

ENDOTHELIN-1 VALUE IN CARDIOVASCULAR COMPLICATIONS DEVELOPMENT FORECASTING IN PATIENTS WITH DIABETES MELITUS TYPE 2 AND CORONARY ARTERY DISEASE*

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Chronic heart failure (CHF) is an essential medico-social problem in the world, and in Ukraine. According to national researches in European countries, the CHF prevalence among adult population is 1–5% and it grows proportionally to age. Especially high is the CHF prevalence among elderly people. Increase of elderly people share is considered one of the main reasons of CHF high prevalence in economically developed countries [1–4].

Frequent reasons of CHF are coronary artery disease and hypertension. The relative risk of heart failure development against the background of diabetes melitus 2 type (DM) exceeds the risk of CHF emergence at hypertension, obesity. [5].

The influence of DM type 2 on development and forecast of CHF is caused by a number of mechanisms which are closely connected

among themselves. Firstly, it is group of cardiovascular risk factors entering insulinresistance syndrome: dyslipidaemia, hypertension, obesity and inflammation [6].

Secondly, DM contributes to the coronary atherosclerosis development and realizes CHF negative impact for progressing of coronary artery disease. Thirdly, DM type 2 types contributes development of heart failure because of existence of a specific cardiomyopathy [7].

At heart failure increase in endothelin-1 level in peripheral blood is noted [8]. Concentration of immunoreactive endothelin-1 is considerably increased in patients with hypertension of the II-III stage [9, 10].

It is known that endothelin-1 in many respects defines the endothelium dysfunctions, which is the trigger in pathogenesis of cardiovascular pathology (atherosclerosis, hypertension,

* The research was carried out as part of investigation work at the Department of Internal Medicine № 2, Clinical Immunology and Allergology at Kharkiv National Medical University «Ішемічна хвороба серця за умов поліморбідності: патогенетичні аспекти розвитку, перебігу, діагностики й удосконалення лікування», (State registration number 0118U000929).

Institution, which financed the research: 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 16.01.2019.

thrombogenesis), and considerably advances emergence of clinical symptoms of a disease [11].

The constant hyperglycemia strengthens the vascular diseases connected with diabetes melitus and CHF. In high concentrations glucose has direct toxic effect on endothelial cells of vessels [12].

Further studying of pharmacological correction opportunities of endothelin-1 system can become a basis for new therapeutic approaches

MATERIALS AND METHODS

98 patients with CHF of functional class I–III, being on treatment in cardiological department of the twenty seventh Kharkiv city clinical hospital, have been examined. Among examined patients there were 41 (41,8%) men and 57 (58,2%) women. Middle age was $63,7 \pm 1,0$ years. Clinical signs of heart failure in NYHA I functional class was observed in 22 (22%) patients, functional class II in 56 patients (57%), functional class III in 20 (21%) patients with stage III HF. All patients were divided into 2 groups: 1 — patients with CHF and DM type 2 (n = 68), 2 — patients with CHF without DM type 2 (n = 30).

The control group (14 men, 6 women, middle age was $46,9 \pm 1,8$ years) was made by almost healthy people who haven't CHF signs. Patients were matched for gender and age.

All patients received basic therapy according to the standards for the treatment of chronic heart failure and type 2 diabetes, as well as the recommendations of the European Society of Cardiology. All drugs were prescribed to patients after blood sampling for the study. Analyzing the dynamics of clinical manifestations, biochemical and instrumental indicators, they monitored the efficiency of the therapy.

According to the Helsinki Declaration, all patients were informed about the clinical trial and agreed to determine investigated levels: Endothelin-1, nitrite of sodium, sodium nitrate, level of magnesium, lipid profile, echocardiography and glycated hemoglobin, signed a written consent.

The criteria for exclusion of patients from the study were the following: congenital and acquired heart defects; hypotension (AT < 90/60 mm Hg); the symptomatic nature of arterial hypertension; presence of concomi-

tant endocrine, autoimmune, severe renal failure and oncopathology; the presence of chronic obstructive pulmonary disease; exacerbation of chronic inflammatory processes or the presence of acute inflammatory diseases, acute stroke, acute left or right ventricular failure; alcoholism, drug addiction.

Definition of endothelin-1 role in forecasting of cardiovascular complications development in patients with diabetes melitus type 2 and hypertension on the basis of mathematical model creation, by means of clinical, biochemical and haemodynamic datum of patients was the purpose of this fragment of a research.

The verification of the diagnosis of coronary artery disease (CAD) was carried out in accordance with the standards of the European Society of Cardiologists, the Association of Cardiologists of Ukraine, the protocols of the Ministry of Health of Ukraine. The presence of CHF was established by the classification of the Working Group on Cardiac Insufficiency of the Ukrainian Scientific Society of Cardiologists, and the functional class (FC) was evaluated according to the criteria of the New York Heart Association (NYHA).

The examining complex included endothelin-1 definition (Biomedica), nitrite of sodium, sodium nitrate (R&D Systems, Total Nitric Oxide Assay), an enzymatic method of lipidic indicators — total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), glycated hemoglobin (HbA_{1c}), magnesium («Ultra» of Kone LabSystems firm) by immunoferrmental method. Tool methods included: an electrocardiography at rest (EKA-1T), radiological survey of thorax organs, an echocardiography (Radmir ULTIMA Pro30) with definition of end-diastolic and end-systolic sizes (EDS, ESS), end-diastolic and end-systolic volumes (EDV, ESV) and ejection fraction (EF).

The received results are presented in the average value form \pm standard deviation from average value ($M \pm m$). Statistical data processing was carried out by means of a Statistica

package, version 6,0. Assessment of differences between groups at the distribution close to normal, was carried out by means of Student criterion. Mathematical model calculations were

made by means of the Logistic Regression module of the Statistica package for Windows 5.5 application programs. Statistically reliable distinctions were considered at $p < 0,05$.

RESULTS AND THEIR DISCUSSION

Endothelin-1 level has been investigated in patients depending on sex and age in patients with CHF (tabl 1).

At distribution of all patients depending on sex and age the following results have been received. It is revealed that endothelin-1 level is reliable higher in women and also in persons older than 60 years.

In the analysis of the received results it is revealed that endothelin-1 in blood plasma in patients with CHF and DM type 2 is on 3,5% higher than in patients with CHF without DM type 2, and on 32% higher, than in control group. The NO₂ and NO₃ levels were reliable higher on 26% and 34% respectively in patients with CHF without DM type 2 that demonstrates negative impact of a hyperglycemia on nitrogen oxide metabolites production.

The key role in pathogenesis of development and progressing of vascular complications of

DM type 2 belongs to a chronic hyperglycemia. So, the level of blood glucose and HbA_{1c} was authentically higher in patients with FC III, than in patients with FC I and II.

The cardiovascular complications development risk stratification concept in patients with DM type 2 and CAD provides the general strategy of prevention, treatment and forecast taking into account personal, medical and social characteristics of the patient.

Proceeding from it, the methodology of interrelations reflecting metabolic violations studying in patients with CAD has to meet the requirements of the system analysis and evidential medicine.

The most suitable for solution of objective is the method of logistic regression. The predicted variable has only two values for dichotomizing logistic regression: «1» — the event has taken place and «0» — otherwise. The result of cal-

Table 1

Sex and age influence on the endothelin-1 level

Indicators	Sex		Age		
	Men (n = 41)	Women (n = 57)	Before 44 years (n = 5)	From 45 to 59 years (n = 29)	More than 60 years (n = 64)
Endothelin-1 (fmol/l)	3.08 ± 0.14	3.45 ± 0.21	2.84 ± 0.02	3.19 ± 0.11	3.31 ± 0.04
P		p ₁₋₂ < 0.05		p ₁₋₂ > 0.05 p ₂₋₃ > 0.05	p ₂₋₃ > 0.05 p ₁₋₃ < 0.05

Table 2

Indicators of an endothelin, nitrogen oxide metabolites at patients with CHF and DM type 2 in comparison on patients with CHF without DM type 2

Groups of the examined patients	n	Endothelin-1 (mmol/l)	NO ₂ (mmol/l)	NO ₃ (mmol/l)	Magnesium (mmol/l)
Patients with CHF and DM type 2	68	3.16 ± 0.19*	6.17 ± 0.71*	17.31 ± 1.51*	0.71 ± 0.02*
Patients with CHF without DM type 2	30	3.05 ± 0.47**	9.01 ± 0.47**	19.07 ± 0.67**	0.64 ± 3.1*
Control group	20	2.0 ± 0.4	19.03 ± 0.15	24.12 ± 0.8	1.1 ± 0.3

Note:

* $p < 0.01$ in comparison with control group,

statistically significant difference in groups of patients with CHF with DM type 2 and CHF.

**Indicators of carbohydrate exchange depending
on CHF functional class (FC)**

Indicator	I FC (n = 10)	II FC (n = 12)	III FC (n = 46)
Blood glucose (mmol/l)	6.28 ± 0.77*	7.19 ± 0.56*	8.14 ± 0.44*
HbA _{1c} (mmol/l)	7.85 ± 1.00	10.12 ± 0.48*	10.90 ± 0.96*

Note:

* p < 0,01 in comparison with control group.

calculation when carrying out the forecast gets to an interval 0–1 and can be interpreted as probability of the predicted event.

Such properties of the regression equation are provided with application of the following regression equation (logit transformation):

$$P = \frac{1}{1 + e^{-y}}$$

where

p — the possibility of happening of predicted event;

e — basis of natural logarithms 2,71;

y — the standard linear regression equation:

$$y = x_1 \times k_1 + x_2 \times k_2 + \dots + x_n \times k_n + c,$$

where

y — dependent variable size,

x_i — independent variables value,

k_i — coefficients at independent variables,

c — constant.

Each coefficient is proportional to the contribution of an independent variable to the predicted indicator. The stepwise regression method was used, that allows to include only predictors with an essential contribution into the forecast to the model. The relative contribution of each predictor is expressed by statistics size (Wald Chi-Square).

Variables, that estimate a condition of carbohydrate and cardiohaemodynamic in patients with CHF and DM type 2, were included in model.

After elimination of less significant predictors the following set of 6 variables has been received:

- endothelin-1 level,
- glycosylated hemoglobin,
- NO₂,
- ejection fraction (EF),
- NO₃,
- DM.

Cardiovascular complications existence was coded by value «1», and their absence — by «0».

The logistic model, that includes given indicators, allowed to predict cardiovascular complications development with 90 % sensitivity and 87% specificity.

For increase in forecast quality we have replaced quantitative variables with their representation in the ranged look. The indicator rank (in our case 0 or 1) intended depending on that more or less its value than a point of division (cut-off value) — the size at which the sum of sensitivity and specificity of the studied independent indicator in relation to predicted is maximum. The choice of a point of division was carried out by creation of ROC (Receiver Operator Characteristic) of curves on the plane sensitivity — specificity.

The area under such the curve is the integrated characteristic of predictive qualities of the studied predictor.

Calculation of the complicated current DM development possibility in patients with CHF was determined by the following formula:

$$\text{Cardiovascular complications risk} = 1 / (1 + \text{Exp}(-Y)),$$

where

$$Y = \text{endothelin-1} \times 3,37 + \text{HbA}_{1c} \times 3,01 + 2,33 + \text{NO}_2 \times 1,97 + \text{EF} \times 51 \% - \text{DM} \times 1,57 - 3,94$$

The variables, which were entered to the equations, were coded as «1» under following conditions: endothelin-1 > 21 mg/ml; HbA_{1c} > 11,4 %; NO₂ > 6,17 mg/ml; variability of NO₃ > 17,31; EF > 51 %.

If conditions weren't satisfied, variables were coded by zero value.

When using of the coded variables, the forecast result has been improved. The sensitivity was 95%, specificity — also 95 %.

Totally false forecast of cardiovascular complications development has made only 5 %.

So, among all the indicators, that were studied, the greatest sensitivity in cardiovascular complications forecasting, had endothelin-1, therefore we can claim, that this indicator is a cardiovascular risk marker.

The mathematical model of predicting the development of heart-related acceleration can

be used in all patients with chronic heart failure and diabetes mellitus type 2 to stratify the risk of complications. Since the study was conducted on a small sample of patients, further research is needed on a larger sample of patients, which will give more reliable results for predicting a complicated course, as well as conducting population-based studies.

CONCLUSIONS

1. In patients with chronic heart failure and diabetes mellitus type 2 the carbohydrate exchange decompensation is associated with endothelial dysfunction.
2. Endothelin-1 level was much higher in patients with CHF that accompanying DM type 2 that allows to consider the endothelial dysfunction as an universal pathogenetic link, that unites immunoinflammatory violations, hyperglycemia and DM vascular complications in patients with CHF of ischemic genesis.
3. The mathematical model of cardiovascular complications development forecasting, that has been developed, has shown the endothelin-1 value as a cardiovascular risk marker.

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DEVELOPMENT FORECASTING
IN PATIENTS WITH DIABETES MELITUS TYPE 2
AND CORONARY ARTERY DISEASE**

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On the basis of 98 patients inspection with chronic heart failure of ischemic genesis and diabetes melitus type 2 an endothelin-1 influence and cardiovascular complications existence were studied. As a result of the conducted researches it is established that endothelin-1 level in patients with diabetes melitus type 2 and chronic heart failure is higher, than in patients with chronic heart failure without diabetes melitus type 2. It was found that blood glucose and glycose hemoglobin levels were significantly higher in patients with FC III than in patients with FC I and FC II. Due to the fact that the cardiovascular complications risk development stratification concept in patients with diabetes mellitus type 2 and coronary artery disease involves a general strategy of prevention, treatment and prognosis taking into account personal, medical and social characteristics of the patient. The developed mathematical model of cardiovascular complications development forecasting has shown endothelin-1 and nitrogen oxide metabolites value as cardiovascular risk markers.

Key words: endothelin-1, nitrogen oxide metabolites, diabetes melitus, chronic heart failure, cardiovascular complications, cardiovascular complications risk.

**ЗНАЧЕННЯ ЕНДОТЕЛІНУ-1
У ПРОГНОЗУВАННІ РОЗВИТКУ
СЕРЦЕВО-СУДИННИХ УСКЛАДНЕНЬ
У ХВОРИХ НА ЦУКРОВИЙ ДІАБЕТ 2 ТИПУ
ТА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ**

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На підставі обстеження 98 хворих на хронічну серцеву недостатність ішемічного генезу та цукровий діабет 2 типу вивчено значення ендотеліну-1 та наявність серцево-судинних ускладнень. У результаті проведених досліджень встановлено, що рівень ендотеліну-1 у хворих на цукровий діабет та хронічну серцеву недостатність вище, ніж у хворих на хронічну серцеву недостатність. Визначено, що у патогенезі розвитку і прогресування судинних ускладнень цукрового діабету 2 типу ключова роль належить хронічній гіперглікемії. Встановлено, що рівень глюкози крові та глікозильованого гемоглобіну був вірогідно вище у пацієнтів з III функціональним класом, ніж у хворих з I і II функціональним класом. У зв'язку з тим, що поняття стратифікації ризику розвитку серцево-судинних ускладнень у хворих на цукровий діабет 2 типу та ішемічну хворобу серця передбачає загальну стратегію профілактики, лікування і прогнозу з урахуванням особистісних, медичних і соціальних характеристик пацієнта. Розроблена математична модель прогнозування розвитку серцево-судинних ускладнень показала значення ендотеліну-1 та метаболітів оксиду азоту, як маркерів серцево-судинного ризику.

Ключові слова: ендотелін-1, метаболіти оксиду азоту, цукровий діабет 2 типу, хронічна серцева недостатність, серцево-судинні ускладнення, ризик серцево-судинних ускладнень, логістична модель.

**ЗНАЧЕНИЕ ЭНДОТЕЛИНА-1
В ПРОГНОЗИРОВАНИИ РАЗВИТИЯ
СЕРДЕЧНО-СОСУДИСТЫХ ОСЛОЖНЕНИЙ
У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ 2 ТИПА
И ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА**

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На основании обследования 98 больных с хронической сердечной недостаточностью ишемического генеза и сахарный диабет 2 типа изучено влияние эндотелина-1 и наличие сердечно-сосудистых осложнений. В результате проведенных исследований установлено, что уровень эндотелина-1 у больных с сахарным диабетом 2 типа и хроническую сердечную недостаточность выше, чем у больных с хронической сердечной недостаточностью без сахарного диабета 2 типа. Установлено, что уровень глюкозы крови и гликозилированного гемоглобина был достоверно выше у пациентов с III функциональным классом, чем у больных с I и II функциональным классом хронической сердечной недостаточности. В связи с тем, что понятие стратификации риска развития сердечно-сосудистых осложнений у больных сахарным диабетом 2 типа и ишемическую болезнь сердца предусматривает общую стратегию профилактики, лечения и прогноза с учетом личностных, медицинских и социальных характеристик пациента. Разработанная математическая модель прогнозирования развития сердечно-сосудистых осложнений показала значение эндотелина-1 и метаболитов оксида азота, как маркеров сердечно-сосудистого риска.

Ключевые слова: эндотелин-1, метаболиты оксида азота, сахарный диабет, хроническая сердечная недостаточность, сердечно-сосудистые осложнения, риск сердечно-сосудистых осложнений, логистическая модель.