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ФАКТОРЫ РИСКА РАЗВИТИЯ РАННИХ СТРУКТУРНЫХ ИЗМЕНЕНИЙ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ У ПАЦИЕНТОВ ПЕРВИЧНЫМ ГИПОТИРЕОЗОМ

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Risk Factors Promoting Early Cardiovascular Structure Disorders in Patients with Primary Hypothyroidism

Резюме

Цель. Выявление факторов, способствующих развитию ранних структурных изменений сердечно-сосудистой системы у пациентов первичным гипотиреозом в зависимости от компенсации заболевания. **Материалы и методы.** Обследовано 163 женщины с первичным гипотиреозом в возрасте 62 [55;67] лет, которые были разделены на группы: 1 группа — 54 пациентки в возрасте 62,0 [57;68] лет с субкомпенсированным заболеванием, 2 группа — 15 пациенток в возрасте 59 [53;66] лет с некомпенсированным заболеванием и 3 группа — 94 пациентки в возрасте 63 [53;66] лет с компенсированным гипотиреозом. Всем пациенткам выполнено физикальное обследование, трансторакальная эхокардиография, оценка продольной сократительной функции левого желудочка методом «speckle tracking», оценка функции эндотелия, липидного профиля. Проводился регрессионный анализ с использованием в качестве предикторов тиреотропного гормона, свободного Т4, возраста, давности заболевания, причины гипотиреоза, наличия менопаузы и натурального логарифма тиреотропного гормона, а в качестве зависимых переменных — ряда параметров состояния сердца и липидного обмена. **Результаты.** При проведении математического моделирования показано, что наибольшее значение в процессах ремоделирования миокарда левого желудочка у пациентов первичным гипотиреозом имеет сочетание таких параметров, как возраст, давность заболевания и уровень тиреотропного гормона. В то же время, значимое влияние на показатель величины комплекса интима медиа оказывает только возраст. **Заключение.** Модифицируемыми факторами, определяющими ремоделирование левого желудочка, морфофункциональное состояние стенки сосудов у пациентов гипотиреозом, являются индекс массы тела и уровень тиреотропного гормона, а немодифицируемыми — возраст и давность заболевания.

Ключевые слова: *первичный гипотиреоз, модель поражения сердца, ремоделирование левого желудочка, липидный обмен*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Objective. To develop the pattern of early cardiovascular disorders in patients with primary hypothyroidism based on the analysis of relationship between patient's thyroid status and some functional cardiovascular parameters depending on compensation status. **Materials and methods.** The examination of 163 women aged 62 [55;67] years with primary hypothyroidism was performed. The patients were divided into groups: 1 group included 54 patients aged 62.0 [57;68] years with subcompensated disease, 2 group consisted of 15 patients aged 59 [53;66] years with non-compensated disease and 3 group included 94 patients aged 63 [53;66] years with compensated hypothyroidism. Physical examination, transthoracic echocardiography, assessment of global left ventricle longitudinal strain by speckle tracking method, endothelial function and laboratory tests were performed to all patients. Regression analysis using thyroid stimulating hormone, free T4, age, duration of the disease, cause of hypothyroidism, menopause presence and natural thyroid stimulating hormone logarithm as predictors and some cardiovascular parameters of heart condition and lipid metabolism as dependent valuables was made. **Results.** Mathematic modeling demonstrated that the combination such factors as age, duration of disease and thyroid stimulating hormone level is the most important in left ventricle remodeling processes. However, the age only has significant influence on intima media thickness. **Conclusion.** Left ventricle remodeling, morphologic functional status of blood vessel wall and decrease of glomerular filtration rate are basically determined by such modified and non-modified factors as body mass index, age, duration of hypothyroidism and thyroid stimulating hormone level.

Key words: *primary hypothyroidism, heart disorder pattern, left ventricle remodeling, lipid metabolism*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BA — brachial artery, BMI — body mass index, DBP — diastolic blood pressure, EF — ejection fraction, fT4 — free T4, GFR — glomerular filtration rate, GLPS AVRG — averaged global longitudinal peak systolic strain, HDL-C — high-density lipoprotein cholesterol, IARH — increase in artery diameter in reactive hyperemia test, IMT — intima media thickness, LDL-C — low density lipoprotein cholesterol, LVMMI — left ventricular myocardial mass index, LV — left ventricle, Me — median, non-HDL-C — non-high density lipoprotein cholesterol, RWT — relative wall thickness, SBP — systolic blood pressure, TC — total cholesterol, TG — triglycerides, TSH — thyroid stimulating hormone, Q1 — 25th percentile, Q3 — 75th percentile

Diseases of the circulatory system are the leading cause of death not only in the Russian Federation but in the whole world [1]. In recent years, the role of other possible risk factors that affect the development and progression of cardiovascular pathology was studied, along with already well-established factors (smoking, arterial hypertension (AH), hypercholesterolemia, etc.) [1]. Thyroid insufficiency may be one of the risk factors. Opinions still differ on whether primary hypothyroidism is a risk factor for cardiovascular events. The role of subclinical hypothyroidism as a predictor of cardiovascular morbidity and mortality is especially debatable. This is probably because such an effect is most often assessed via surrogate markers, for example, impaired lipid metabolism, endothelial dysfunction, increased rigidity of the vascular wall, and cardiac function [2–4].

Results of several observational studies supported the hypothesis that hypothyroidism accelerated the course of atherosclerosis of coronary arteries [4]. However, according to a number of authors, subclinical hypothyroidism is associated with an increased risk of heart failure but not with the risk of coronary heart disease or peripheral vascular atherosclerosis; and the normalization of TSH (thyroid stimulating hormone) in elderly patients leads to no significant changes in intima media thickness and manifestations of the atherosclerosis of carotid arteries [5].

In recent decades, the role of hypothyroidism in the development of vascular endothelial dysfunction was demonstrated, as well as the association between thyroid hormone deficiency and the development of AH and left ventricular (LV) dysfunction [3–5].

A number of authors describe a moderate increase in triglycerides and low-density lipoprotein cholesterol (LDL-C) levels in patients with subclinical hypothyroidism compared with euthyroid subjects [5]. On the

contrary, a population-based study in 1,350 participants demonstrated no difference in mean total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) in patients with subclinical hypothyroidism compared with euthyroid subjects even after adjustment for sex, age and body mass index (BMI) [6]. However, the same study showed that average TSH levels were higher in individuals with dyslipidemia, suggesting the relationship between TSH and TC, as well as TSH and LDL-C in overweight women [6].

Data on the effect of substitution therapy on the cardiovascular system in patients with hypothyroidism of different types are also inconclusive. A number of studies demonstrated that the administration of levothyroxine in patients with subclinical hypothyroidism leads to a significant decrease in TC and LDL-C levels [5]. Other authors claim that replacement therapy with levothyroxine increases the risk of general and cardiovascular mortality in patients 80+ with primary hypothyroidism and heart failure [7]. There are no data describing the state of the cardiovascular system depending on the degree of disease compensation.

Objective of the study: to establish the key risk factors for the development of structural changes in the heart and blood vessels in patients with primary hypothyroidism depending on its compensation.

Materials and Methods

One hundred and sixty-three women with primary hypothyroidism were examined (diagnosed in accordance with the recommendations of the Russian Association of Endocrinologists, 2021); the primary hypothyroidism was caused by autoimmune thyroiditis in 104 (63.2%) patients (39 in Group 1 (72.2%), 11 in Group 2 (73.3%), and 64 in Group 3 (68.0%)), by postoperative hypothyroidism—in 54 (33%) patients (15 (27.8%), 4 (26.7%), and 29 (31.6%), respectively), and by diffuse goiter—in 3 (1.8%) patients (3 (3.19%) only in Group 1).

The study was open-label, prospective, with three groups. Inclusion criteria for this study were consent to participate, the presence of subcompensated, uncompensated, or compensated primary hypothyroidism, age 18+, female. Exclusion criteria were the presence of oncological, systemic diseases, decompensated heart and lung failure, diabetes mellitus. The study was carried out in accordance with the principles of the World Medical Association Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee of the Izhevsk State Medical Academy.

All 163 patients meeting the inclusion and exclusion criteria were divided into three groups. Group 1 included 54 patients aged 62.0 [57; 68] with subcompensated hypothyroidism (TSH level > 4.0 μIU/L, free T4 (fT4) > 10 pmol/L); Group 2 included 15 patients aged 59 [53; 66] years with uncompensated hypothyroidism (TSH > 10 μIU/L, fT4 < 10 pmol/L), and Group 3 included 94 patients aged 63 [53; 66] with a disease compensated due to replacement therapy with levothyroxine (TSH > 4 μIU/L and fT4 > 10 pmol/L) [2]. All patients took levothyroxine agents. The patients received no menopausal hormone therapy.

Evaluation of concomitant treatment showed that statins were almost not prescribed for patients in all examined groups; beta blockers were prescribed significantly more often in the group of patients with decompensated hypothyroidism, while the number of patients receiving treatment with angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, calcium antagonists, diuretics, and combination therapy did not differ significantly between groups 1, 2, and 3 (Table 4).

All patients underwent a comprehensive general clinical examination with BMI calculation, determination of TC, TG, LDL-C and high-density lipoprotein cholesterol (HDL-C) levels, as well as cholesterol that is not related to high-density lipoprotein cholesterol (non-HDL-C). Transthoracic echocardiography was performed in accordance with the recommendations of the European and American Association of Echocardiography using Vivid 7 Dimension ultrasound device (GE Healthcare, USA) with an M4S phased array sector transducer and scanning frequency of 1.5–4.3 MHz [8]. Relative LV wall thickness (LVWT), Simpson's ejection fraction (EF), LV myocardial mass (according to the recommendations of the American Association of Echocardiography, ASE, 2016), LV myocardial mass index (LVMMI) were calculated. LV longitudinal strain was assessed using the ECHOPAC workstation version BT-08 integrated in an ultrasound scanner in an automated functional imaging application. This software is based on Speckle Tracking technology. Averaged global longitudinal peak systolic deformity (GLPS AVRG) was considered a parameter of global longitudinal LV systolic function [9]. Endothelial function was assessed by Doppler scanning of the brachial artery (BA) using an Esaote MyLab 70 device (Italy) with ultrasound at rest and in case of reactive hyperemia after three-minute clamping of shoulder vessels with a cuff. Flow-dependent dilation was calculated as the ratio of the change in BA diameter during reactive hyperemia to the diameter of the artery at rest expressed as a percentage of the initial diameter. Artery diameter increase by 10% or more was considered normal when conducting a reactive hyperemia test (IARH). Intima media thickness (IMT) was also determined [10].

Statistical processing was carried out in MS Excel, STATISTICA 10.0 Statsoft and RStudio using nonparametric criteria. To describe the quantitative criteria in

the group, median, 1st and 3rd percentiles (Me [1Q; 3Q]) were calculated. To compare independent samples, the Mann–Whitney test and the Kruskal–Wallis test for multiple comparisons were used. Nonparametric correlation analysis was performed using Spearman's rank correlation coefficient. The conclusion about statistical significance was made at $p < 0.05$.

Regression analysis was carried out in the RStudio statistical package based on the stats standard library. Linear and quadratic models were constructed by a search method among all possible combinations of factors. After creating quadratic models, insignificant interactions were excluded step by step. When carrying out regression analysis, the factors presented in Table 1 and designated as X_i, $i = \overline{1.7}$ were taken as the parameters that presumably affect the cardiovascular system. The following parameters were used as dependent variables (responses), which parameters are shown in Table 2 and designated as Y_i, $i = \overline{1.11}$. The quality of models was determined by the adjusted coefficient of determination R^2_{adj}, and the closer the value R^2_{adj} to 1, the better the model described the relationship between the response and factors. Response variation explained by the studied factors was also evaluated using R^2_{adj} [11].

Table 1. *The Factors Probable Affected Cardiovacular System in Patients with Hypothyroidism*

Symbol	Name
X_1	TSH
X_2	fT4
X_3	Age
X_4	Duration
X_5	Diagnosis
X_6	Menopause
$X_8 = ln\ X_1$	TSH_ln

Note: TSH — thyroid stimulating hormone, fT4 — free L-thyroxine, TSH_ln — linear logarithm of thyroid stimulating hormone

Table 2. *Dependent Variables Studied in Patients with Hypothyroidism*

Symbol	Name	R^2_{adj}	p-value
Y_1	Diameter increase in reactive hyperemia test	0,338	<0,001
Y_2	Total cholesterol	0,118	0,007
Y_3	Triglycerides	0,001	0,277
Y_4	Cholesterol LDL	0,123	0,003
Y_5	Cholesterol HDL	0,050	0,042
Y_6	Cholesterol non-HDL	0,040	0,044
Y_7	Glomerular filtration rate	0,241	<0,001
Y_8	Body mass index	0,049	0,023
Y_9	GLPS AVRG	0,064	0,024
Y_{10}	Relative wall thickness	0,099	<0,001
Y_{11}	Left ventricular mass index	0,513	<0,001
Y_{12}	Complex intima media value	0,306	<0,001

Note: GLPS AVRG — global left ventricle longitudinal strain average

Results

Comparative clinical and demographic characteristics of the examined patients are presented in Table 3. The average age of the examined patients was 62 [55; 67] years; no significant differences were found between the groups. Disease duration on average was 5 [1; 13] years; patients with compensated hypothyroidism had had that condition reliably longer than the patients in other groups. The average dose of levothyroxine was 50 [50; 100] μg; the dosage of levothyroxine in the group of compensated and subcompensated hypothyroidism differed significantly. Despite the absence of compensation, patients in Group 2 took a relatively high dose of levothyroxine (Table 3). The causes and duration of decompensation or subcompensation cannot be determined since patients in Groups 1 and 2 were examined irregularly and occasionally missed taking medications.

BMI in the examined patients averaged 29.14 [25.2; 32.9] kg/m^2; body weight in the group of uncompensated hypothyroidism was significantly higher than in other groups. Seventy-one of the examined patients (43.5%) had obesity of Grade 1 and higher; 49 (30.0%) patients were overweight; differences in the incidence of obesity and overweight between the groups were insignificant (Table 4).

Average office systolic blood pressure (SBP) was 140 [130; 159] mm Hg, diastolic (DBP)—85 [80, 92] mm Hg; however, blood pressure did not depend on disease compensation.

In general, AH was found in 114 (69.9%) examined patients; there were no significant differences between the groups. In 92 (56.4%) patients, AH was observed before the development of primary hypothyroidism.

Exertional angina of different functional classes was diagnosed in 55 (33.7%) patients. Eight (4.2%) patients had myocardial infarction, 8 (4.7%) patients had acute cerebrovascular accident; there were no significant differences in the frequency of these events in the examined groups (Table 4).

Assessment of lipid profile revealed increased average values of total cholesterol up to 6.1 [5.4; 7.0] mmol/L. Patients with uncompensated hypothyroidism demonstrated a tendency towards a more pronounced increase in total cholesterol compared with compensated and subcompensated disease, as well as a significant increase

in LDL-C up to 5.1 [4.8; 5.3] mmol/L compared to the other two groups. Also, non-HDL-C increased to 4.51 [3.7; 5.3] mmol/L in the entire population of examined patients, while TG and HDL-C levels were within the reference range: 1.4 [1.0; 1.96] mmol/L and 1.64 [1.32; 1.9] mmol/l, respectively (Table 5).

Table 3. *Clinical and Demographic Characteristics of Examined Patients*

Parameter	All sample (n=189)	Group 1 (n=70)	Group 2 (n=25)	Group 3 (n=94)	Kraskell-Wallis test, H, p	p-value
Age, years	62[55;67]	62,0[57;68]	59[53;66]	63[53;66]	1,4 p=0,49	p_{12}=0,15 p_{13}=0,9 p_{23}=0,2
Duration, years	5 [1;13]	4 [1;10]	5[0,4;10]	8,0 [4;15]	9,2 p=0,001	p_{12}=0,33 p_{13}=0,02 p_{23}=0,014
Levothyroxine dose, μg	50 [50;100]	50 [50;75]	75 [50;100]	50 [50;100]	8,3 p=0,01	p_{12}=0,1 p_{13}=0,006 p_{23}=0,8
Thyroid stimulating hormone, mIU/L	4,1 [1,97;9,1]	8 [5,06;10,6]	30 [17,9;44,0]	1,96 [0,74;2,8]	117,73 p=0,000	p_{12}=0,0001 p_{13}=0,0001 p_{23}=0,0001
Free T4, pM/L	13,6 [11,2;16,0]	13,8 [11,2;17,5]	7,9 [6,5;10,2]	14,4 [13,1;17,2]	19,59 p=0,0001	p_{12}=0,0002 p_{13}=0,05 p_{23}=0,001
Body mass index kg/m^2	29,14 [25,2;32,9]	29,3 [25,0;32,8]	35,17 [26,9;38,9]	28,6 [25,9;32,7]	5,4 p=0,05	p_{12}=0,003 p_{13}=0,85 p_{23}=0,0006
Systolic blood pressure, mm Hg	140 [130; 159]	140,0 [127;157]	140,0 [120; 165]	144,5 [132; 160]	1,57 p=0,45	p_{12}=0,95 p_{13}=0,43 p_{23}=0,69
Dyastolic blood pressure, mm Hg	85 [80, 92]	80,0 [77; 90]	90 [80; 94]	83,5 [75; 92]	2,6 p=0,26	p_{12}=0,95 p_{13}=0,43 p_{23}=0,69

Note: p_{12}, p_{13}, p_{23} — *p*-values– significant differences between respective groups

Table 4. *Qualitative characteristics in examined groups*

Parameter	Total sample n=163	Group 1 n=54	Group 2 n=15	Group 3 n=94	Chi-square, p-value
Arterial hypertension (n, %)	114 (69,9%)	36 (66,6%)	9 (60%)	69 (73,4%)	χ^2 12=0,23, p12=0,63 $\chi^2$13=0,76, p13=0,38 χ^2 23=1,14, p23=0,28
Obesity (n, %)	71 (43,5;)	22 (40,7%)	9 (60%)	40 (42,5%)	χ^2 12=1,76, p12=0,18 $\chi^2$13=0,05, p13=0,83 χ^2 23=1,76, p23=0,18
Overweight (n, %)	49 (30,0%)	13 (24,07%)	6 (40%)	30 (31,9%)	χ^2 12=1,49, p12=0,22 $\chi^2$13=1,02, p13=0,31 χ^2 23=0,38, p23=0,53
Angina (n, %)	55 (33,7%)	21 (38,8%)	5 (33,3%)	29 (30,8%)	χ^2 12=1,24, p12=0,26 $\chi^2$13=1,02, p13=0,31 χ^2 23=0,04, p23=0,84
History of myocardial infarction (n, %)	7 (4,3%)	3 (5,5%)	0 (0%)	4 (4,2%)	χ^2 12=0,87, p12=0,35 $\chi^2$13=0,13, p13=0,72 χ^2 23=0,66, p23=0,41
History of Stroke (n, %)	8 (4,9%)	4 (7,4%)	0)0%)	4 (4,2%)	χ^2 12=1,18, p12=0,27 $\chi^2$13=0,67, p13=0,41 χ^2 23=0,66, p23=0,41

Note: χ^2 12, χ^2 13, χ^2 23 — Chi-square values between respective groups, p_{12}, p_{13}, p_{23} — p-values– significant differences between respective groups

Table 5. *Lipid Parameters in Examined Patients*

Parameter	All sample	Group 1	Group 2	Group 3	Kraskell-Wallis test, H, p	p-values
Total cholesterol, mM/L	6,1 [5,4;7,0]	6,05 [5,3;6,9]	7,1 [6,0; 8,5]	6,1 [5,4;6.7]	4,26, p=0,23	p_{12} = 0,16 p_{13}=0,8 p_{23}=0,12
Triglycerides, mM/L	1,4 [1,0;1,96]	1,35 [0,99; 1,98]	1,45 [1,1; 2,4]	1,4 [1,0; 1,9]	0,7, p=0,7	p_{12} = 0,29 p_{13}=0,63 p_{23}=0,48
LDL cholesterol, mM/L	3,9 [3,26;4,8]	3,9 [3,4; 4,9]	5,1 [4,8; 5,3]	3,8 [3,2; 4,58]	6,64, p=0,03	p_{12} = 0,04 p_{13}=0,65 p_{23}=0,016
HDL cholesterol, mM/L	1,64 [1,32;1,9]	1,6 [1,4; 1,82]	1,73 [1,3; 2,05]	1,67 [1,25; 1,98]	0,24, p=0,88	p_{12} = 0,66 p_{13}=0,68 p_{23}=0,49
Non-HDL cholesterol, mM/l	4,51 [3,7;5,3]	4,67 [3,59; 5,47]	4,98 [3,7; 5,76]	4,4 [3,8; 5.13]	0,69, p=0,7	p_{12} = 0,61 p_{13}=0,95 p_{23}=0,52

Note: p12, p13, p23 — p-values– significant differences between respective groups, LDL — low density lipids, HDL — high density lipids

Table 6. *Investigated Parameters of Echocardiography, Endothelium Function in Patients with Hypothyroidism*

Parameter	All sample	Group 1	Group 2	Group 3	Kraskell-Wallis test, H, p	p-values
Ejection fraction, % by Simpson	65,7 [62,0; 69,0]	66,5 [62,5; 70,0]	61,0 [60,5; 68,0]	66,0 [63,0; 69,0]	5,19, p=0,07	p12 =0,03 p13=0,84 p23=0,03
Left ventricular mass index, mg/m^2	96,8 [81,2; 113,2]	98,5 [85,4; 116]	130,7 [113,1; 160,4]	96,6 [81,1; 112,0]	9,2 p=0,0098	p_{12} =0,001 p_{13}=0,86 p_{23}=0,001
Relative wall thicknes, cm	0,38 [0,35;0,41]	0,38 [0,35; 0,40]	0,44 [0,35; 0,45]	0,39 [0,36; 0,42]	6,5, p=0,03	p_{12} =0,03 p_{13}=0,12 p_{23}=0,053
GLPS AVRG, %	-19,8 [-21,6; -18,3]	-19,4 [-20,4; -16,6]	-17,0 [-20,0; -14,2]	-20,0 [-21,9; -18,5]	5,07, p=0,07	p_{12} =0,78 p_{13}=0,37 p_{23}=0,03
Diameter increase in reactive hyperemia test, %	8,0 [4,65; 12,8]	6,8 [3,2; 12,9]	11,1 [6,5; 13,3]	7,8 [4,9, 12,1]	0,8,p=0,8	p_{12} =0,89 p_{13}=0,80 p_{23}=0,90
Complex intima media value, mm	1,1 [0,9; 1,2]	1,1 [1,1, 1,2]	1,1 [0,7; 1,2]	1,1 [0,9; 1,2]	1,9 p=0,38	p_{12} =0,20 p_{13}=0,31 p_{23}=0,43
Ve/Va	0,78 [0,66; 0,87]	0,76 [0,64; 0,87]	0,71 [0,59, 1,19]	0,79 [0,66; 0,88]	0,4, p=0,81	p_{12} =0,28 p_{13}=0,56 p_{23}=0,44

Note: p_{12}, p_{13}, p_{23} — *p*-values — significant differences between respective groups, GLPS AVRG — global left ventricle longitudinal strain average

As seen in Table 6, an increase in the average value of IMT to 1.1 [0.9; 1,2] mm was detected in all groups of examined patients, regardless of TSH level.

Endothelial dysfunction in the form of a reduced average value of the increase in the diameter of the brachial artery in a reactive hyperemia test (IDRH) less than 10% was found in all groups of examined patients, including the general sample, regardless of TSH level; differences between the groups were insignificant (Table 6).

Ejection fraction in all groups was within the reference range; in the group of patients with uncompensated hypothyroidism, there was a decrease in the parameter compared to that in the group with subcompensated and compensated hypothyroidism (Table 6).

Signs of left ventricular remodeling were found in patients of all of the compared groups; average LVMMI in examined subjects was 96.8 [81.2; 113.2] g/m^2, and average RWT was 0.38 [0.35; 0.41] (Table 6). In the group

Table 7. *Significant ratios for Quadratic Model of the Left ventricular mass index* $\hat{Y}_{11}$

Variables	Regression Ratio b_i	p-value
X_3	1,296	<0,001
X_4	2,426	0,067
$X_{5.1}$	803,8	0,009
$X_{5.2}$	45,19	0,318
X_8	-32,99	0,002
$X_1 \cdot X_3$	0,028	0,017
$X_1 \cdot X_4$	-0,094	<0,001
$X_1 \cdot X_{5.1}$	-0,947	0,821
$X_1 \cdot X_{5.2}$	1,196	0,006
$X_2 \cdot X_8$	1,133	0,010
$X_3 \cdot X_{5.1}$	-14,23	0,012
$X_3 \cdot X_{5.2}$	-0,830	0,233

Note: X_3 — Age, X_4 — Duration, X_5 — Diagnosis, X_8 — linear logarithm TSH_ln

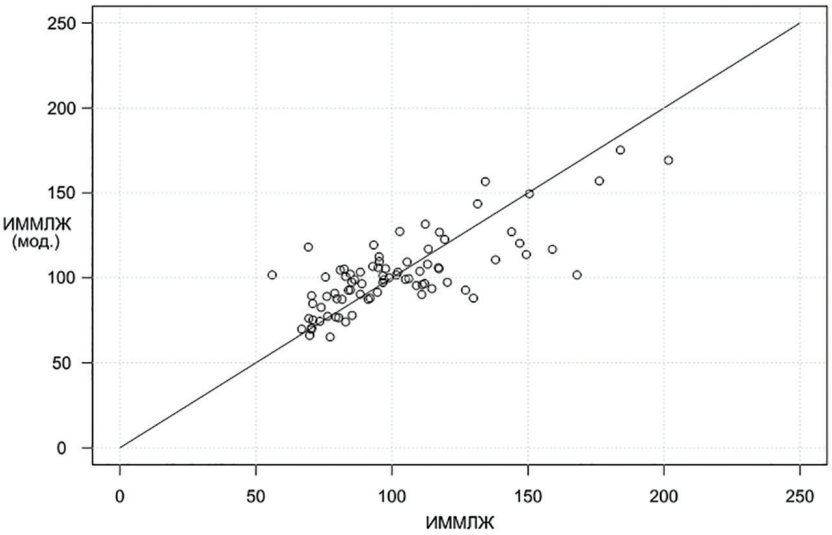

Figure 1. *Relationship Between the Model and Actual Values of the Left ventricular Mass Index*

Note: ИММЛЖ (мод.) — Left ventricular mass index model, ИММЛЖ — Left ventricular mass index

of uncompensated hypothyroidism, LVMMI was significantly higher than in the other two groups.

Impaired LV diastolic filling in the form of decreased Ve/Va ratio less than 1.0 was found in 121 (74.2%) patients (39 (72.24%), 11 (73.3%) and 78 (82.9%) patients in groups 1, 2, and 3, respectively); differences between the groups were not significant (Table 6).

Global contractility of the left ventricular myocardium in the entire examined sample was −19.4 [−20.4; −16.6]%; in the group of subcompensated hypothyroidism this parameter was significantly lower than in patients with disease compensation. In Group 1, a decrease in GLPS AVRG of less than 19% was revealed in 17 (31.4%) patients, in Group 2: in 4 (26.6%) patients, and in Group 3: in 27 (28.7%) patients.

The following significant correlations were registered: between age and IMT (r = 0.54, p = 0.00006), between BMI and GLPS AVRG (r = 0.32, p = 0.0009), between IMT and RWT (r = 0.36, p = 0.0004), as well as negative correlations between age and between HDL-C level and BMI (r = −0.33, p = 0.00006), between the level of fT4 and LVMMI (r = −0.39, p = 0.0002).

Quadratic models for LVMMI, IARH and IMT had the highest values R^2_{adj} and were significant at the level p < 0.001. Response variation, which can be explained by the studied factors, was as follows: for LVMI 51.3%, IARH 33.8%, and IMT 30.5%.

Significant coefficients (p < 0.05) of the regression model of the relationship between LVMMI and the studied factors are presented in Table 6.

As seen in Table 6, the most significant factors at the level p < 0.001 that affect LVMMI were the age factor and the interaction of TSH and disease duration factors. Nominal discrete variables X_5 and X_6 were converted to binary dummy variables ($X_{5.1}$, $X_{5.2}$) and ($X_{6.1}$, $X_{6.2}$), respectively, to be included in the regression model (Table 6).

As seen in Figure 1, the model allows satisfactory reproduction of LVMMI values from the studied factors for the group of patients under consideration.

Only the age factor turned out to be a significant factor at the level p < 0.001 that has an effect on IMT.

Discussion

According to a number of studies, patients with hypothyroidism have a different incidence of arterial hypertension, coronary heart disease, and heart failure; the effect of substitution therapy on surrogate markers of progression of cardiovascular lesions is inconclusive [3, 4, 5, 14]. Authors also have different opinions on the nature and severity of hemodynamic and lipid disorders, depending on the degree of thyroid insufficiency [5, 7, 15]. According to our data, patients with hypothyroidism are most often women in postmenopausal period; AH is found in 69.9%, CHD—in 33.7%, a history of MI and acute cerebrovascular accident—in of 4.3% and 4.9%, respectively.

Also, patients with primary hypothyroidism have such risk factors as obesity (43.5%), overweight (30%),

increased levels of total cholesterol, LDL cholesterol, non-HDL cholesterol with normal HDL cholesterol and triglyceride levels, which is consistent with the data obtained by other authors [6, 12].

It should be noted that the degree of thyroid insufficiency has a significant influence on the severity of lipid metabolism disorders and structural changes in the left ventricle. However, with compensated disease, these parameters do not normalize completely. In addition, the levothyroxine dose has no significant effect on the severity of the identified structural and functional changes. Correlation analysis showed that the level of free T4 significantly affects LVMMI and, consequently, the severity of left ventricular hypertrophy.

Assessment of correlations revealed that age is the main factor affecting LVMMI and IMT in patients with primary hypothyroidism with thyroid insufficiency of various degrees.

With age, the body replaces parenchymal cells with connective tissue, morphological changes develop in the myocardium, cardiomyocytes die, total peripheral vascular resistance increases, and collagen rigidity increases; all this leads to impaired myocardial extensibility and contractility [13]. The combination of impaired relaxation of the left ventricular myocardium, increased LVMMI, signs of endothelial dysfunction, and thickening of the intima media of peripheral vessels, typical for damage to the cardiovascular system in both hypothyroidism and aging, probably aggravates the severity of pathological changes [6].

The revealed relationship between BMI and global longitudinal contractility of the left ventricular myocardium in the examined patients is consistent with the data obtained by other authors who studied the relationship between BMI and longitudinal LV deformity in patients with chronic kidney disease [14]. This is probably because obesity leads to negative metabolic and neurohumoral changes that can intensify myocardial remodeling. Probable reasons for this are the activation of peroxidation processes, which increases oxygen consumption by the myocardium and decreases myocardial contractility, which is aggravated by thyroid insufficiency.

Mathematical modeling showed that the combination of such parameters as age, disease duration and TSH level is of greatest importance in the processes of the remodeling of the left ventricular myocardium in patients with primary hypothyroidism. At the same time, only age has a significant effect on IMT.

It should be noted that despite the disease compensation, changes in the cardiovascular system in patients with hypothyroidism persist. The development of hypothyroidism may trigger such processes as oxidative stress, inflammation and dyslipidemia, and routine replacement therapy does not lead to a complete normalization of cardiovascular parameters [15]. Apparently, it is the combination of these factors that leads to persistent cardiovascular changes. Additional research is required to find additional factors affecting structural and functional changes in the cardiovascular system in patients with primary hypothyroidism.

Conclusion

1. The most significant risk factors for LV and vascular wall remodeling in patients with primary hypothyroidism are TSH level > 4 mIU/L, disease duration over 6 years, and elderly age (65+).

2. As part of a cardioprotective strategy for managing patients with hypothyroidism, it is advisable to achieve reference ranges of TSH, free T4, and correction of excess body weight.

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Список литературы / References:

1. Вайсман Д.Ш., Александрова Г.А., Леонов С.А. и др. Достоверность показателей и структуры причин смерти от болезней системы кровообращения в Российской Федерации при международных сопоставлениях. Современные проблемы здравоохранения и медицинской статистики. 2019; 3 (1): 69-84. doi: 10.24411/2312-2935-2019-10055.
   Vaysman D.Sh., Aleksandrova G.A., Leonov S.A., et al., The accuracy of indicators and the structure of causes of death from diseases of the circulatory system in the Russian Federation in international comparisons. Current problems of health care and medical statistics. 2019; 3: 69-84. doi: 10.24411/2312-2935-2019-10055. [in Russian]
2. Diab N., Daya N.R., Juraschek S.P. et al. Prevalence and Risk Factors of Thyroid Dysfunction in Older Adults in the Community. Sci Rep. 2019; 9(1): 13156. doi: 10.1038/s41598-019-49540-z.
3. La Vignera, S., Condorelli R., Vicari E. et al. Endothelial dysfunction and subclinical hypothyroidism: A brief review. J Endocrinol Invest 2012; 35: 96–103. doi: 10.3275/8190.
4. Abdel-Moneim A., Gaber A.M., Gouda S. et al. Relationship of thyroid dysfunction with cardiovascular diseases: updated review on heart failure progression. Hormones (Athens). 2020; 19(3): 301-309. doi: 10.1007/s42000-020-00208-8.
5. Blum M.R., Gencer B., Adam L., et al. Impact of thyroid hormone therapy on atherosclerosis in the elderly with subclinical hypothyroidism: a randomized trial. J Clin Endocrinol Metab. 2018; 103(8): 2988–2997. doi: 10.1210/jc.2018-00279.
6. Garvey W., Garber A., Mechanick J., et al. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on the 2014 Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease. Endocr Pract. 2014; 20(9): 977-89. doi: 10.4158/EP14280.PSG.
7. Grani G., Cooper D. Levothyroxine Treatment Increases Mortality in Patients with Heart Failure. Clinical Thyroidology. 2020; 31(3): 95-98. doi: 10.1089/ct.2019.
8. Nagueh S.F., Smiseth O.A., Appleton C.P., et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2016; 29(4): 277-314. doi: 10.1016/j.echo.2016.01.011.
9. Ammar K.A., Paterick T.E., Khandheria B.K., et al. Myocardial mechanics: understanding and applying three-dimensional speckle tracking echocardiography in clinical practice. Echocardiography. 2012; 29(7): 861-872. doi: 10.1111/j.1540-8175.2012.01712.x.
10. Шабров А.В., Апресян А.Г., Добкес А.Л., и др. Современные методы оценки эндотелиальной дисфункции и возможности их применения в практической медицине. Рациональная фармакотерапия в кардиологии. 2016; 12(6): 733-742. doi: 10.20996/1819-6446-2016-12-6-733-742.
    Shabrov A.V., Apresyan A.G., Dobkes, A.L. et al. Current methods of endothelial dysfunction assessment and their possible use in the practical medicine. Rational Pharmacotherapy in Cardiology. 2016; 12(6): 733-742. doi: 10.20996/1819-6446-2016-12-6-733-742. [in Russian]
11. Bar-Gera H. The Target Parameter of Adjusted R-Squared in Fixed-Design Experiments. The American Statistician. 2017; 71 (2): 112-119. doi.org/10.1080/00031305.2016.1200489.
12. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019; 290: 140-205. doi: 10.1016/j.atherosclerosis.2019.08.014.
13. Fujimoto N., Hastings J.L., Bhella P.S., et al. Effect of ageing on left ventricular compliance and distensibility in healthy sedentary humans. J Physiol. 2012; 15; 590(8): 1871-80. doi: 10.1113/jphysiol.2011.218271.
14. Krishnasamy R., Hawley C.M., Stanton T. et al. Association between left ventricular global longitudinal strain, health-related quality of life and functional capacity in chronic kidney disease patients with preserved ejection fraction. Nephrology (Carlton). 2016; 21(2): 108-15. doi: 10.1111/nep.12557.
15. Swaid B., Kheiri B., Sundus S., et al. The effect of levothyroxine treatment in individuals with subclinical hypothyroidism on surrogate markers of atherosclerosis: a meta-analysis of randomized controlled trials. J Community Hosp Intern Med Perspect. 2019; 9(4): 305-309. doi: 10.1080/20009666.2019.1625704.