

CLINICAL CHARACTERISTICS OF MEN AND WOMEN IN YOUNG AND MIDDLE AGE WITH ARTERIAL HYPERTENSION AT DIFFERENT GALECTIN-3 PLASMA LEVELS ACCORDING TO THE RESULT OF LINEAR REGRESSION ANALYSIS

Valeriy Ivanov

Department of Internal Medicine No. 3¹

Tetiana Onyshchuk

Department of Therapeutic Disciplines and Family Medicine¹

vra4ixa@ukr.net

¹National Pirogov Memorial Medical University

56 Pirogova str., Vinnytsya, Ukraine, 21018

Abstract

The aim of the research was to describe the clinical characters of male and female patients with stage II arterial hypertension (AH) of young and middle age with different gradations of galectin-3 plasma levels according to multiple linear stepwise regression analysis.

Materials and methods: 160 patients with AH of different sex (male and female) and age (young (18–44 years), middle (45–60 years)) were examined (clinical, laboratory and instrumental). Multiple linear regression was used to determine the clinical presentation of patients with AH at different levels of the neurohormone (StatSoft's Statistica MultipleRegression v. 10.0 module). which were divided into groups that vi told for the entirely different patient characteristics. multiple linear regression was performed for each indicator separately and the results have been shaped in the form of regression equations.

Results. Patients with young and middle-aged AH have been found to be relatively high (RH) levels of galectin-3 associated with: the presence of a complex of metabolic risk factors – obesity and dyslipidemia; in combination with multiple features of structural and functional changes in the cardiovascular system, such as the presence of concentric left ventricular (LV) hypertrophy in combination with myocardial relaxation disorders ($E/e' \text{ aver} > 7.2$) and signs of hemodynamic overload of the left atrium (LA) (LA volume index (LAVi) $> 34 \text{ ml/m}^2$); the presence of valve dysfunctions in the form of mitral (1–2 degree) and aortic regurgitation (1 stage); the presence of structural remodeling of the carotid arteries (intima-media thickness (IMT) $> 0.91 \text{ mm}$). Plasma abdominal obesity was the most informative marker of RH galectin-3 in plasma, $\text{IMT} > 0.91 \text{ mm}$ and $\text{LAVi} > 34 \text{ ml/m}^2$.

Conclusions. The association of plasma galectin-3 levels with various clinical and instrumental indicators indicates a certain effect of the neurohormone on the course of AH in young and middle-aged male and female patients. Of indisputable interest is the determination of the features of the course of AH and the clinical profile of patients at different gradations (relatively low (RL), relatively moderate (RM) and relatively high (RH) galectin-3 plasma level.

Keywords: hypertension, galectin-3, aldosterone, obesity, dyslipidemia.

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1. Introduction

Arterial hypertension (AH) is the dominant disease among all cardiovascular diseases (CVD), due to its high prevalence, morbidity and disability, which causes its cardiovascular complications [1, 2]. Our present day is marked by a number of works devoted to the search for new biomarkers that participate in the pathogenesis of AH and which affect the course of the disease in male and female patients, young and middle-aged [3, 4]. It is galectin-3, a protein in the galectin group that is expressed by many cells, such as neutrophils, macrophages, labrocytes, fibroblasts and osteoclasts, and is involved in many biological processes such as cell growth and proliferation, apoptosis, endogenous inflammation, myocardial fibrosis and others [5, 6]. A considerable amount of experimental work indicates that galectin-3 expression is closely associated with myocardial fibrosis [7, 8] and type I collagen accumulation, and an increased level of factor is usually associated with progressive myocardial dysfunction [9, 10]. To this end, the study concerned the determination

of the features of AH and the clinical profile of patients with different levels of galectin-3, what is possible in the future will allow the selection of neurohumoral variants of AH and, accordingly, how pharmacologically influence to one or another neurohumoral variant.

2. Materials and methods

To determine the clinical profile of patients with different levels of galectin-3, we have applied multiple linear regression (“Multiple Regression” module of StatSoft package “Statistica” v. 10.0). When performing the analysis to select the most informative indicators, a “*Forward-sterwise*” procedure was used to turn on the features step by step.

The plasma level of galectin-3 in pg/ml was taken as the initial parameter of the analysis, and analysis was performed using a statistical matrix that included 160 patients with AH young and middle age from 19 to 60 years (mean 44.5 ± 0.9 , median – 46 and interquartile range – 37 and 55). Patients were in the day patient department of the Khmelnytsky Regional Cardiac Dispensary (KRCD) for the period 2016–2018, in accordance with the main provisions of the World Health Association Declaration of Ethics for Human Medical Research (2000) and the MOH Order No. 281 from 11/01/2000. The study protocol was approved by the Biomedical Ethics Commission of National Pirogov Memorial Medical University (excerpt from protocol No. 4 of 26.04.2016). All patients signed informed consent to participate in the study. The subjects included in the study, namely 160 patients with stage II AH were divided into four groups depending on age: male and female patients of young age (18–44 years) and male and female patients of middle age (45–60 years) (40 people in each group).

The criteria for inclusion in the study were:

- 1) verified according to existing AH stage II recommendations (ESH and ESC, 2013) [11, 12];
- 2) lack of continuous antihypertensive treatment;
- 3) the age of patients from 18 to 60 years;
- 4) the patient’s informed consent to participate in the study.

The following were considered as exclusion criteria for the study:

- 1) AH I or III stage according to existing recommendations (2013);
- 2) symptomatic arterial hypertension (AH);
- 3) the presence of continuous antihypertensive treatment;
- 4) age under 18 and over 60;
- 5) diseases of the endocrine system (diabetes, pathology of the thyroid gland and others);
- 6) concomitant diseases of the respiratory system, gastrointestinal tract and kidneys, which are accompanied by disorders of organ function and require active treatment;
- 7) alcohol abuse and severe neuro-psychiatric disorders.

Laboratory diagnostic methods included determination of blood lipid spectrum. Indicators of lipid metabolism were considered total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL) in serum, which was evaluated by the colorimetric photometric method in mmol / L. Each patient was informed about the rules of blood delivery to a lipid profile (refusal of alcohol for 24 hours, and for 30 minutes refusal of smoking, psycho-emotional and physical exertion). The presence of dyslipidemia was assessed in the case of TC level >5 mmol/l or/and, LDL >3 mmol/l or/and HDL <1.0 mmol/l in men and <1.2 mmol/l in women or/and TG >1.7 mmol/l. The presence of abdominal obesity was ascertained in the case of BMI >30 kg/m², aldosterone level by enzyme immunoassay (ELISA) by ELISA using IBL International GmbH (Canada). The reference values were the level of aldosterone 40–160 pg/ml and galectin-3 in the serum.

Blood sampling for the determination of galectin-3 level was performed on an empty stomach in a supine position at 8:30 (after a 20-minute rest) from a cubital vein in an amount of 5 ml EDTA evacuator (1 mg per 1 ml of blood). Whole blood was centrifuged for 20 min (at 1600 rpm). The resulting plasma was transferred into Eppendorf-type polypropylene tubes. The material was stored at a temperature of 30 °C for a maximum of 8 months before the study. Hemolyzed sera were not included in the study. Plasma levels of galectin-3 in serum were determined using the enzyme-linked immunosorbent assay (ELISA) using the Human Galectin-3 Platinum Elisa reagent kit (BenderMedSystems GmbH, Austria).

134 clinical, laboratory and instrumental indicators were analyzed as variables (influential factors). The latter were deliberately divided into different groups responsible for fundamentally different patient characteristics. Multiple regression analysis was performed separately for each selected group of factors, the final results were presented in the form of linear regression equations, which showed the most powerful regression relationship between the analyzed parameters and the output parameter.

The informativeness of the obtained regression equation was estimated by the coefficient of determination (R^2), which demonstrated the strength of the relationship between the equation variables and the output parameter; the nature of its significance is Fisher's actual and proper F (F) criterion and significance level (p), the standard error of communication – St. Error of estimate. In the presence of two or more variables in the regression equation, the influence of each variable on the output parameter (neurohormone level) in percent (%) was calculated, which was calculated as the ratio of the beta coefficient of the variable to the sum of the beta coefficients of all variables of the equation.

In addition, a critical level was determined for the quantitative variables – the median of the parameter value calculated for the galectin level is 1.1 and 2.4 pg / ml, which reflect the upper bound of the relatively low (RL) and the lower bound of the relatively high (RH) level of neurohormones in plasma in accordance.

3. Results

The data in **Table 1** characterize the indices that showed the strongest regression associations with galectin-3 levels, which in turn are six completely different groups that characterized:

- 1) duration of hypertensive history in years – (factor A);
- 2) the neurohumoral background of the subjects (plasma aldosterone level in pg/ml – factor X);
- 3) prevailing risk factors (presence of abdominal obesity in points – factor Y and atherogenic dyslipidemia in points - factor D);
- 4) structural and functional state of the myocardium (presence of concentric myocardial hypertrophy in points – factor K, LAVi in ml/m² – factor Z and E/e' aver – factor W);
- 5) functional status of the valvular apparatus of the heart (presence and nature of mitral regurgitation in points – factor MR and aortic regurgitation in points – factor AR);
- 6) structural condition of the carotid arteries (carotid IMT value in mm – factor T).

The analysis of the coefficients of determination (R^2) of the obtained regression equations showed that they obtained the highest values for risk factors (factors Y+D, $R^2=0.63$) and the level of aldosterone in plasma (factor X, $R^2=0.62$) and the smallest for the duration of the hypertensive history (factor A, $R^2=0.19$) and the functional state of the heart valve apparatus (factors MR+AR, $R^2=0.20$). Therefore, the obtained data suggested that in patients with young and middle-aged AH, plasma galectin-3 levels are most closely associated with aldosterone levels and the presence of risk factors such as abdominal obesity and atherogenic dyslipidemia. It is possible to exclude the fact that these factors may determine the peculiarities of AH in patients with different levels of galectin-3.

The positive signs of the coefficients of the variables of the regression equations indicated that all the variables had a direct relationship with the level of galectin-3. The latter could indicate that an increase in the magnitude of all variables should be accompanied by an increase in the level of galectin-3 in plasma and, conversely, higher levels of galectin-3 predicted higher values of the variable regression equations. In this case, the dominant effect on the baseline parameter was abdominal obesity (the effect on the baseline parameter was 85 % versus 15 % for dyslipidemia, respectively); presence of structural-geometric remodeling of the left ventricle (LV) in the form of the most problematic model – concentric LV hypertrophy in combination with myocardial relaxation disorders (E/e' aver > 7.2) and signs of hemodynamic LA overload ($LAVi > 34$ ml/m²). The latter factor had the greatest impact on the output parameter compared to the others (the impact strength was 65 % versus 19 % and 16 %, respectively); the presence of valve dysfunctions in the form of mitral (1–2 stage) and aortic regurgitation (1 stage), whereby aortic regurgitation had the highest influence on the initial parameter (62 % vs. 38 % respectively); the presence of structural remodeling of the carotid arteries, characterized by an $IMT > 0.91$ mm.

Table 1

Significant regression relationships of galectin-3 in plasma with different indices (results of multifactorial linear stepwise regression)

Metric groups	The nature of the regression association with galectin levels	The informativeness of the regression equation	Critical value	
			For relatively low (RL) levels of galectin	For relatively high (RG) levels of galectin
1. (A) AH duration, years	=1.51+0.25A	R ² =0.19; F (1.16)=10.30 p=0.002 St. Error = 1.24	A<2	A>4
2. (X) The level of aldosterone, pg/ml	=0.61+0.006X	R ² =0.62; F (1.19)=108.58 p<0.00000 St. Error = 0.85	X<185	X>298
3. (Y) Abdominal obesity, in points (1 point – yes and 0 – absent)	=1.44+1.64Y+0.16D	R ² =0.63; F (1.16)=100.87 p<0.00000 St. Error=0.90	Y=0 Body mass index (IBMI) <30 kg/m ²	Y=1 IMT≥30 kg/m ²
(D) Dyslipidemia, in points (1 point – yes and 0 – absent)	The force of influence of the factor Y – 85 % and D – 15 %		D=0 Cholesterol <5 mmol/l and LLD<3 mmol/l and TGs<1.7 mmol/l	D=1 Cholesterol ≥5 mmol/l or LLD≥3 mmol/l or TGs≥1.7 mmol/l
4. (K) Concentric hypertrophy in points (1 point – yes and 0 – absent)	=0.11+0.09Z+0.11K+0.08W	R ² =0.34; F (3.16)=16.73 p=0.00002 St. Error=1.09	K=0 Left ventricular mass index (LVMI) <115 (95) g/m ² or RTM≤0.42	K=1 IMT≥115 (95) g/m ² and relative thickness of the myocardium (RTM)>0.42
(Z) LA volume index (LAVi), ml/m ²	The force of influence of the factor Z – 65 %.		Z<31	Z>34
(W) E/e' aver	K – 19 % and W – 16 %		W<6.6	W>7.2
5. (MR) The presence of mitral regurgitation (MR) in points (1 point – 1, 2 points – 2 stage and 0 – absent)	=1.98+0.08 MR+0.3AR	R ² =0.20; F (2.16)=8.21 p=0.006 St. Error=1.12	MR=2	MR=0
(AR) The presence of aortic regurgitation in points (1 point – yes and 0 – absent)	The force of influence of the factor MR – 38 % and AR – 62 %		AR=1	AR=0
6. (T) Intima-media thickness (T), mm	=1.98+0.52 T	R ² =0.36; F (2.14)=24.13 p<0.0000 St. Error = 0.93	T<0.88	T>0.91

Note: RL – relatively low and RH – relatively high level

Taking into account the preliminary data on the magnitude of the determination coefficients for the various groups of factors, it should be assumed that plasma galectin-3 level >2.4 pg/ml, were associated, from a clinical point of view, with the presence of metabolic risk factors (primarily, abdominal obesity), and with pathophysiological – hyperactivation of renin-angiotensin-aldosterone system (RAAS), which was confirmed by an increase in aldosterone level >298 pg/ml in the blood plasma of patients with stage II AH.

From the clinical implications, the level of galectin-3 >2.4 pg/ml in plasma will be characterized by a more pronounced and more severe structural remodeling of the cardiovascular system compared to the general population of patients with young and middle-aged AH, namely the presence of concentric hypertrophy with impaired hypertrophy myocardium and more severe hemodynamic atrial overload; more severe structural remodeling of the carotid arteries and development

of mitral and aortic regurgitation. The latter clearly demonstrates a more severe course of AH in patients with galectin-3 >2.4 pg/ml in plasma. It is observed that the most informative instrumental marker of RH of galectin-3 levels in patients with young and middle-aged AH is $IMT > 0.91$ mm and $LAVi > 34$ ml/. Therefore, in patients with young and middle-aged AH, plasma galectin-3 levels should be considered as a neurohumoral marker, which is associated with the presence of metabolic risk factors (primarily obesity) and more severe structural and functional lesions of the cardiovascular system structural remodeling of vessels and hemodynamic overload of the heart). The latter provides every reason for clinicians to consider these patients as a group with more severe AH who require the most effective cardio and vasoprotection to improve treatment efficacy.

According to the beta coefficients obtained for each variable (reflecting the power of the effect of the variable on the baseline parameter), a scale for the prediction of galectin-3 levels in plasma and, accordingly, the a priori course of AH in young and middle-aged patients was developed. The minimum beta value was taken as 1. All other beta coefficients were divided by the minimum value and the resulting number was rounded to the integer value (**Table 2**).

Table 2

Galectin-3 RH level determination scale in young and middle-aged AH patients

The most informative factors	Points
AH duration >4 years	3
Abdominal obesity	9
Dyslipidemia	2
Plasma aldosterone level >298 pg/ml	10
Concentric hypertrophy of LV	1
$LAVi > 34$ ml/m ²	4
$E/e'_{aver} > 7.2$	1
Aortic regurgitation 1 stage	2
Mitral regurgitation 2 stage	1
Carotid $IMT > 0.91$ mm	6
Total	39

Draws attention that the total number of all scores was 39. The highest scores were given by variables such as aldosterone levels >298 pg/ml in plasma (10 points) and the presence of abdominal obesity (9 points). In turn, a minimum score (1 point) was calculated for such features as concentric LV hypertrophy, $E/e'_{aver} > 7.2$ and 2 stage mitral regurgitation. The latter were uninformative for the diagnosis of plasma galectin-3 RH levels.

4. Discussion

By means of multiple linear regression analysis, the equation for a priori calculation of the level of galectin-3 in plasma was determined according to the points scored according to **Table 2**. Thus, the plasma level of galectin-3 \geq points were scored 0.13 pg/ml ($R^2=0.61$, $p<0.0001$; prediction sensitivity was 63 %, specificity 86 %). A higher specificity indicated that the derived equation more significantly eliminated the RH level of galectin-3 in plasma. According to this equation, it was determined that at least 19 points should be scored for the diagnosis of plasma galectin-3 levels in the plasma.

Undoubtedly, we were interested in predicting the course of AH in young and middle-aged patients, taking into account simple and accessible criteria that general and family practitioners could use. Therefore, the exclusion from the analysis of plasma aldosterone, which resulted in the maximum score (10 points), indicated the need to take into account most of the criteria obtained in clinical and instrumental examination of patients.

It was observed that in patients with abdominal obesity (9 points), in combination with $IMT > 0.91$ mm (6 points) and $LAVi > 34$ ml/m² (4 points), plasma galectin-3 RH should be predict-

ed – (9+6+4)·0.13=19·0.13=2.47 pg/ml. Confirmation of the obtained data is found in the results of multivariate regression analysis, which established that the level of galectin-3 should be associated not only with anatomical changes of LA, age, sex [13, 14], but with IMT [2]. Therefore, the prior plasma galectin-3 level in this case is ≥ 2.47 pg/ml, which corresponds to its RH level. Instead, in the absence of an abdominal obesity patient, a high level of galectin-3 could only be predicted if all other criteria were summed up to 20 points.

Study limitations. When it is impossible to determine the level of aldosterone, the patient's absence of abdominal obesity and $IMT \leq 0.91$ mm or $LAVi \leq 34$ ml/m² or the duration of AH ≤ 4 years, it is unlikely to think about the RH plasma galectin-3 level and a severe AH (total score) will not be 19 points).

Prospects for further researches are that the data obtained for different grades of galectin-3 provide every reason to consider patients with RH galectin-3 as a group with more severe AH and high cardiovascular risk who need the most effective cardio and vasoprotection. The developed risk stratification scales of galectin-3 RH level provide an opportunity to isolate these patients.

5. Conclusions

It was found that in young and middle-aged patients with AH RH galectin-3 levels are associated with: the presence of a complex of metabolic risk factors – obesity and dyslipidemia; in combination with multiple features of structural and functional changes in the cardiovascular system, such as the presence of concentric LV hypertrophy combined with myocardial relaxation disorders ($E/e' \text{ aver} > 7.2$) and signs of hemodynamic LA overload ($LAVi > 34$ ml/m²); the presence of valve dysfunctions in the form of mitral (1–2 stage) and aortic regurgitation (1 stage); the presence of structural remodeling of the carotid arteries ($IMT > 0.91$ mm). The most informative markers of the RH level of galectin-3 in the plasma were the presence of abdominal obesity, $IMT > 0.91$ mm and $LAVi > 34$ ml/m².

Conflict of interests

No conflict of interest.

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POSSIBILITIES OF USING MINIINVASIVE CATHETER TECHNOLOGIES IN THE TREATMENT OF LUNG BLEEDING

Kateryna Ponomarova

Department of Thoraco-Abdominal Surgery

V. T. Zaytsev Institute of General and Emergency Surgery of NAMS of Ukraine

1 Balakireva entry, Kharkiv, Ukraine, 61018

eponkat@gmail.com

Abstract

Aim – improve the results of the treatment of patients with pulmonary bleeding through widespread use of endovascular surgery methods for hemostasis.

Materials and methods. Method of endovascular embolization of bronchial arteries is widely used in our clinic SI «Zaytsev V. T. Institute of General and Emergency surgery of NAMS of Ukraine» not only as independent surgery in patients with LB, but also as way of preparation of patients with lung bleeding for planned thorax surgery. The most of the often spread nosological forms complicated by bleeding in our research were polycystic lung disease, chronic obstructive pulmonary disease, bronchiectasis disease, community-acquired pneumonia. Indications to the catheter embolization procedure of bronchial arteries are the following: conservative treatment failure, hemoptysis in patients with bilateral inflammatory processes who was not prescribed surgical treatment for a range of reasons, absence of gross structural changes, lung resection, mainly in patients with oncologic lung injury, at massive and life-threatening profuse bleedings as a mean of temporary or constant hemostasis. Discussed treatment method is applied only in bleeding or within a 6–12 hour after its treatment. Successful result in embolization can be obtained in 79–99 %.

Results. As a result of complete physical examination of patients with LB, it has been established that lung hemorrhage was the result of obstructive bronchitis in 14 patients (42 %), there was chronic obstructive pulmonary disease in 7 (21 %) patients and bronchiectasis was diagnosed in 6 (18 %) patients. In 2 (6 %) patients pulmonary hemorrhage was caused by community-acquired pneumonia. Central lung cancer was detected in 4 (12 %) patients.

Conclusion. Therefore bronchial artery angiography gives high efficiency in solving the problem of hemostasis in oncological and nonspecific lung diseases, for determination of localization and source of bleeding. Endovascular occlusion of bronchial arteries in pulmonary hemorrhage permits:

- to elaborate diagnosis because of the presence of specific angiographic signs of malignant tumour;
- to perform effective endovascular hemostasis;
- to gain time for stabilization the patient with the aim of planned surgical treatment.

Keywords: embolization of bronchial arteries, hemostasis, pulmonary bleeding, catheter technologies.

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