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ORIGINAL ARTICLES

ORIGINAL ARTICLE

PREDICTION OF THE RISKS OF THE DEVELOPMENT OF COMORBIDITY OF CORONARY HEART DISEASE AND OBESITY IN THE BACKGROUND OF MILITARY ACTIONS

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Olga V. Gridneva, Pavlo G. Kravchun, Natalia G. Ryndina, Olga I. Kadykova
KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

The aim: Study of prognostic possibilities of batokine complexes (fibroblast growth factor (FGF-21) and vascular endothelial growth factor A (VEGF-A)) in determining the risks of developing coronary heart disease (CHD) and obesity (especially in case of their comorbidity).

Materials and methods: 105 patients aged 25–85 were examined: 70 (main group) –with CHD on the background of obesity and 35 – with isolated CHD (comparison group).

Results: Probable associations with increased risks of comorbidity of CHD and obesity were: increased systolic blood pressure (SBP) (OR = 0.844 [95.0% CI 0.735–0.970], $p = 0.017$), FGF-21 (OR = 1.701 [95.0 % CI 1.219–2.375], $p = 0.002$), VEGF-A (OR = 1.725 [95.0% CI 1.213–2.372], $p = 0.005$), low-density lipoprotein (LDL) (OR = 4.419 [95.0% CI 1.351–14.469], $p = 0.014$). Probable associations were also established for lesions of the left anterior descending artery (LADA) (OR = 1.117 [95.0% CI 0.987–1.263], $p = 0.078$), intermediate branch of the left coronary artery (IBLCA) (OR = 1.336 [95.0% CI 1.099–1.624], $p = 0.004$).

Conclusions: The values of the characteristics of batokine metabolism (FGF-21 and VEGF-A levels) can be used as a significant predictor of the development of obesity in CHD. Increased levels of FGF-21 and VEGF-A in blood serum characterize a significant relationship with the development of such comorbidity, which indicates a significant influence of batokine complexes on the pathogenesis of comorbidity of CHD and obesity.

KEY WORDS: coronary heart disease, obesity, FGF-21, VEGF-A, comorbidity

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INTRODUCTION

Recently, the development of a real epidemic of chronic non-communicable diseases (NCDs) [1] has been determined, which is provoked by the significant prevalence of an unhealthy lifestyle, low physical activity, abuse of alcohol and alcohol-containing substances, significant spread of tobacco smoking, unhealthy diet etc. [2]. Among all NCDs, cardiovascular diseases (CVD) [3, 4], which cause more than 70% of all global deaths, are the leading cause of death in the population [5]. It is precisely because of CVD, according to many scientists, that NCDs are considered threatening and epidemic, because CVD have a significant prevalence and provoke the maximum number of cases of disability and mortality [6, 7].

Thus, conducted studies [8] indicate that CVDs are the cause of more than 17.5 million global deaths annually, causing 17.8 million such cases in 2017 [9, 10], and in 2019 – more than 6,2 million [9]. In Ukraine, mortality due to CVD also occupies the first positions, causing more than 67.0% of all deaths which is 801.6 cases per 100,000 population [11].

Moreover, among all CVDs, the first place in terms of prevalence and causes of death is coronary heart disease (CHD), especially against the background of hyperlipidemia and obesity [3, 4].

The development of CVDs (primarily CHD) is significantly influenced by such negative risk factors as depression and obesity, the occurrence and development of which are associated with the effect of significant psychophysiological and psychoemotional overloads, which are widespread both among the entire world community and in Ukraine (especially in the conditions of today's active hostilities in our country) [12] and provoke a significant number of NCDs [13], among which CVD (most often CHD) and obesity are noted. At the same time, conducted global studies also determined that more than 23% of participants in active military operations experience the impact of over-normal psycho-traumatic overloads [14] (which is quite relevant for our country), because of which there are high risks of the occurrence and development of depression and obesity [15].

At the same time, early diagnosis, and the possibility of predicting the risks of developing CVD (primarily

coronary heart disease) both in the case of monohypertension and against the background of obesity (especially taking into account the increased risks of the development of cardiogenic pathology against the background of active hostilities in Ukraine) become a rather urgent issue. To determine this question, leading scientists are studying the prognostic possibilities of inflammatory mediators, which are produced against the background of pathogenetic changes observed in the background of coronary artery disease and obesity. Among these substances, batokine complexes are of primary importance: fibroblast growth factor (FGF-21) and vascular endothelial growth factor A (VEGF-A), which are mediators of metabolic disorders observed in CHD and obesity (especially in their comorbidity) and have a good cardioprotective effect (due to a reduction in the manifestations of oxidative stress) [16, 17].

Therefore, the study of the prognostic capabilities of batokine complexes (FGF-21 and VEGF-A) in determining the risks of developing CHD and obesity (especially in the case of their comorbidity) is a very relevant and significant problem (primarily in view of the increased risks of the occurrence and development of these diseases against the background of conducting active combat actions in Ukraine), the solution of which requires close attention of researchers and scientists.

THE AIM

The purpose of our study was to study the prognostic capabilities of batokine complexes (FGF-21 and VEGF-A) in determining the risks of developing CHD and obesity (especially in case of their comorbidity).

MATERIALS AND METHODS

We enrolled 105 patients aged 25-85, who were divided into 2 study groups: 70 patients (main group) with CHD on the background of obesity and 35 respondents with isolated coronary artery disease (comparison group). In the main ($n = 70$) group, the average age was 63.6 ± 8.8 years, most of them (72.9 %) were female compared to respondents (27.1 %) who were male; and in the comparison group, the average age was 69.7 ± 7.9 years and, on the contrary, the majority (68.6 %) were men compared to women (31.4 %).

The diagnosis of CHD was established according to current guidelines [18, 19]. The diagnosis of obesity was determined according to the recommendations EASO (2017) [20] and NIH (2000) [21].

Inclusion criteria: age ≥18 years, presence of comorbid CHD and obesity (main group) and isolated CHD (comparison group), consent to participate in the study. Exclusion criteria: age < 18 years, absence of comorbid CHD and obesity (main group) and isolated CHD (comparison group), diffuse and focal diseases, endocrine pathology, allergic reactions, systemic diseases of connective tissue, acute and chronic diseases of internal organs (except CHD and obesity), severe decompensated somatic pathology, mental and oncological diseases, acute cardiovascular disorder, acute and significant decompensation of carbohydrate metabolism, unsatisfactory physical condition, pregnancy and breastfeeding, chronic alcoholism, refusal to participate in the study.

All patients underwent measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP), characteristics of lipid and batokine metabolism. We performed coronary angiography in all the patients to determine the stenosis of the main coronary arteries.

We considered a coronary lesion to be significant in case of stenosis of ≥50%. Among the enrolled patients, significant left anterior descending artery (LADA) (of the left coronary artery [LCA]) lesions were detected in 51 (48,6 %) patients, intermediate branch of LCA (IBLCA) – 12 (11,4 %), right coronary artery (RCA) – 16 (15,2 %), and circumflex artery – in 1 (1,0 %) case. There were no cases of left main disease among the enrolled patients.

Medical-statistical calculation: We calculated the mean value and standard deviation (M ± SD) for continuous variables. Differences between unrelated samples were calculated using Mann-Whitney U-test. Categorical variables were presented in absolute and percent values (with 95 % confidence interval [CI]). Pearson's Chi-squared test was used to assess differences between groups.

Associations of the obtained indicators with the binomial dependent variable were determined using multiple logistic regression analysis with the calculation of standardized β coefficients (odds ratio (OR); and their 95.0% CI). The quality of the obtained models was carried out by calculating the Nagelkerke R^2. For the final model, a multiple binomial regression equation was made to calculate the percentage probability of the desired event. In the regression analysis, we used univariate and multivariate analysis, enter and Backward Wald exclusion of variables in the mathematical model to obtain the most likely independent predictors.

Coding of groups in regression models was as follows: isolated CHD (comparison group) – reference group; comorbid CHD and obesity (main group) – comparison group.

Significance level (p) in the study was taken as lower than 0.05. Statistical calculations were performed in IBM SPSS 25.0 (trial version) for Windows.

Table I. Characteristics of SBP and DBP in patients with CHD and obesity, M ± SD

Characteristics of SBP and DBP	Research groups		p
	main (n = 70)	comparison (n = 35)	
SBP, mm Hg	156.9 ± 14.7	158.0 ± 16.4	0,801
DBP, mm Hg	91.7 ± 7.8	89.3 ± 9.1	0,167

Table II. Characteristics of batokin levels, M ± SD

Batokin levels	Research groups		p
	main (n = 70)	comparison (n = 35)	
FGF-21, pg/ml	241.1 ± 27.1	209.0 ± 13.8	< 0,001
VEGF-A, pg/ml	222.9 ± 7.3	206.0 ± 8.3	< 0,001

Table III. Significant coronary lesions, N (% [95 % CI])

Parameters	Research groups		p
	main (n = 70)	comparison (n = 35)	
LADA lesions	41 (59 [47-70])	10 (29 [15-45])	0,004
IBLCA lesions	12 (17 [9-27])	0 [0-5]	0,009
RCA lesions	16 (23 [14-34])	0 [0-5]	0,002

Table IV. Lipid profile characteristics, M ± SD

Lipid profile characteristics	Research groups		p
	main (n = 70)	comparison (n = 35)	
HDL, mmol/l	1,53 ± 0,29	1,36 ± 0,32	0,009
TG, mmol/l	2,00 ± 1,00	1,53 ± 0,81	0,010
LDL, mmol/l	3,37 ± 1,15	2,57 ± 1,35	< 0,001
VLDL, mmol/l	0,90 ± 0,45	0,70 ± 0,37	0,017
AC, c.u.	2,87 ± 0,83	2,42 ± 0,95	0,008

Table V. Associations of batokine complexes with comorbidity of CHD and obesity

Batokine complexes	Univariate analysis		Multivariate analysis	
	OR (95,0 % CI)	p	OR (95,0 % CI)	p
FGF-21	1,317 (1,182–1,468)	< 0,001	1,265 (1,132–1,414)	< 0,001
VEGF-A	1,095 (1,056–1,136)	< 0,001	1,080 (1,028–1,135)	0,002

Table VI. Associations of significant clinical-laboratory and clinical-instrumental characteristics with comorbidity of CHD and obesity

Reliable characteristics	B-coefficient	OR (95,0 % CI)	p
SBP*	–0,169	0,844 (0,735–0,970)	0,017
FGF-21**	0,531	1,701 (1,219–2,375)	0,002
VEGF-A***	0,542	1,725 (1,213–2,372)	0,005
LADA#	0,111	1,117 (0,987–1,263)	0,078
IBLCA##	0,290	1,336 (1,099–1,624)	0,004
LDL###	1,486	4,419 (1,351–14,469)	0,014

Notes: * – the range: 130-180 mm Hg (n=105); ** – the range: 205.37-241.29 pg/ml (n=105); *** – the range: 199.16-289.08 pg/ml (n=105); # – the range: 20-70 % (n=105); ## – the range: 10-60 % (n=105); ### – the range: 1.17-6.81 mmol/l (n=105)

RESULTS

The characteristics of SBP and DBP in patients with CHD and obesity were analyzed – Table I. There were no statistically significant differences in the levels of SBP and DBP in patients with CHD and obesity. – Table I.

The levels of batokines (FGF-21 and VEGF-A) significantly exceeded the normative values for CHD both in

the main (respectively 241.1 ± 27.1 and 222.9 ± 7.3 pg/ml) and in the comparison group (respectively 209,0 ± 13.8 and 206.0 ± 8.3 pg/ml). In CHD with obesity, the levels of both batokines were probably ($p < 0.001$) higher than the indicators of patients with isolated CHD – Table II.

The group of CHD and obesity was characterized by the higher frequency of significant LADA, IBLCA and RCA lesions, as compared to CHD alone (Table III).

The peculiarities of the lipid profile in CHD and obesity were determined: the levels of high-density lipoproteins (HDL) were within the normative limits, but significantly ($p = 0.009$) prevailed in CHD and obesity compared to isolated CHD (respectively, 1.53 ± 0.29 and 1.36 ± 0.32 mmol/l); the levels of triglycerides (TG) probably ($p = 0.010$) exceeded the normative values in the main group significantly outweighing the indicators of the comparison group (2.00 ± 1.00 and 1.53 ± 0.81 mmol/l, respectively); the levels of low-density lipoprotein (LDL) in all groups were within the normative limits, probably ($p < 0.001$) prevailing among the subjects of the main group compared to the comparison group (3.37 ± 1.15 and 2.57 ± 1.35 mmol/l, respectively), as well as the levels of very low-density lipoproteins (VLDL) (respectively 0.90 ± 0.45 and 0.70 ± 0.37 mmol/l; $p = 0.017$) and the atherogenic coefficient (AC) (respectively, 2.87 ± 0.83 and 2.42 ± 0.95 c.u.; $p = 0.008$) – Table IV.

Determination of associations of batokine levels with the comorbidity of CHD and obesity by both univariate and multivariate logistic regression analysis established significant predictive effects on the development of the combined course of CHD and obesity as an increase in FGF-21 indicators (respectively OR = 1.317 [95.0% CI 1.182– 1.468]; $p < 0.001$ and OR = 1.265 [95.0% CI 1.132–1.414]; $p < 0.001$) and VEGF-A (respectively OR = 1.095 [95.0% CI 1.056–1.136]; $p < 0.001$ and OR = 1.080 [95.0% CI 1.028–1.135]; $p = 0.002$).

In this way, significantly increased chances for the development of comorbid development of CHD and obesity were determined, both by univariate and multivariate analysis, when the levels of FGF-21 increased above the normative indicators (the corresponding increase in the chances by 1.317 and 1.265 times) and VEGF-A (respectively by 1.095 and in 1.080 times) – Table V.

When adding other clinical-laboratory and clinical-instrumental indicators (for which their probable associations with the comorbidity of CHD and obesity were previously obtained) according to multivariate analysis, the final result was determined the influence of all significant characteristics (SBP), lesions of the LADA and the IBLCA and LDL levels) of examined patients with the significant development of comorbidity of coronary artery disease and obesity – Table VI.

Significant associations with increased risks of comorbidity of CHD and obesity were: increased SBP (OR = 0.844 [95.0% CI 0.735–0.970]; $p = 0.017$), FGF-21 (OR = 1.701 [95.0% CI 1.219–2.375]; $p = 0.002$), VEGF-A (OR = 1.725 [95.0% CI 1.213–2.372]; $p = 0.005$) and LDL (OR = 4.419 [95.0% CI 1.351–14.469]; $p = 0.014$). Probable associations were also established for lesions of the LADA (OR = 1.117 [95.0% CI 0.987–1.263]; $p = 0.078$) and IBLCA (OR = 1.336 [95.0% CI 1.099–1.624]; $p = 0.004$). These results indicate a decrease in the odds (by 15.6%) of developing comorbidity of IBLCA and obesity when SBP levels increase above the normal values. Also, an increase in such chances was determined when the levels of FGF-21 (1.701-fold increased odds), VEGF-A (1.725-fold increased odds) and LDL (4.419-fold increased odds) increased above the norm. Increased chances of comorbidity of CHD and obesity with a lesion of 1.0% of LADA (1.117–fold increase in chances) and IBLCA (1.336-fold increase in chances) were also determined – Table VI.

DISCUSSION

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. Thus, Zheng X. [22] evaluated the relationships between FGF-21 and the development of negative clinical outcomes (combination of death or severe disability (on the modified Rankin scale ≥ 3) within 1 year after a stroke) in 3412 patients from China with acute ischemic stroke. They established the development of negative clinical consequences in 745 (21.83%) patients (550 developed severe disability and 195 died). After multivariate adjustment, a higher level of FGF-21 in the plasma of patients was highly associated with an increased risk of negative clinical outcomes (OR = 1.52; 95.0% CI 1.11–1.29). At the same time, each 1-SD increase in the logarithmic transformation of FGF-21 (by 0.67 pg/ml) had a probable association with 19.0%; 3.0% and 33.0% increased risks of overall negative clinical outcomes, severe disability and death, respectively. Adding FGF-21 to other risk factors significantly improved the prediction of adverse clinical outcomes in patients with ischemic stroke (net reclassification index = 10.8%; $p = 0.011$; integrated improvement in discrimination = 0.3%; $p = 0.038$).

At the same time, Lee C.H. [23] determined the possibility of predicting the development of CHD using serum FGF-21 in 3528 Chinese patients with type 2 diabetes mellitus (determining increased risks of developing obesity) and CHD. They determined that

serum FGF-21 levels are an independent predictor of CHD and can be used as a biomarker to identify an increased risk of CHD.

They established that, baseline serum log-transformed FGF-21 levels were significantly higher in CHD than those who did not CHD (222.7 pg/mL [92.8–438.4] versus 151.1 pg/mL [75.6–274.6]; $p < 0.001$). On multivariable Cox regression analysis, baseline serum FGF-21 levels, independently predicted incident CHD (hazard ratio = 1.55; 95,0 % CI 1.10–2.19; $p = 0.013$).

In turn, Palmer B.R. [24], found that determination of serum VEGF-A levels has value as a prognostic biomarker in patients with CHD; and Hrovat K. et al. [25] in the study of patients with coronary artery disease noted the importance of determining VEGF-A in CHD.

CONCLUSIONS

Based on the research, it was determined that the values of the characteristics of batokine metabolism (FGF-21 and VEGF-A levels) can be used as a significant predictor of the development of obesity in CHD. Increased levels of FGF-21 and VEGF-A in blood serum characterize a significant relationship with the development of such comorbidity, which indicates a significant influence of batokine complexes on the pathogenesis of comorbidity of CHD and obesity. In addition, the results indicate a direct relationship between the pathogenesis of the comorbidity of CHD and obesity with SBP values, LDL levels, and lesions of LDL and PGLC damage, which should be taken into account to ensure therapeutic and preventive measures.

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ORCID and contributionship:

Olga V. Gridneva: 0000-0002-9197-4956 [A, B, D-F]
Pavlo G. Kravchun: 0000-0002-8285-6763 [D- F]
Natalia G. Ryndina: 0000-0002-4543-8343 [D, E]
Olga I. Kadykova: 0000-0002-0108-0597 [D, E]

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Olga V. Gridneva
Kharkiv National Medical University.
41 Pushkinska st., 61022 Kharkiv, Ukraine
tel: +380632858556
e-mail: gridneva_o.v.5@gmail.com

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A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article