examined patients with AH + DM (Group 3)
(regression analysis) ($R^2 = 0.54$, $F = 7.66$, $p = 0.0002$)**

Indicator, n = 57	Beta (δ)	B	Extent of exposure (%)	p-level
NGAL	- 0.497	- 13.074	27.31 %	0.0001
TG	- 0.204	- 21.647	12.81 %	0.0815
HDL-C	0.160	41.339	10.05 %	0.1703

Table 4

**The impact of various factors on the CTF-1 level
in the examined patients with AH + OB + type 2 DM (Group 4)
(regression analysis) ($R^2 = 0.67$, $F = 5.35$, $p = 0.0006$)**

Indicator, n = 51	Beta (δ)	B	Extent of exposure (%)	p-level
Catestatin	- 0.435	- 18.218	18.45 %	0.0011
Cystatin C	0.456	0.436	19.34 %	0.0008
Leptin	- 0.322	- 1.016	13.65 %	0.0112
Atherogenic index (AI)	0.206	5.324	8.74 %	0.0883
Age	0.158	0.685	6.70 %	0.1919

Table 5

**The impact of various factors on the CTF-1 level
in all examined patients without the Control group
(regression analysis) ($R^2 = 0.55$, $F = 6.88$, $p = 0.000001$)**

Indicator, n = 211	Beta (δ)	B	Extent of exposure (%)	p-level
BMI	0.331	14.107	19.58 %	0.0000
Creatinine, $\mu\text{mol/L}$	0.145	2.556	8.58 %	0.0267
SBP	0.102	1.561	6.03 %	0.1393
DBP	- 0.100	- 1.994	5.91 %	0.1427

Note:

$$K_j = ((100 \times \text{BETA}) \times R^2) / \sum (\text{BETA}_j) \text{ in } \%$$

Similar data were obtained in patients with AH and obesity (Table 2).

In comorbid patients with AH and type 2 DM, the aspect of disease is different (Table 3). In such cases, CTF-1 levels are influenced by NGAL, triglyceride levels, and HDL-C.

In patients with AH, type 2 DM, and OB, the results indicate that catestatin, cystatin C, and leptin have the most pronounced effect on the CTF-1 level (Table 4).

Summarizing the data obtained, it can be argued that in the majority of the patients examined, catestatin, an important peptide that regulates the functioning of the cardiovascular system, has the most significant effect on the CTF-1 level. It is also known that this biomarker has antihypertensive, antiapoptotic, cardio-protective, and hypoglycemic effects [12–14].

Cystatin C is an early marker for chronic kidney disease. At the same time, it has been found that the level of cystatin C increases with heart failure and a number of other diseases, so it is considered to be as a predictor of cardiovascular complications associated with impaired renal function and a marker of the severity of heart failure and acute coronary syndrome [15–17].

N-terminal brain natriuretic peptide (NT-proBNP), a hormone secreted by cardio-

myocytes in the ventricles of the heart in response to cardiac stress and ventricular dysfunction, plays an important role in the cascade of cardiovascular events. There are studies, demonstrating the predictive value of this indicator for the development of cardiovascular events, primarily in the diagnosis and treatment of heart failure [18–20].

Regarding the relationship between CTF-1 and leptin, it should be noted that this adipocyte (leptin) is a signal marker that reflects the accumulation of adipose tissue, correlates with the amount of adipose tissue, stimulates angiogenesis, proliferation of hematopoietic cells and pancreatic β -cells [21–23].

The so-called «classical» indicators, which include data on the blood lipid spectrum, creatinine, BMI, and levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP), also have an important impact on the CTF-1 level [24, 25] (Table 5). Thus, the study indicates that comorbid patients with AH, type 2 DM, and OB are predicted to develop complications from the cardiovascular system and CTF-1 is a marker of their development. In the examined patients as a whole, the level of CTF-1 is closely related to the peptide-hormonal complex: catestatin, leptin, cystatin C, brain natriuretic peptide, and lipocalin associated with neutrophil gelatinase.

CONCLUSIONS

1. The serum concentration of Cardiostrophin-1 in patients with arterial hypertension increases significantly in a progression with the rate of accession of comorbid pathology and its severity.
2. The Cardiostrophin-1 level in patients with comorbid pathology is affected by catestatin, leptin, cystatin C, NT-pro BNP, as well as

the level of triglycerides, HDL-C, creatinine, and BMI.

3. Cardiostrophin-1 can be considered as a universal biomarker for the development and progression of cardiovascular disorders in patients with comorbid pathology of arterial hypertension, type 2 diabetes, and obesity.

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DEPENDENCE OF CARDIOTROPHIN-1 ON BIOCHEMICAL AND HORMONAL FACTORS IN PATIENTS WITH COMORBID PATHOLOGY: ARTERIAL HYPERTENSION, TYPE 2 DIABETES MELLITUS AND OBESITY

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The prevalence of arterial hypertension, type 2 diabetes mellitus (type 2 DM), and obesity is constantly increasing worldwide. Today, a complex of factors, which primarily include chronic emotional stress, pandemics of infectious diseases, military conflicts, have led to a significant increase in chronic non-communicable diseases.

The aim of the study. To determine the dependence of Cardiostrophin-1 on a number of biochemical and hormonal indicators in patients with arterial hypertension, type 2 DM, and obesity, representatives of the Ukrainian population.

Materials and methods. The study included 211 patients aged 49 to 65 years, who were divided into groups depending on the pathology: patients with arterial hypertension — 49 persons, Group I; patients with arterial hypertension in combination with class 1 obesity — 54 persons, Group 2; patients with arterial hypertension in combination with type 2 DM — 57 persons, Group 3; patients with arterial hypertension, type 2 DM, class 1 obesity — 51 persons, Group 4; as well as 20 persons — the Control group.

Determination of the content of Cardiostrophin-1, catestatin, leptin, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), N-terminal brain natriuretic peptide (NT-proBNP), 25-OH vitamin D (Vitamin D₃), blood levels was carried out by enzyme immunoassay on Labline-90 analyzer (Austria), using commercial test systems manufactured by FineTest (ELISA, China), BT LAB (ELISA, China), DBC (ELISA, China), Elabscience (ELISA, Canada), Monobind Inc. (ELISA, USA).

Statistical data analysis was performed, using the statistical software package Statistica, 12 (Stat Soft Inc, USA), Microsoft Office Excel 2013. Data are shown as mean (M) and standard deviations (δ). An error of less than 5% was considered to be significant (p < 0.05). Stepwise regression analysis was used to determine the extent of exposure of the studied indicators to the CTF-1 level, with its effectiveness assessed by one-way analysis of variance (ANOVA).

Results. Thus, the study indicates that comorbid patients with arterial hypertension, type 2 DM, and obesity are predicted to develop complications from the cardiovascular system and Cardiostrophin-1 is a marker of their development. In the examined patients as a whole, the level of Cardiostrophin-1 is closely related to the peptide-hormonal complex: catestatin, leptin, cystatin C, brain natriuretic peptide, and lipocalin associated with neutrophil gelatinase.

Conclusions: The serum concentration of Cardiostrophin-1 in patients with arterial hypertension increases significantly in a progression with the rate of accession of comorbid pathology and its severity. The Cardiostrophin-1 level in patients with comorbid pathology is affected by catestatin, leptin, cystatin C, NT-pro BNP, as well as the level of triglycerides, HDL-C, creatinine, and BMI. Cardiostrophin-1 can be considered as a universal biomarker for the development and progression of cardiovascular disorders in patients with comorbid pathology of arterial hypertension, type 2 DM, and obesity.

Key words: Cardiostrophin-1, comorbid pathology, type 2 diabetes mellitus, arterial hypertension, obesity, regression analysis.

ЗАЛЕЖНІСТЬ КАРДІОТРОФІНУ-1 ВІД БІОХІМІЧНИХ І ГОРМОНАЛЬНИХ ЧИННИКІВ У ПАЦІЄНТІВ З КОМОРБІДНОЮ ПАТОЛОГІЄЮ: АРТЕРІАЛЬНОЮ ГІПЕРТЕНЗІЄЮ, ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ ТА ОЖИРІННЯМ

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Розповсюдженість артеріальної гіпертензії, цукрового діабету 2 типу (ЦД2) та ожиріння невпинно зростає в усьому світі. Комплекс факторів, до яких, в першу чергу, належить хронічний емоційний стрес, пандемії інфекційних захворювань, військові конфлікти, призвели до значного збільшення на тепер хронічних неінфекційних захворювань.

Мета дослідження. Визначити залежності кардіотрофіну-1 від ряду біохімічних і гормональних показників у пацієнтів з артеріальною гіпертензією, цукровим діабетом 2 типу і ожирінням, представників української популяції.

Матеріали та методи. В дослідження включено 211 пацієнтів у віці від 49 до 65 років, які були розподілені на групи залежно від патології: хворі на артеріальну гіпертензію — 49 осіб, 1 група; хворі на артеріальну гіпертензію з ожирінням I ступ. — 54 особи, 2 група; хворі на артеріальну гіпертензію з ЦД2 — 57 осіб, 3 група; пацієнти з артеріальною гіпертензією, ЦД2, ожирінням I ступ. — 51 особа, 4 група; а також 20 осіб — контрольна група.

Визначення вмісту кардіотрофіну-1, катестатину, лептину, цистатину С, ліпокаліну, асоційованому з желатиназою нейтрофілів (NGAL), N-термінального мозкового натрійуретичного пептиду (NT-proBNP), 25-ОН вітаміну D (Vitamin D₃), рівня інсуліну у сироватці крові проводили імуноферментним методом на аналізаторі «Labline-90» (Австрія) з використанням комерційних тест-систем виробництва фірми «Fine Test» (Китай), «BT LAB» (Китай), «DVC» (Китай), «Elabscience» (Канада), «Monobind Inc.» (США).

Статистичний аналіз даних виконано за допомогою пакету статистичних програм Statistica, 12 (Stat Soft Inc, США), Microsoft Excel 2013. Для визначення ступеню впливу на рівень кардіотрофіну-1 показників, що вивчаються, використовували покроковий регресійний аналіз з оцінкою його ефективності за допомогою однофакторного дисперсійного аналізу (ANOVA). Достовірною вважалася похибка менше 5% ($p < 0,05$).

Результати. Доведено, що у пацієнтів з артеріальною гіпертензією при розвитку коморбідної патології, а саме поєднанні з ЦД2 та ожиріння, має місце збільшення ризику розвитку серцево-судинних ускладнень, біомаркером яких є кардіотрофін-1. У обстеженого загалу пацієнтів рівень кардіотрофіну-1 тісно пов'язаний з пептидно-гормональним комплексом: катестатином, лептином, цистатином С, мозковим натрійуретичним пептидом та ліпокаліном, асоційованим з желатиназою нейтрофілів.

Висновки. Концентрація сироваткового рівня кардіотрофіну-1 у пацієнтів з артеріальною гіпертензією прогресивно значуще збільшується з темпом приєднання коморбідної патології та її тяжкості. На рівень кардіотрофіну-1 у пацієнтів з коморбідною патологією здійснює вплив катестатин, лептин, цистатин С, NT-pro BNP, а також рівень тригліцеридів, ХС-ЛПВЩ, креатиніну, ІМТ. Кардіотрофін-1 можна вважати універсальним біомаркером розвитку і прогресування серцево-судинних порушень у пацієнтів з коморбідною патологією артеріальної гіпертензії, цукрового діабету 2 типу та ожиріння.

Ключові слова: кардіотрофін-1, коморбідна патологія, цукровий діабет 2 типу, артеріальна гіпертензія, ожиріння, регресійний аналіз.