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Clinical and pathogenetic role of immunoinflammatory activation and endothelial dysfunction in patients with coronary heart disease associated with hypothyroidism based on the results of cognitive modeling

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Key words: coronary disease, hypothyroidism, biological markers, lipids, cardiac remodeling, myocardial ischemia, statistical model.

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Objective – to study the relationship between the level of thyroid hormones and clinical, autonomic, structural and functional characteristics of heart affections, activity of immune inflammation markers, endothelial dysfunction by means of cognitive modeling.

Methods. 60 patients with coronary heart disease with concomitant hypothyroidism were examined (the average level of TSH 13.05±3.30 mU/ml, the average level of FT_4 11.45±0.72 pmol L, the average age of patients – 60.5 (54.0; 64.5) years, among them 16 (27 %) were men and 44 (73 %) women. The complex clinical examination including clinical, biochemical, immune-enzyme and instrumental methods of examination, correlation and regression analysis of the data was carried out.

Results. The correlation analysis showed that in patients with coronary heart disease, comorbid with hypothyroidism, the reduction of left ventricular ejection fraction was mostly associated with the increasing levels of neopterin and tumor necrosis factor-α ($r=-0.37$ and $r=-0.38$ respectively; $p<0.05$); condition of myocardial stiffness correlated with the concentration of C-reactive protein ($r=+0,56$; $p<0,05$); level of total cholesterol (TC) – with concentration of neopterin ($r=+0.39$; $p<0.05$) and plasminogen activator inhibitor-1 (PAI-1) ($r=+0.50$; $p<0.05$); heart rate variability parameters and indicators of myocardial ischemic changes correlated with the level of neopterin and endothelin-1. The value of FT_4 had a correlation with the concentration of neopterin ($r=-0.34$; $p<0.05$) and PAI-1 ($r=-0.52$; $p<0.05$), left ventricular myocardium mass index (LVMI) ($r=-0.44$; $p<0.05$), early and late diastolic filling velocities of the left ventricle and their ratio ($r=+0.50$, $r=-0,42$ and $r=-0.41$, respectively, $p<0.05$), standard deviation of normal-to-normal intervals (SDNN) in the active ($r=+0.45$; $p<0.05$) and passive ($r=+0.36$; $p<0.05$) periods, TC ($r=-0.33$; $p<0.05$). The performed regression analysis confirmed the direction of relations, also allowed to build the cognitive model of the clinical course of ischemic heart disease in patients with hypothyroidism, where the FT_4 acts as a connecting link.

Conclusions. The cognitive model developed on the basis of correlation and regression analyzes demonstrates clinical and pathogenetic role of immune inflammation markers and endothelial dysfunction in the progression of structural and functional heart disorders, ischemic and autonomic changes in CHD patients with concomitant hypothyroidism, where FT_4 level acts as a connecting link.

Ключові слова: ішемічна хвороба серця, гіпотиреоз, біологічні маркери, ліпіди, ремоделювання серця, ішемія міокарда, статистична модель.

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Клініко-патогенетична роль імунозапальної активації та ендотеліальної дисфункції у хворих на ішемічну хворобу серця, що асоційована з гіпотиреозом, за результатами когнітивного моделювання

Н. С. Михайловська, Т. В. Олійник

Мета роботи – дослідження взаємозв'язків між рівнем гормонів щитоподібної залози та клінічними, вегетативними, структурно-функціональними особливостями ураження серця, активністю маркерів імунного запалення, ендотеліальної дисфункції шляхом когнітивного моделювання.

Матеріали та методи. Обстежили 60 хворих на ішемічну хворобу серця з супутнім гіпотиреозом (середній рівень ТТГ – 13,05±3,30 мкМО/мл; середній рівень T_4 вільний – 11,45±0,72 пМоль/л, медіана віку хворих – 60,5 (54,0; 64,5) років, серед них 16 (27 %) чоловіків та 44 (73 %) жінки. Здійснили комплексне клінічне обстеження з використанням загальноклінічних, біохімічних, імуноферментних та інструментальних методів обстеження; кореляційний і регресійний аналіз даних.

Результати. Кореляційний аналіз показав: у хворих на ішемічну хворобу серця, що коморбідна з гіпотиреозом, зниження фракції викиду лівого шлуночка найсуттєвіше асоціювалось зі зростанням рівня неоптерину та фактора некрозу пухлини-α ($r=-0,37$ та $r=-0,38$ відповідно; $p<0,05$); стан жорсткості міокарда корелював із концентрацією С-реактивного білка ($r=+0,56$; $p<0,05$); рівень загального холестерину (ЗХС) – із концентраціями неоптерину ($r=+0,39$; $p<0,05$) та інгібітора тканинного активатора плазміногену-1 (ІТАП-1) ($r=+0,50$; $p<0,05$); параметри варіабельності серцевого ритму та індикатори ішемічних змін міокарда мали взаємозв'язок із рівнем неоптерину та ендотеліну-1. Концентрація T_4 вільного найсуттєвіше корелювала з рівнями неоптерину ($r=-0,34$; $p<0,05$) та ІТАП-1 ($r=-0,52$; $p<0,05$), індексом маси міокарда ($r=-0,44$; $p<0,05$), швидкістю раннього та пізнього діастолічного наповнення лівого шлуночка, а також їхнім співвідношенням ($r=+0,50$, $r=-0,42$ та $r=-0,41$ відповідно, $p<0,05$), стандартним відхиленням NN інтервалів за активний ($r=+0,45$; $p<0,05$) і пасивний ($r=+0,36$; $p<0,05$) періоди, ЗХС ($r=-0,33$; $p<0,05$). Регресійний аналіз показав спрямованість виявлених взаємозв'язків, а також дав можливість побудувати когнітивну модель перебігу ішемічної хвороби серця у хворих із гіпотиреозом, де рівень T_4 вільного виступив сполучною ланкою.

Висновки. Когнітивна модель, що розроблена на підставі кореляційного та регресійного аналізів, доводить клініко-патогенетичну роль маркерів імунного запалення та ендотеліальної дисфункції у прогресуванні структурно-функціональних порушень серця, ішемічних і вегетативних змін у хворих на ІХС із супутнім гіпотиреозом, де рівень T_4 вільного є сполучною ланкою.

Клинико-патогенетическая роль иммуновоспалительной активации и эндотелиальной дисфункции у больных ишемической болезнью сердца, ассоциированной с гипотиреозом, по результатам когнитивного моделирования

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Ключевые слова: ишемическая болезнь сердца, гипотиреоз, биологические маркеры, липиды, ремоделирование сердца, ишемия миокарда, статистическая модель.

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Цель работы – исследование взаимосвязей между уровнем гормонов щитовидной железы и клиническими, вегетативными, структурно-функциональными особенностями поражения сердца, активностью маркеров иммунного воспаления, эндотелиальной дисфункции путём когнитивного моделирования.

Материалы и методы. Обследовано 60 больных ишемической болезнью сердца с сопутствующим гипотиреозом (средний уровень ТТГ – 13,05±3,30 мкМО/мл, средний уровень T_4 свободный – 11,45±0,72 пмоль/л, медиана возраста больных – 60,5 (54,0; 64,5) лет, среди них 16 (27 %) мужчин и 44 (73 %) женщины. Проводили комплексное клиническое обследование с использованием общеклинических, биохимических, иммуноферментных и инструментальных методов обследования; корреляционный и регрессионный анализ полученных данных.

Результаты. Проведённый корреляционный анализ показал, что у больных ишемической болезнью сердца, коморбидной с гипотиреозом, снижение фракции выброса левого желудочка наиболее существенно ассоциировалось с ростом уровня неоптерина и фактора некроза опухоли-α (r=-0,37 и r=-0,38 соответственно; p<0,05) состояние жёсткости миокарда коррелировало с концентрацией С-реактивного белка (r=+0,56; p<0,05); уровень общего холестерина (ОХС) – с концентрацией неоптерина (r=+0,39; p<0,05) и ингибитора тканевого активатора плазминогена-1 (ИТАП-1) (r=+0,50; p<0,05); параметры вариабельности сердечного ритма и индикаторы ишемических изменений миокарда имели взаимосвязь с уровнем неоптерина и эндотелина-1. Концентрация T_4 свободного наиболее существенно коррелировала с уровнями неоптерина (r=-0,34; p<0,05) и ИТАП-1 (r=-0,52; p<0,05), индексом массы миокарда левого желудочка (r=-0,44; p<0,05), скоростью раннего и позднего диастолического наполнения левого желудочка а также их соотношением (r=+0,50, r=-0,42 и r=-0,41 соответственно; p<0,05), стандартным отклонением NN интервалов за активный (r=+0,45; p<0,05) и пассивный (r=+0,36; p<0,05) периоды, ОХС (r=-0,33; p<0,05). Проведённый регрессионный анализ установил направленность выявленных связей, а также позволил построить когнитивную модель течения ишемической болезни сердца у больных с гипотиреозом, где уровень T_4 свободного выступил связующим звеном.

Выводы. Разработанная на основании корреляционного и регрессионного анализов когнитивная модель доказывает клинико-патогенетическую роль маркеров иммунного воспаления и эндотелиальной дисфункции в прогрессировании структурно-функциональных нарушений сердца, ишемических и вегетативных изменений у больных ИБС с сопутствующим гипотиреозом, где уровень T_4 свободного выступает связующим звеном.

Introduction

Ukraine takes one of the leading places among European countries in terms of population mortality from coronary heart disease (CHD). According to statistics Ukraine has more than 9 million CHD patients, among them 34.9 % are the patients with angina pectoris [1]. Parallel with traditional risk factors, the coronary heart disease is significantly affected by the comorbidities, in particular by the endocrine pathology with the hypothyroidism, as one of the most principal [2]. The reduction of thyroid function is considered to be an additional risk factor, provoking cardiovascular diseases, as this pathology is associated with the development of atherogenic dyslipidemia, diastolic hypertension, endothelial dysfunction, myocardial remodeling, which in their turn are the predictors of adverse cardiovascular events [3].

It is proved that the structural changes in the myocardium due to reduction of the thyroid gland function lead to a violation of intracardiac hemodynamics: reduced myocardial contractile function, its electrical instability, disruption of atrioventricular conduction, lengthening of diastole, reduced left ventricular ejection fraction [4,5]. Hypothyroidism is accompanied with the violation of functional state of the autonomic nervous system; it leads to the imbalance of sympathetic and parasympathetic influences on the heart and increases the variability of the QT interval, which significantly affects the course of both CHD and hypothyroidism [6].

It is established that the decrease in the concentration of thyroid hormones promotes activation of lipid peroxidation and the occurrence of hypercholesterolemia [7]. Scientific data evidence the relationship between hypothyroidism and such "new" risk factors of atherosclerosis as C-reactive protein, endothelial dysfunction, immune inflammation, pro-coagulating blood changes, etc. [7].

Today the factors of atherosclerosis progression and destabilization of the coronary heart disease course in patients with concomitant thyroid hypofunction are insufficiently clarified. The pathogenetic mechanisms of thyroid hormones participation in the development of immune inflammation, endothelial dysfunction, the occurrence of adverse cardiovascular events in the abovementioned category of patients need follow-up study.

Objective

To study the relationship between the level of thyroid hormones and clinical, autonomic, structural and functional characteristics of heart affections, activity of immune inflammation markers, endothelial dysfunction by means of cognitive modeling.

Materials and Methods

The study involved 60 patients with coronary heart disease with concomitant hypothyroidism (HT) (the average level of TSH 13.05±3.30 mU/ml; the average level of FT_4 11.45±0.72 pmol/L, the average age of the patients – 60.5 (54.0; 64.5) years, among them 16 (27 %) are men and 44 (73 %) women).

The CHD diagnosis and the stable angina functional class were based on a comprehensive analysis of complaints, data of physical examination, results of laboratory

and instrumental examinations according to the national standards (Order of MOH Ukraine № 436 from 03.07.2006) [8]. The presence of hypothyroidism and the degree of its severity were set according to the Protocol of medical care provision for patients with endocrine system pathology (№ 124 from 05.09.2011) [9] and recommendations of the European Thyroid Association [10].

Comprehensive clinical examination of patients, considering their complaints, anamnesis, objective and additional (laboratory and instrumental) methods of investigation according to the generally accepted standards, was conducted. The following methods of investigation were used: general clinical examination – to assess the clinical manifestations of disease; biochemical examination – to determine the level of total cholesterol, triglycerides, low- and high-density lipoproteins; immune-enzyme examination – to determine the level of C-reactive protein (CRP) (Biomerica, USA), tumor necrosis factor-α (TNF-α) (eBioscience, Austria), neopterin (IBLinternational, Germany), endothelin-1 (ET-1) (Biomedica, Austria), Plasminogen Activator Inhibitor-1 (PAI-1) (Technoclone, Austria), thyroid stimulating hormone (TSH), free thyroxine (FT_4); instrumental examination – two-dimensional and pulse-wave Doppler echocardiography ("SONOACE" 8000SE company "Medison", Korea), daily monitoring of ECG by Holter (Kardiosens K, Ukraine) by the standard technique – to determine the characteristics of structural and functional changes in the heart, heart rhythm variability rate, heart ectopic activity, severity of myocardial ischemia.

Statistical data processing was carried out using the license program package "Statistica 6.0 for Windows" (StatSoft Inc., № AXXR712D833214FAN5). The hypothesis of normality of the studied parameters distribution was tested by the Shapiro-Wilkie criterion. To estimate the relationships between parameters the method of correlation analysis with calculation of Pearson (if distribution is normal) and Spearman (if distribution is different from normal) correlation coefficients was used. To determine the direction and power of the investigated factors influence the method of constructing the equations of pair linear regression with further building the cognitive model in the form of a sign directed graph that displays positive and negative functional relationships between the studied factors was used. The impact was considered as positive when the increase (decrease) of one factor led to the increase (decrease) of another factor, and negative when the increase (decrease) of one factor led to a decrease (increase) of another factor. Data were considered reliable by the level of statistical significance of $p<0.05$.

Results

In previous studies it was found out that the course of coronary artery disease, comorbid with hypothyroidism is associated with greater severity of immune inflammation and endothelial dysfunction, autonomic, structural and functional changes in heart, electrical activity of the myocardium, as compared to both the patients with CHD without comorbid diseases, and to the CHD patients with concomitant structural changes in the thyroid gland in euthyroid state [11–13].

Taking into account the complex pathogenesis of coronary heart disease in patients with hypothyroidism, it's advisable to use the method of cognitive modeling to determine clinical and pathogenetic role of immune inflammation and endothelial dysfunction. The development of cognitive model allowed us to identify the main clinical and pathogenetic factors and assess their impact on the course of this pathology.

To build a cognitive model we, in the first place, have identified the most important factors in terms of the investigated problem, using the correlation analysis. The carried out correlation analysis proved the existence of relationship between the level of thyroid hormones and indicators of immunoinflammatory activation and endothelial dysfunction, structural, functional and autonomic changes in heart, electrical activity of myocardium, lipid parameters, as evidenced by the revealed correlation interrelations of FT_4 with a concentration of neopterin ($r=-0.34$; $p<0.05$), PAI-1 ($r=-0.52$; $p<0.05$), LVM ($r=-0.50$; $p<0.01$), LVMI ($r=-0.44$; $p<0.05$), the ratio of the mitral valve velocity Ve/Va ($r=-0.41$; $p<0.05$), with standard deviation of normal cardiointervals (SDNN) in active ($r=+0.45$; $p<0.05$) and passive ($r=+0.36$; $p<0.05$) periods, TC ($r=-0.33$; $p<0.05$).

After the correlation analysis of markers of systemic inflammation and endothelial dysfunction with lipid parameters in patients with coronary heart disease with concomitant hypothyroidism a reliable direct relation of PAI-1 level concentration with total cholesterol (TC) ($r=+0.50$; $p<0.05$), and neopterin levels with TC ($r=+0.39$; $p<0.05$) and low density lipoprotein cholesterol ($r=+0.62$; $p<0.05$) was found out. The reliable relation of ET-1, TNF-α and CRP levels with lipid parameters was not identified.

In the study of structural and functional characteristics of the heart in patients with coronary heart disease with concomitant hypothyroidism the reliable direct medium strength correlation of PAI-1 with left ventricular diastolic diameter (LVDD) ($r=+0.50$; $p<0.05$), left ventricular systolic diameter (LVSD) ($r=+0.60$; $p<0.05$); reliable direct medium strength correlation of TNF-α with left ventricular ejection fraction (LVEF) ($r=-0.38$; $p<0.05$), LVDD ($r=+0.54$; $p<0.05$), LVSD ($r=+0.56$; $p<0.05$); reliable direct medium strength correlation of CRP levels with an left ventricular stiffness index (LVSI) ($r=+0.56$; $p<0.05$); reliable negative medium strength correlation of neopterin and TNF-α with LVEF ($r=-0.37$ and $r=-0.38$ correspondingly; $p<0.05$) were found out. The reliable relation between the endothelin-1 level and structural and functional characteristics of heart was not discovered.

The study of the relationship of heart rate variability in patients with coronary artery disease and concomitant hypothyroidism with indicators of systemic inflammation and endothelial dysfunction showed, that the level of endothelin-1 negatively with average power correlated with SDNN ($r=-0.41$; $p<0.05$) in passive period, and with spectral power at low frequencies (LF) ($r=-0.40$; $p<0.05$) in passive period; neopterin level negatively with average power correlated with SDNN ($r=-0.40$; $p<0.05$) in active and passive periods ($r=-0.40$ and $r=-0.54$ respectively; $p<0.05$), with spectral power at the very low frequencies (VLF) ($r=-0.46$; $p<0.05$) in passive period, LF ($r=-0.46$; $p<0.05$) in passive period. PAI-1, ET-1 and CRP levels had no significant correlations with heart rate variability.

The study of relationship between markers of immune inflammation and endothelial dysfunction symptoms with ectopic activity of the heart and ischemic changes in patients with coronary heart disease with concomitant hypothyroidism made it possible to reveal the presence of positive medium strength correlation of PAI-1 with the total number of episodes of supraventricular extrasystoles (SVE) ($r=+0.46$; $p<0.05$), duration of episodes of myocardial ischemia ($r=+0.46$;

Table 1. The equation of a straight linear regression of relationships between the studied factors

№ of model	Dependence	Model	R^2	The level of significance	№ of model	Dependence	Model	R^2	The level of significance
1	PAI-1 from FT_4	$w_6 = -2.04w_1$	0.39	0.05	11	LVEF from TNF-α	$w_9 = 52.89 - 0.75w_{10}$	0.27	0.05
2	neopterin from FT_4	$w_4 = -0.91w_1$	0.61	0.05	12	CRP from TNF-α	$w_{12} = 3.06w_{10}$	0.59	0.05
3	TC from FT_4	$w_5 = -0.40w_1$	0.75	0.05	13	TNF-α from neopterin	$w_{10} = 0.08w_4$	0.65	0.05
4	LVMI from FT_4	$w_2 = -1.63w_1$	0.77	0.05	14	PAI-1 from TNF-α	$w_6 = 21.78w_{10}$	0.71	0.05
5	Ve/Va from FT_4	$w_7 = 0.05w_1$	0.86	0.05	15	ET-1 from neopterin	$w_8 = 0.02w_4$	0.38	0.05
6	SDNN pas. from FT_4	$w_3 = 4.82w_1$	0.78	0.05	16	TC from neopterin	$w_5 = 0.33w_4$	0.79	0.05
7	SDNN pas. from neopterin	$w_3 = -3.46w_4$	0.84	0.05	17	TC from ITAП-1	$w_5 = 4.84 + 0.03w_6$	0.26	0.05
8	SDNN pas. from ET-1	$w_3 = 66.39 – 35.61w_8$	0.31	0.05	18	LVSI from CRP	$w_{13} = 0.19 + 0.01w_{12}$	0.30	0.05
9	LVEF from neopterin	$w_9 = -2.73w_4$	0.75	0.05	19	QTc from CRP	$w_{11} = 54.45w_{12}$	0.73	0.05
10	LVEF from ET-1	$w_9 = 55.91 - 11.48w_8$	0.33	0.05	20	QTc from neopterin	$w_{11} = 21.07w_4$	0.36	0.05

p < 0.05); direct medium strength correlation of CRP with the total number of SVE and corrected QT interval duration (QTc) (r = +0.33; p < 0.05); positive correlation of TNF-α with duration of episodes of myocardial ischemia (r = +0.42; p < 0.05); positive correlation of neopterin level with the duration of QTc (r = +0.43; p < 0.05). The reliable association of ET-1 with the manifestations of ectopic activity of the heart and myocardial ischemic changes was not found.

So, in the result of the correlation analysis in patients with coronary heart disease, comorbid with hypothyroidism, the most important clinical and pathogenetic factors, used to build cognitive model were distinguished: the levels of FT_4, neopterin, CRP, PAI-1, ET-1, TNF-α, total cholesterol, SDNN pas., LVEF, LVMI, Ve/Va, LVSI, QTc.

During the second phase of cognitive model construction of factors influencing the course of coronary heart disease in patients with hypothyroidism the arc graph was formed; it established relations between the tops (w) with a graphical display of the resulting directed graph. The most statistically reliable variables are presented in the form of straight linear regression equations (*Table 1*).

During the third phase, after weighting tops and arcs, we received a cognitive model of relationships between immune inflammation and endothelial dysfunction markers with indicators of cardiac remodeling, ectopic activity of the heart, autonomic disorders in patients with coronary heart disease, comorbid with hypothyroidism (*Fig. 1*).

Therefore, the regression analysis confirmed the most significant correlation relations and set the direction of these relations and made it possible to build a cognitive model of the course of coronary heart disease in patients with hypothyroidism, where the FT_4 acts as a connecting link.

Our received results are confirmed by a number of clinical and experimental works [14,15]. Obtained data suggest that hypothyroidism can potentially increase the risk of coronary heart disease progression not only due to development of endothelial dysfunction and systemic inflammation, but also through the stimulation of systemic inflammation, expression of proinflammatory cytokines, that, according to scientific data, leads to vascular remodeling and destabilization of atherosclerotic plaque [16]. In their turn, proinflammatory cytokines play an important role in the processes of hypercoagulable state of blood, endothelial dysfunction, vascular and heart remodeling [17].

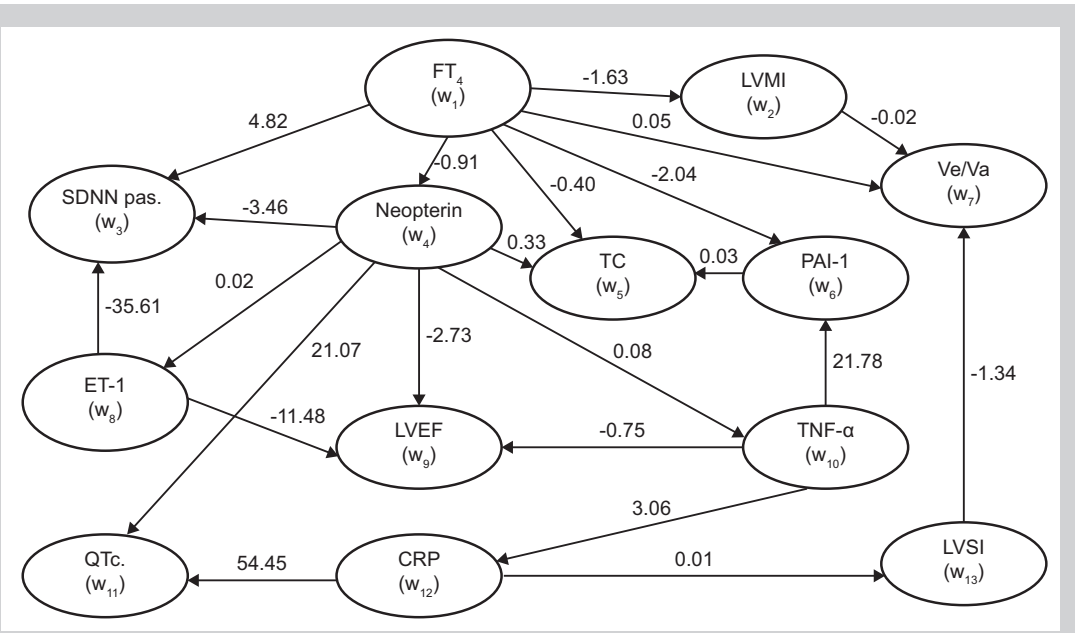

Fig. 1. Cognitive model of relationships between immune inflammation and endothelial dysfunction markers with indicators of cardiac remodeling, ectopic activity of the heart, autonomic disorders in patients with coronary heart disease, comorbid with hypothyroidism.

Conclusions

1. In patients with coronary heart disease, comorbid with hypothyroidism, the LVEF decrease was associated with the increased levels of neopterin and TNF-α ($r = -0.37$ and $r = -0.38$ respectively; $p < 0.05$); myocardial stiffness condition – with the concentration of CRP ($r = +0.56$; $p < 0.05$); total cholesterol levels – with the concentrations of neopterin ($r = +0.39$; $p < 0.05$) and PAI-1 ($r = +0.50$; $p < 0.05$); HRV parameters and indicators of myocardial ischemic changes – with the levels of neopterin and ET-1.

2. The cognitive model, developed on the basis of regression analysis, demonstrates (proves) the clinical and pathogenetic role of immune markers of inflammation and endothelial dysfunction in the progression of structural and functional disorders, ischemic and autonomic changes in CHD patients with concomitant hypothyroidism, where FT4 level acts as a connecting link.

References

[1] Kovalenko, V. M., & Kornatskyi, V. M. (2016). Problemy zdorov'ia i medychnoi dopomohy ta model pokrashchennia v suchasnykh umovakh [Problems of health and medical care and improved model in modern conditions]. Kyiv. [in Ukrainian].

[2] Mitchenko, O. I., Logvinenko, A. O., & Romanov, V. Yu. (2010). Optymizatsiia likuvannia dyslipidemii ta porushen vuhlevodnoho obminiv u khvorykh z metabolichnym syndromom ta dysfunktsiieiu shchytopodibnoi zalozy [The optimisation of lipid and carbohydrate exchange correction in patients with metabolic syndrome and thyroid dysfunction]. *Ukrainskyi kardiolohichnyi zhurnal*, 1, 73–80. [in Ukrainian].

[3] Didushko, O. M. (2014). Hiperleptynemiia yak odyn iz chynnykiv porushennia funktsii nyrok u khvorykh na hipotyreoz [Hyperleptinemia as one of the factors for renal dysfunction in patients with hypothyroidism]. *Mezhdunarodnyj e´ndokrinologicheskij zhurnal,* 6(62), 29–32. [in Ukrainian].

[4] Meena, C., Meena, R., Nawal, R., Meena, V., Bharti, A., & Meena, L. (2012). Assessment of Left Ventricular Diastolic Dysfunction in Subclinical Hypothyroidism. *Acta Informatica Medica*, 20(4), 218. doi: 10.5455/aim.2012.20.21-218-220.

[5] Biondi, B. (2012). MECHANISMS IN ENDOCRINOLOGY: Heart failure and thyroid dysfunction. *European Journal of Endocrinology*, 167(5), 609–618. doi: 10.1530/EJE-12-0627.

[6] Shved, M., & Prypkhan, I. (2015). Osoblyvosti klinichnykh oznak, zmin natriiuretychnoho pro peptydu NT-pro BNP, diastolichnoi funktsii livoho shlunochka ta variabelnosti rytmu sertsia u khvorykh na stabilnu stenokardiiu navantazhennia u poiednanni z hipofunktsiieiu shchytopodibnoi zalozy [Features of the Clinical Signs, Changes of the Natriuretic Propeptide (NT-proBNP), Left Ventricular Diastolic Function and Heart Rate Variability in the Patients with the Stable Angina Pectoris Combined with Thyroid Hypofunction]. *Lvivskyi klinichnyi visnyk*, 1(9), 8–13. [in Ukrainian].

[7] Dal Lin, C., Tona, F., & Osto, E. (2015). Coronary Microvascular Function and Beyond: The Crosstalk between Hormones, Cytokines, and Neurotransmitters. *International Journal of Endocrinology*, 2015, 1–17. doi: 10.1155/2015/312848.

[8] Nakaz Ministerstva okhorony zdorovia Ukrainy «Pro zatverdzhennia protokoliv nadannia medychnoi dopomohy za spetsialnistiu "Kardiolohiia"» vid 3 lypnia 2006 №436 [Order of the Ministry of Health of Ukraine On approving the protocols of care, specialty 'Cardiology' July, 3. 2006, №436]. Retrieved from: http://www.moz.gov.ua/ua/portal/dn_20060703_436.html [Accessed 25 Dec. 2016]. [in Ukrainian].

[9] Tronko, M. D. (Ed) (2007). Standarty diahnostyky ta likuvannia endokrynnykh zakhvoriuvan [Standards for the diagnosis and treatment of endocrine diseases]. Kyiv. [in Ukrainian].

[10] Jonklaas, J., Bianco, A., Bauer, A., Burman, K., Cappola, A., Celi, F., et al. (2014). Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*, 24(12), 1670–1751. doi: 10.1089/thy.2014.0028.

[11] Mykhailovska, N. S., Oleynik, T. V., & Mykhailovskiy, Y. M. (2015). Osoblyvosti zmin vehetatyvnoho statusu u patsiientiv z ishemichnoiu khvoroboiu sertsia ta hipotyreozom u vzaiemozv'iazku z hormonamy hipofizarno-tyreoidnoi systemy [Features of autonomic status changes in patients with coronary heart disease and hypothyroidism in relation to the hormones of the pituitary, thyroid system]. *Semeinaia medytsyna*, 4(60), 106–109. [in Ukrainian].

[12] Mykhailovska, N. S., & Oleynik, T. V. (2015). Osoblyvosti remodeliuvannia miokarda u khvorykh na ishemichnu khvorobu sertsia zalezhno vid funktsionalnoho stanu shchytopodibnoi zalozy [Features of myocardial remodeling in patients with coronary heart disease depending on thyroid function]. *Pathologia*, 2(34), 17–21. doi: http://dx.doi.org/10.14739/2310-1237.2015.2.48619. [in Ukrainian].

[13] Mykhailovska, N. S., & Oliinyk, T. V. (2015). Osoblyvosti imunozapalnoi aktyvatsii ta funktsionalnoho stanu endoteliiu u khvorykh na ishemichnu khvorobu sertsia, asotsiiovanu z hipotyreozom [Features of immunoinflammatory activation and endothelial functional status in patients with coronary heart disease associated with hypothyroidism]. *Problemy endokrynnoi patolohii*, 4, 37–43. [in Ukrainian].

[14] Blankova, Z. N., Ageev, F. T., Seredenina, E. M., Ryabceva, O. Yu., Svirida, O. N., & Iryuganov, N. Sch. (2014). Gipotireoz i serdechno-sosudistye zabolevaniya [Hypothyroidism and cardiovascular disease]. *Russkij medicinskij zhurnal*, 13, 980–987. [in Russian].

[15] Valgimigli, M., Percoco, G., Malagutti, P., Campo, G., Ferrari, F., Barbieri, D., et al. (2005). Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare-Metal Stent for Acute Myocardial Infarction. *JAMA*, 293(17), 2109. doi: 10.1001/jama.293.17.2109.

[16] Kopitsa, N. P., Lytvyn, O. I., Petyunina, O. V., Tytarenko, N. V., & Petenyova, L. L. (2006). Rol´ neopterina v prognozirovanii serdechnoj nedostatochnosti u bol´nykh, perenesshikh infarkt miokarda [The role of neopterin in prognosing of heart failure in patiens after myocardial infarction]. *Ukrainskyi terapevtychnyi zhurnal*, 4, 19–22. [in Ukrainian].

[17] Ruzhencova, U. Yu. (2016). Vzaimosvyaz´ mezhdu simpaticheskoj nervnoj sistemoj i e´ndotelinom-1 v kapillyarnom krovotoke u bol´nykh ishemicheskoj bolezn´yu serdca – znachenie GNB3 S825T polimorfizma [The relationship between the sympathetic nervous system and endothelin-1 in the capillary blood flow in patients with coronary heart disease – the value GNB3 S825T polymorphism]. *Lechaschij vrach*, 1, 87–92. [in Russian].

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