ISSN print 2414-4495, ISSN online 2710-1444, https://msz.knmu.edu.ua, msz.journal@knmu.edu.ua

Therapy

UDC: 616.12-005.4:613.25]-008.9

CHARACTERISTICS OF THE BATOKINE EXCHANGE DYNAMICS IN PATIENTS WITH CORONARY HEART DISEASE AND OBESITY ON THE BACKGROUND OF THERAPY

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The article analyzes the dynamics of batokine levels: vascular endothelial growth factor A (VEGFa) and fibroblast growth factor (FGF-21) in patients with comorbidity of coronary heart disease (CHD) and obesity against the background of therapy. The aim of the research was to study the dynamics of FGF-21 and VEGFa levels in individuals with comorbidity of CHD and obesity against the background of therapy. 130 people aged from 25 to 85 were examined: Group I included 70 patients with CHD in combination with obesity, Group II – 35 patients with isolated CHD, The control group (Group III) included 25 healthy people without any cardiovascular diseases. The Group I included 26 (37.1%) patients with the I^{st} degree of obesity, 24 (34.3%) patients with the II^{nd} degree of obesity, and 20 (28.6%) with the III^{rd} degree of obesity. During the study, standard ethical requirements for similar studies were met, which was confirmed by the conclusion of the Bioethics Committee of the Kharkiv National Medical University. In the research FGF21 and VEGFA levels were established. These indicators were restored after treatment. The dynamics of the decrease in the levels of FGF21 (by 23.6 pg/ml) and VEGFA (by 11.1 pg/ml) after treatment was better in patients of the I group ($p<0.001$). In the II group, there was a decrease in the levels of FGF21 (by 10.5 pg/ml; $p=0.001$) and VEGFA (by 2.2 pg/ml; $p=0.154$). According to obesity levels, the dynamics of FGF21 recovery was better for grades I (by 29.1 pg/ml; $p=0.004$) and II (by 55.7 pg/ml; $p<0.001$). A significant ($p<0.001$) increase in the level of FGF21 after treatment by 22.5 pg/ml was observed in degree III obesity. Probable ($p<0.001$) better dynamics of recovery of VEGFA level was observed in obesity of III degree (decrease by 13.8 pg/ml), compared to II and I degrees (decrease by 9.8 pg/ml and 10.2 pg/ml). Treatment of patients with CHD on the background of obesity determined its effectiveness in restoring the levels of FGF21 and VEGFA.

Keywords: *coronary heart disease and obesity comorbidity, isolated coronary heart disease, batokines, FGF21, VEGFA.*

Цитуйте українською: Гріднева ОВ. Характеристика динаміки батокінового обміну хворих при ішемічній хворобі серця та ожирінні на тлі терапії. Медицина сьогодні і завтра. 2023;92(3):8с. In press. https://doi.org/10.35339/msz.2023.92.3.gri [англійською].

Cite in English: Gridneva OV. Characteristics of the batokine exchange dynamics in patients with coronary heart disease and obesity on the background of therapy. Medicine Today and Tomorrow. 2023;92(3):8p. In press. https://doi.org/10.35339/msz.2023.92.3.gri

ISSN print 2414-4495, ISSN online 2710-1444, https://msz.knmu.edu.ua, msz.journal@knmu.edu.ua

Introduction

The global scientific community notes a significant increase in the prevalence of non-communicable diseases (NCDs). This situation is caused by the significant prevalence of an unhealthy lifestyle, a decrease in the physical activity of the population, high levels of abuse of alcoholic beverages and tobacco smoking, a significant prevalence of unhealthy and unbalanced nutrition, etc. [1]. According to the World Health Organization (WHO), among European countries, more than 60.0% of the total burden of diseases belongs to seven main risk factors for the development of diseases: arterial hypertension (12.8%), smoking (12.3%), alcohol abuse (10.1%), increased blood cholesterol levels (8.7%), overweight (7.8%), low consumption of vegetables and fruits (4.4%), sedentary lifestyle (3.5%).

These risk factors provoke the development of the most common diseases, the most common of which are NCDs (77.0%), external causes, injuries and poisoning (14.0%) and infectious diseases (9.0%). These diseases provoke high levels of mortality and disability of the population. Thus, the European region due to NCDs has 86.0% of the 9.6 million total number of deaths and 77.0% of the 150.3 million total number of Disability-adjusted life years (DALYs). Among all countries of the world, NCDs cause 70.0% of the total number of deaths (40 million) [2]). High negative medical and social impacts on the world population of NCDs are also confirmed by other researchers [3], who indicate the level of DALYs due to NCDs at the level of 60.0% of the total number and 80.0% of Years lived with disability (YLD).

Official statistical data determine cardiovascular diseases (CVD) occupy the first place (70.0% of all global deaths) among all NCDs in terms of mortality among the working population [4]. CVDs reduce the quality of life of the entire world population and provoke significant levels of mortality and disability of the population and significant health care costs [5–8]. CVD annually provokes 16.5–17.5 million global deaths [9], which determines the loss of 330 million DALYs and 35.6 million YLDs [10; 11].

Domestic rates of CVD mortality also rank first and account for 67.0% of all deaths. The standardized mortality rate caused by CVD in Ukraine is 801.6 cases per 100,000 populations [12].

According to forecasts, the prevalence of CVD and the levels of disability and mortality caused by it will progressively increase [13] and by 2030 will increase to 24.1–24.3 million people and above [14].

The main pathogenetic factor in the development of CVD is atherosclerotic lesions, with the appearance of which the development of coronary heart disease (CHD), cerebrovascular pathology and other diseases that subsequently cause myocardial infarction, arrhythmias, strokes, etc. The main etiological factors of CVD are hyperlipidemia, blood pressure, diabetes mellitus, excess body weight, alcohol, and low physical activity [15–17]. At the same time, CHD is the primary cause of CVD, especially if it is comorbid with obesity [18].

Recently, a variety of inflammatory mediators have been used to study the features of the comorbidity of CHD and obesity, among which batokines (fibroblast growth factor – FGF-21 and vascular endothelial growth factor A – VEGFa), which are produced in CHD and obesity, are quite relevant. Thus, the study of the dynamics of batokine metabolism against the background of applied therapy for CHD and obesity is a very relevant and significant problem.

The **aim** of the research – to study of the dynamics of FGF-21 and VEGFa levels in individuals with comorbidity of CHD and obesity against the background of therapy.

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Materials and Methods

130 people aged from 25 to 85 were examined. They were divided into 3 groups. Group I included 70 patients with coronary heart disease (CHD) in combination with obesity, Group II – 35 patients with isolated CHD. The control group (Group III) included 25 healthy people without any CVD. The Group I included 26 (37.1%) patients with the Ist degree of obesity, 24 (34.3%) patients with the IInd degree of obesity, and 20 (28.6%) with the IIIrd degree of obesity. The patients of the Group I had an average age of (63.6±8.8) years, Group II – (69.7±7.9) years, Group III – (59.8±14.6) years.

During the study, standard ethical requirements for similar studies were met, which was confirmed by the conclusion of the Bioethics Committee of the Kharkiv National Medical University. All patients of the study signed an informed voluntary consent. The statistical difference by age and gender characteristics was determined at a statistically significant level ($p \leq 0.001$).

The criterion for inclusion in all research groups was reaching the age of 18 years. The I Group included patients with coronary heart disease and obesity. In the II Group included patients with isolated CAD. In the III Group included persons without diffuse focal diseases, endocrine pathology, allergic reactions, diseases of internal organs, severe decompensated somatic pathology, mental and oncological diseases, pregnancy, chronic alcoholism.

Patients of I Group and II Group received: statins and metabolic agents, antiplatelet agents, diuretics, β-blockers and angiotensin II receptor blockers, calcium channel blockers, nitrates, ACE inhibitors, hypoglycemic agents, cardiac glycosides, and anticoagulants. The diagnosis of CHD was established according to current guidelines [19]. The diagnosis of obesity was made according to the existing recommendations of EASO (2017) [20].

Determination of indicators of batokines was carried out using generally accepted methods.

During the medical statistical calculation, the presence of reliable differences from the normal nature of the distribution was determined. Therefore, the calculations were carried out using non-parametric medical and statistical methods. The average value (M) and standard deviation (SD, σ) were calculated. Results were presented as M±SD.

Probability of differences in quantitative characteristics in two mutually independent groups was performed using the Mann-Whitney U-test, and in interdependent groups – Wilcoxon matched-pairs signed-ranks T-test.

The threshold value of the probability level of all calculated features was taken at the level of 0.05 ($p=0.05$). Statistical calculations were performed using IBM SPSS 25.0 for Windows (USA).

Results and Discussion

The levels of batokines (FGF21 and VEGFA) obtained by the study before the use of therapy significantly exceeded the normative values both in I Group (respectively [241.1±27.1] pg/ml and [222.9±7.3] pg/ml) and in the comparison group (respectively [209.0±13.8] pg/ml and [206.0±±8.3] pg/ml) and were significantly ($p<<0.001$) higher than the indicators of the control group (respectively [197.1±6.8] pg/ml and [182.3±6.4] pg/ml). In CHD with obesity, the levels of both batokines were probably ($p<0.001$) higher than the indicators recorded in patients with isolated CHD (*Table 1*).

With significant obesity (IIIrd and IInd degrees), the levels of batokines probably ($p<0.001$) exceeded the values of obesity of the Ist degree (FGF21 [208.1±12.7] pg/ml, [271.3±7.8] pg/ml, and [238.4±9.5] pg/ml, respectively; VEGFA – [229.1±6.4] pg/ml, [223.7±4.3] pg/ml, and [217.5±6.1] pg/ml, respectively) (*Table 2*).

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Table 1. Characteristics of batokines levels of the subjects, M±SD (n=130)

Batokines levels	Research groups			p*	p**	p***
	I (*n*=70)	II (*n*=35)	III (*n*=25)			
FGF21, pg/ml	241.1±27.1	209.0±13.8	197.1±6.8	<0.001	<0.001	<0.001
VEGFA, pg/ml	222.9±7.3	206.0±8.3	182.3±6.4	<0.001	<0.001	<0.001

Notes: *p** – statistical significance of differences between I and II groups;
*p*** – between I and III groups; *p**** – between II and III groups.

Table 2. Characteristics of the levels of batokines patients of the main group depending on the existing degree of obesity, M±SD (n=70)

Batokines levels	Degrees of obesity			p*	p**	p***
	I (*n*=26)	II (*n*=24)	III (*n*=20)			
FGF21, pg/ml	238.4±9.5	271.3±7.8	208.1±12.7	<0.001	<0.001	<0.001
VEGFA, pg/ml	217.5±6.1	223.7±4.3	229.1±6.4	<0.001	<0.001	0.002

Notes: *p** – statistical significance of differences between Ist and IInd degrees of obesity;
*p*** – between Ist and IIIrd degrees of obesity;
*p**** – between IInd and IIIrd degrees of obesity.

In the dynamics after treatment, a significant (p<0.001) decrease in the levels of batokines (FGF21 and VEGFA) was noted both in Group I (by 23.6 pg/ml and 11.1 pg/ml, respectively) and in Group II (by 10.5 pg/ml [p=0.001] and 2.2 pg/ml [p=0.154]). In general, after treatment, the values of FGF21 and VEGFA probably (p<0.001) significantly prevailed in Group I (respectively, [217.5±10.9] pg/ml and [211.8±6.15] pg/ml) compared to the Group III (respectively, [198.5±6.4] pg/ml and [203.8±3.5] pg/ml) (*Table 3*).

Depending on the degree of obesity, a decrease in the levels of batokines was observed in almost all groups, except for the value of FGF21, which after treatment marked a probable (p<0.001) increase by 22.5 pg/ml at IIIrd degree (*Table 4*). With the Ist and IInd degrees, FGF21 in dynamics probably decreased by 29.1 (p = 0.004) and 55.7 (p<0.001) pg/ml, respectively. VEGFA levels were significantly (p<0.001) decreased by 10.2 pg/ml, 9.8 pg/ml, and 13.8 pg/ml (IIIrd, IInd and Ist degrees, respectively). FGF21 levels significantly

Table 3. Characteristics of batokines levels of the subjects examined after treatment, M±SD (n=130)

Batokines levels	Research groups				p*	p**	p***
	I (*n*=70)		II (*n*=35)				
	indicator	dynamics	indicator	dynamics			
FGF21, pg/ml	217.5±10.9	-23.6	198.5±6.4	-10.5	<0.001	<0.001	0.001
VEGFA, pg/ml	211.8±6.15	-11.1	203.8±3.5	-2.2	<0.001	<0.001	0.154

Notes: p* – statistical significance of differences between I and II groups after treatment; p** – in the I Group before and after treatment; p*** – in the II Group before and after treatment.

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Table 4. Characteristics of batokines levels patients of the main group according to the degree of obesity after treatment, M±SD (n=70)

Batokines levels	Degrees of obesity			*p**	*p***	*p****
	I (*n*=26)	II (*n*=24)	III (*n*= 0)			
FGF21, pg/ml	209.3 ± 5.6	215.6 ± 6.4	230.6 ± 7.8	0.001	< 0.001	< 0.001
VEGFA, pg/ml	207.3 ± 3.8	213.9 ± 6.2	215.3 ± 5.1	< 0.001	< 0.001	0.383
dynamics				*p^*	*p^^*	*p^^^*
FGF21, pg/ml	-29.1	-55.7	+22.5	0.004	< 0.001	< 0.001
VEGFA, pg/ml	-10.2	-9.8	-13.8	< 0.001	< 0.001	< 0.001

Notes: p* – statistical significance of differences between Ist and IInd degrees of obesity after treatment; p** – between Ist and IIIrd degrees of obesity after treatment; p*** – between IInd and IIIrd degrees of obesity after treatment; p^ – with Ist degree of obesity before and after treatment; p^^ – with IInd degree obesity before and after treatment; p^^^ – with IIIrd degree obesity before and after treatment.

(p<0.001) prevailed in IIIrd degree of obesity ([230.6±7.8] pg/ml) compared to IInd ([215.6±6.4] pg/ml) and Ist ([209.3±5.6] pg/ml) in degrees; as well as VEGFA values: (215.3±5.1) pg/ml, (213.9±6.2) pg/ml (p=0.383), and (207.3±3.8) pg/ml (p<0.001), respectively.

Our results regarding the significant associations and effects of the levels of batokin complexes on the risks of developing CHD and obesity and their comorbid combination are completely consistent with other conducted studies. Zheng X. et al. [21] evaluated the relationships between FGF-21 and the development of negative clinical outcomes. They established the development of negative clinical consequences in 21.83% patients (550 developed severe disability and 195 died).

Lee C.H. et al. [22] established increased levels of serum FGF-21 in CHD compared to individuals without CHD (222.7 pg/ml [92.8–438.4] vs. 151.1 pg/ml [75.6–274.6]; p<0.001).

Conclusions

Thus, restoration of FGF21 and VEGFA levels after treatment was confirmed. The dynamics was better in CHD with obesity compared to CHD isolated: the corresponding probable (p<0.001) reduction by 23.6 pg/ml, and 11.1 pg/ml, and by 10.5 pg/ml (p=0.001) and 2.2 pg/ml (p=0.154). Better dynamics of FGF21 restoration was observed in Ist and IInd degrees of obesity (decrease by 29.1 pg/ml [p=0.004] and 55.7 pg/ml [p< <0.001]) compared to IIIrd (probable [p< <0.001] increase by 22.5 pg/ml). More effective dynamics of restoration of VEGFA levels was observed in IIIrd degree of obesity compared to IInd and Ist (probably [p<0.001] decrease by 13.8 pg/ml, 9.8 pg/ml, and 10.2 pg/ml, respectively).

Conflict of interest is absent.

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Гріднева О.В.

ХАРАКТЕРИСТИКА ДИНАМІКИ БАТОКІНОВОГО ОБМІНУ ХВОРИХ ПРИ ІШЕМІЧНІЙ ХВОРОБІ СЕРЦЯ ТА ОЖИРІННІ НА ТЛІ ТЕРАПІЇ

В статті проаналізовано динаміку рівнів батокінів (фактора росту фібробластів (fibroblast growth factor, FGF-21) та фактору росту ендотелію судин А (vascular endothelial growth factor A, VEGFa) хворих на ішемічну хворобу серця (ІХС) та ожиріння на тлі терапії. Обстежено 130 осіб віком від 25 до 85 років, з яких сформували 3 групи: до І групи увійшло 70 пацієнтів з ІХС на тлі ожиріння, до ІІ – 35 пацієнтів з ізольованою ІХС, контрольну (ІІІ) групу склали 25 здорових людей без серцево-судинних захворювань. Серед хворих І групи переважали пацієнти з І-м ступенем ожиріння (26 осіб, або 37,1 %). Також серед них було 24 (34,3 %) пацієнти з ІІ-м ступенем ожиріння та 20 (28,6 %) – з ІІІ-м ступенем ожиріння. Метою дослідження було вивчення динаміки рівнів FGF-21 та VEGFa в осіб із ІХС та ожирінням на фоні терапії. Під час дослідження дотримано стандартних етичних вимог до подібних досліджень, що підтверджено висновком комісії з біоетики Харківського національного медичного університету. За результатами дослідження було констатовано відновлення рівнів FGF21 і VEGFA після лікування. Динаміка зниження рівнів FGF21 і VEGFA після лікування була кращою у пацієнтів І групи (було зафіксоване зниження рівнів FGF21 на 23,6 пг/мл, VEGFA – на 11,1 пг/мл, $p<0,001$) у той час як зниження рівнів FGF21 ІІ групі відбулося на 10,5 пг/мл ($p=0,001$), а VEGFA –

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на 2,2 пг/мл (p=0,154). За рівнями ожиріння краща динаміка відновлення FGF21 після лікування була при I-му (зниження на 29,1 пг/мл; p=0,004) та II-му (на 55,7 пг/мл; p<0,001) ступенях ожиріння. У той же час при III-му рівні було зафіксовано вірогідне збільшення FGF21 на 22,5 пг/мл (p<0,001). Краща динаміка відновлення рівнів VEGFA після лікування була при III-му ступені ожиріння порівняно з II-м та I-м ступенями (зниження показника відбулося на 13,8 пг/мл, 9,8 пг/мл та на 10,2 пг/мл відповідно; p<0,001). Таким чином, застосоване лікування хворих із ІХС на фоні ожиріння визначило його ефективність за відновленням рівнів FGF21 і VEGFA після лікування.

Ключові слова: *коморбідність ішемічної хвороби серця та ожиріння, ізольована ішемічна хвороба серця, батокіни, FGF21, VEGFA.*

Надійшла до редакції 17.07.2023

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