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Poltava State Medical University, Poltava, Ukraine

## Aspects of the development of hypothyroid cardiomyopathy associated with chronic systemic inflammation

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**Abstract. Background.** Cardiovascular manifestations are rated first among the symptoms of hypothyroidism. Since the highest prevalence of both coronary heart disease (CHD) and hypothyroidism is observed in the age group over 50 years old, the problem of combination of these nosologies in older people is increasing. Aim of the study is to investigate the structural and functional state of the left ventricular myocardium in hypothyroidism and CHD associated with chronic systemic inflammation. **Materials and methods.** To reach the objectives of the study, a randomized controlled clinical trial has been conducted in parallel groups of patients with hypothyroidism, CHD and combination of both. To form the main group, a screening analysis of 556 medical histories of patients with hypothyroidism and CHD during the period of 2006–2015 has been made, which were selected for further study. **Results.** It has been found that myocardial hypertrophy develops in all groups of patients, a decrease in thyroid function leads to remodeling of the left ventricular myocardium with the development of eccentric hypertrophy and the progression of systolic heart failure in comorbidity. A direct correlation between reduced ejection fraction and elevated interleukin-8 level has been detected. Evaluation of the state of chronic systemic inflammation revealed a significant increase in the level of interleukin-8 in patients with coronary heart disease associated with hypothyroidism ( $7.66 \pm 2.18$  pg/ml;  $p < 0.05$ ). This indicates that the persistence of pro-inflammatory state in patients with combined pathology is a negative prognostic factor for the development of cardiovascular complications. **Conclusion.** During echocardiography of patients with hypothyroidism, the impaired central hemodynamics can be determined by the indicators of the diastolic and systolic heart function. In patients with isolated hypothyroidism and in combination with coronary heart disease, thickening of the left ventricular myocardial walls is noted, which proves the specificity of changes in the heart geometry that leads to the development of eccentric hypertrophy. This can be considered as the marker of a “hypothyroid” heart whose severity can determine the severity of hypothyroidism. Activation of chronic systemic inflammation is more pronounced in conditions of comorbidity, with a negative prognostic effect on the state of the cardiovascular system.

**Keywords:** thyroid gland; heart; hypothyroidism; hypothyroid cardiomyopathy; myocardial hypertrophy; pro-inflammatory cytokines

### Introduction

One of the most common endocrine disorders among the population is hypothyroidism, which usually develops slowly over time and inapparently, so it can often be difficult to diagnose in time. The growing rates of the pathology makes this problem one of the most urgent, which determines the need to identify the features of the clinical course of the disease [1, 2].

Currently, it has been confirmed that the impact of chemicals substances in the environment is crucial in thyroid pathologies. The property of fluoride to suppress the function of the thyroid gland has been known since the 1930s. Adding fluoride to tap water for reducing the risk of caries development leads to constant maintenance for hypothyroidism [3, 4].

Coronary heart disease (CHD) is called the disease of the century or a new global epidemic of a non-infectious



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Для кореспонденції: Шаєнко Златослава Олександрівна, к.мед.н., доцент кафедри ендокринології з дитячими інфекційними хворобами, Полтавський державний медичний університет, вул. Шевченка, 23, м. Полтава, 36011, Україна; e-mail: [Zlataligonenko@gmail.com](mailto:Zlataligonenko@gmail.com); контактний тел.: +380500333392

For correspondence: Zlatoslava Shaienko, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Shevchenka st., 23, Poltava, 36011, Ukraine; e-mail: [Zlataligonenko@gmail.com](mailto:Zlataligonenko@gmail.com); phone: +380500333392

Full list of authors' information is available at the end of the article.

nature, as it dominates and continues to grow steadily, rising the morbidity and mortality rates, has significant social and clinical significance [5]. Recent reports show that subacute chronic systemic inflammation (CSI) contributes greatly to the pathogenesis of CHD. CSI is considered as the chronic activation of the body's immune system with hyperproduction of a wide spectrum of inflammatory cytokines [6–8].

Currently, numerous investigations have been carried out on the mechanisms of the impact of an underactive thyroid on the cardiovascular system. Even minor thyroid disorders can be accompanied by an increase in cardiometabolic risk [9, 10]. The nature of the cardiac structural and functional changes in hypothyroidism is determined by the level of blood pressure, the state of neurogenic, humoral, hormonal-metabolic and cellular mechanisms of cardiovascular regulation [11, 12]. Notably, subclinical hypothyroidism has a serious impact on the formation and development of cardiovascular diseases [13]. Scientific data report on the correlation between hypothyroidism and the “novel” risk factors for atherosclerosis as C-reactive protein, endothelial dysfunction, chronic systemic inflammation, procoagulant blood changes, etc. [14, 15].

Decreased activity of the thyroid gland leads to changes in the autonomic nervous system, enhanced regional and central (cerebral) hemodynamics, which is accompanied by diffuse ischemia of the brain and is clinically manifested by syncopal states, altered lipid metabolism, remodeling of the myocardium, which are not identical to atherosclerotic disorders that require a more detailed study for further optimization of the diagnostic search and provision of the adequate therapy [16, 17].

Therefore, the study of the features of the clinical course of CHD with hypothyroidism is relevant, as it is determined by the significant prevalence, unresolved issues regarding the pathogenetic mechanisms of its combination, and the insufficient effectiveness of treatment and prevention.

**Aim of the study.** Our paper is aimed at the study of the structural and functional state of the myocardium of the left ventricle in hypothyroidism and CHD associated with chronic systemic inflammation.

## Materials and methods

To meet the objectives of our study, the randomized controlled clinical trial was conducted in parallel groups followed by a comparison with a control group. To form the main group, a screening analysis of 556 medical histories of patients with hypothyroidism and CHD, who received treatment in the endocrinological and cardiology units at V.M. Sklifosovsky Poltava Regional Clinical Hospital of Poltava Regional Council during the period of 2006–2015 has been made. Medical histories of patients with hypothyroidism, cardiac and cardiothyroid pathologies were selected for further study.

The next stage of randomization was carried out directly with the patients who were treated in the endocrinological and cardiology units at V.M. Sklifosovsky Poltava Regional Clinical Hospital of Poltava Regional Council. At this stage, the involvement of patients into the study was made based on the analysis of complaints, medical history, physical examination of patients, results of the laboratory and instrumental examinations, analysis of compliance with inclusion/exclusion criteria.

Prior the study, all patients signed the written informed consent to participate in the clinical trial in compliance with the requirements of the Declaration of Helsinki of 1975 and the Order of the Ministry of Health of Ukraine No. 690 as of 23.09.2009 “On approval of the Procedure for conducting clinical trials of medicinal products and examination of clinical trial materials” and “Standard provision on ethics commissions”.

All patients have been assigned into four main groups.

Group I (n = 81; women = 72, men = 9; the average age  $46.0 \pm 6.1$  years) involved hypothyroid patients. Group II (n = 67; women = 27, men = 40; the average age  $59.0 \pm 8.8$  years) involved patients with CHD. Group III (n = 47; women = 39, men = 8; the average age  $55.0 \pm 7.5$  years) involved hypothyroid patients with CHD.

The comparison group involved 20 subjects (11 women, 9 men aged  $22.0 \pm 1.7$  years), without cardiovascular diseases and thyroid disorders.

The inclusion criteria for patients to be included into the clinical trial were the diagnosed primary hypothyroidism; postoperative hypothyroidism; co-occurrence of hypothyroidism with autoimmune thyroiditis; coronary heart disease: persistent forms of angina pectoris of I–III functional class; atherosclerotic and postinfarction cardiosclerosis, as well as combined pathology; the absence of decompensated chronic complications and concomitant diseases.

The diagnosis was verified on the basis of clinical manifestations of the disease, findings of clinical, biochemical and instrumental studies.

Thyroid-stimulating hormone (TSH), free thyroxine ( $fT_4$ ), free triiodothyronine ( $fT_3$ ), anti-thyroid-peroxidase antibodies (TPOAb) were determined by the ELISA method (a kit of Xema-Medica LLC).

The concentration of interleukin-1 $\beta$ , interleukin-8 was determined by enzyme immunoassay in blood serum (Vec-tor-Best JSC).

Echocardiography was made using the Vivid S60N ultrasonic diagnostic scanner (GE Vingmed, Norway) according to conventional technique, guided by the recommendations of the American and European Society of Echocardiography.

Statistical analysis: the hypothesis of normality of distribution of the studied parameters was checked using the Shapiro-Wilk test. In a normal distribution, quantitative traits were presented in the form of  $M \pm m$ . For a non-normal distribution, median, 25<sup>th</sup> and 75<sup>th</sup> percentile ( $Me$  [Q25; Q75]) were used. In a normal distribution, the reliability of differences was assessed using the Student's t test for independent and dependent samples. Non-parametric tests were used for a distribution different from normal: the Mann-Whitney U test for independent samples and the Wilcoxon test for dependent samples. Intergroup differences in qualitative characteristics were assessed using Pearson's  $\chi^2$  test (number of degrees of freedom  $ds = 1$ ) (for a small sample with Yates's correction). To assess the relationship between the parameters, we used the method of correlation analysis with the calculation of Pearson's correlation coefficients (in a normal distribution) and Spearman's correlation coefficient (in a distribution different from normal). Differences were considered reliable at the level of statistical significance  $p < 0.05$ .

## Results

Thyroid function of all subjects was assessed by measuring the  $fT_3$  and  $fT_4$ , TSH, TPOAb.

The group of patients with hypothyroidism showed a significant elevation of TSH ( $10.6 [2.0; 28.9] \mu IU/L$ ;  $p < 0.05$ ), which indicated decreased activity of the thyroid gland as compared to the group of healthy individuals. This tendency was also noted in the group of patients with hypothyroidism in combination with coronary heart disease: TSH was  $5.3 [1.9; 19.3] \mu IU/L$  ( $p < 0.05$ ).

Evaluation of the function of the thyroid gland in patients with coronary heart disease and healthy individuals showed no significant differences in the parameters:  $fT_3$   $4.19 \pm 0.91$  pmol/L,  $fT_4$   $16.18 \pm 2.31$  pmol/L, TSH  $2.06 [1.47; 2.6] \mu IU/L$ , which indicated normal function of the thyroid gland.

Echocardiography revealed thickening of the walls of the myocardium of the left ventricle in patients with hypothyroidism, indicating a significant thickness of the interventricular septum (IVS) ( $10.30 \pm 0.82$  mm;  $p < 0.05$ ) and the left ventricular posterior wall (LVPW) ( $10.27 \pm 0.82$  mm;  $p < 0.05$ ) as compared to the control. Moreover, left ventricular hypertrophy was indicated by an increase in the left ventricular myocardial mass (LVMM) ( $198.91 \pm 10.42$  g;  $p < 0.05$ ), left ventricular myocardial mass index (LVMMI) ( $104.04 \pm 10.89$  g/m<sup>2</sup>;  $p < 0.05$ ) and the relative thickness of the left ventricular wall (RTLWV) ( $0.41 \pm 0.05$  cm;  $p < 0.05$ ), as compared to the corresponding parameters of the comparison group (Table 1).

The above changes indicated the progression of the left ventricular myocardial hypertrophy and changes of heart geometry in patients with hypothyroidism, while a significant decrease in ejection fraction (EF) to  $53.44 \pm 1.94$  % ( $p < 0.05$ ) was noted as compared to the control group, indicating disrupted central hemodynamics in underactive thyroid.

In patients with coronary heart disease, the thickness of the IVS and LVPW was  $11.67 \pm 0.75$  mm ( $p < 0.05$ ) and  $11.47 \pm 0.71$  mm ( $p < 0.05$ ), respectively, that was significantly greater the corresponding parameters in the control group. Increased parameters of LVMM ( $244.68 \pm 7.82$  g;  $p < 0.05$ ), LVMMI ( $128.25 \pm 5.19$  g/m<sup>2</sup>;  $p < 0.05$ ), RTLWV

( $0.47 \pm 0.05$  cm;  $p < 0.05$ ) indicated more pronounced manifestations of the left ventricular remodeling in patients of group II. EF in this group of patients was  $53.88 \pm 1.61$  % ( $p < 0.05$ ).

In case of comorbidity, patients of group III showed the signs of LV myocardial hypertrophy (IVS  $11.20 \pm 0.73$  mm,  $p < 0.05$ ; LVPW  $10.90 \pm 0.78$  mm,  $p < 0.05$ ; LVMM  $234.06 \pm 6.93$  g,  $p < 0.05$ ; LVMMI  $120.4 \pm 5.0$  g/m<sup>2</sup>,  $p < 0.05$ ; RTLWV  $0.42 \pm 0.07$  cm,  $p < 0.05$ ), as compared to the control group; however, the EF parameter ( $49.9 \pm 2.1$  %;  $p < 0.05$ ) decreased significantly as compared to the group I and II.

Evaluation of the state of chronic systemic inflammation revealed a significant increase in the level of interleukin-8 in patients with coronary heart disease in combination with hypothyroidism ( $7.66 \pm 2.18$  pg/ml;  $p < 0.05$ ). This indicate that the persistence of pro-inflammatory state in patients with combined pathology is a negative prognostic factor for the development of cardiovascular complications.

Assessment of the values of LV MMI and RWT, made according to A. Ganau [3], identified the following types of LV remodeling:

- normal geometry of the LV: LV MMI was within the normal range and RWT was less than 0.45;
- concentric remodeling of the LV: LV MMI was within the normal range and RWT was greater than 0.45;
- concentric LV hypertrophy: LV MMI was greater than normal and RWT was greater than 0.45;
- eccentric LV hypertrophy: LV MMI was greater than normal and RWT was less than 0.45.

Among the hypothyroid patients, 38 subjects (46.92 %) had normal heart geometry, 31 subjects (38.27 %) had eccentric hypertrophy, 11 subjects (13.58 %) had concentric hypertrophy and one subject (1.23 %) had concentric remodeling; among the patients with coronary heart disease, 13 subjects (19.4 %) had normal heart geometry, 13 subjects (19.4 %) had eccentric hypertrophy, 38 subjects (56.7 %) had concentric hypertrophy, and three subjects (4.5 %) had concentric remodeling; among the patients with hypothyroidism combined with CHD, six subjects (10.7 %) had normal heart geometry, 30 subjects (63.8 %) had eccentric hypertrophy,

**Table 1. Parameters of structural and functional changes of the myocardium in patients with hypothyroidism, coronary heart disease and in combination of both,  $M \pm m$**

Parameter	Groups, number of subjects			
	I (n = 81)	II (n = 67)	III (n = 47)	Comparison group (n = 20)
IVS, mm	$10.30 \pm 0.82^*$	$11.67 \pm 0.75^*$	$11.20 \pm 0.73^*$	$7.95 \pm 0.53$
LVPW, mm	$10.27 \pm 0.82^*$	$11.47 \pm 0.71^*$	$10.90 \pm 0.78^*$	$8.10 \pm 0.51$
LVMM, g	$198.91 \pm 10.42^*$	$244.68 \pm 7.82^*$	$234.06 \pm 6.93^*$	$131.93 \pm 2.96$
LVMMI, g/m <sup>2</sup>	$104.04 \pm 10.89^*$	$128.25 \pm 5.19^*$	$120.4 \pm 5.0^*$	$78.07 \pm 3.06$
RTLWV, cm	$0.41 \pm 0.05^*$	$0.47 \pm 0.05^*$	$0.42 \pm 0.07^*$	$0.32 \pm 0.03$
EF, %	$53.44 \pm 1.94^*$	$53.88 \pm 1.61^*$	$49.9 \pm 2.1^{*,1,2}$	$62.41 \pm 0.51$
IL-1 $\beta$	$2.20 \pm 0.34$	$2.25 \pm 0.48$	$2.35 \pm 0.50$	$2.34 \pm 0.65$
IL-8	$4.78 \pm 1.63$	$3.18 \pm 1.39$	$7.66 \pm 1.63^{#,1,2}$	$3.02 \pm 2.65$

Notes: \* — the difference is reliable with the parameters of healthy individuals,  $p < 0.05$  (Mann-Whitney U test); # — the difference is reliable with the parameters of healthy individuals,  $p < 0.001$  (Mann-Whitney U test); <sup>1</sup> — the difference is reliable between the parameters of group I and III,  $p < 0.05$  (Student's t test); <sup>2</sup> — the difference is reliable between the parameters of group II and III,  $p < 0.05$  (Student's t test).

10 subjects (21.3 %) had concentric hypertrophy, and two subjects (4.2 %) had concentric remodeling. Thus, a decrease in thyroid function contributes to remodeling of the heart by the development of eccentric hypertrophy of the left ventricular myocardium, which can be considered a marker of a “hypothyroid” heart, the prominence of which can determine the severity of hypothyroidism.

Underactive thyroid leads to interstitial edema of tissues, activation of the parasympathetic part of the autonomic nervous system, progression of dyslipidemia and contributes to obesity. The combination of the above factors leads to an increase in the mass and mass index of the left ventricular myocardium, the development of eccentric hypertrophy of the myocardium, resulted in a decrease in left ventricular ejection fraction and accelerating heart failure.

## Discussion

The findings of the study have found that myocardial hypertrophy develops in all groups of patients, causing the development of changes of the geometry of the heart. Remodeling of the LV myocardium, leading to the development of eccentric hypertrophy, is characteristic of patients with hypothyroidism, which can be considered a marker of “hypothyroid” heart, the prominence of which can determine the severity of hypothyroidism [18].

The predominance of concentric hypertrophy of the LV myocardium was noted in patients with coronary heart disease. In patients of group III, a change of the geometry of the heart leads to the development of eccentric hypertrophy of the myocardium, which is accompanied by a significant decrease in EF with an increase in LV systolic dysfunction. The revealed direct relationship between the decrease in EF and the increase in the level of IL-8 indicates that the persistence pro-inflammatory state in patients with hypothyroidism combined with coronary heart disease is a negative prognostic factor [19].

It has been established that the development of impaired systolic and diastolic heart failure, the severity of which progresses with lowering the level of thyroid hormones is characteristic of CHD with underlying hypothyroidism. The typical echocardiographic signs are thickening of the walls and an increase in the mass of the myocardium, the prominence of which is related to the severity of thyroid dysfunction [20]. Heart remodeling processes in patients with coronary heart disease with hypothyroidism are associated with the predominance of the development of concentric hypertrophy and an increase in the number of patients with eccentric LV hypertrophy [21].

Perspectives of further research will encompass optimization the treatment of patients with hypothyroidism in combination with CHD, which is associated not only with replacement therapy with levothyroxine, but also with measures aimed at alleviation of CSI. Solving this issue will be of great importance for Ukraine, as the number of such comorbid patients is quite large and is tending to increase.

## Conclusions

On echocardiography of patients with hypothyroidism, the disruption of central hemodynamics can be determined by the indicators of the state of diastolic and systolic heart func-

tion. In patients with isolated hypothyroidism and in combination with coronary heart disease, thickening of the walls of the left ventricular myocardium is noted, which proves the specificity of changes of the geometry of the heart that leads to the development of eccentric hypertrophy. This can be considered as the marker of “hypothyroid” heart, the prominence of which can determine the severity of hypothyroidism. Activation of chronic systemic inflammation is more pronounced in conditions of comorbidity with a negative prognostic effect on the state of the cardiovascular system.

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#### Information about authors

Olena Horodynska, MD, PhD, Assistant at the Department of Internal Medicine 1, Poltava State Medical University, Poltava, Ukraine; e-mail: medredactor@i.ua; <https://orcid.org/0000-0002-6728-5392>  
Oksana Muravlova, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: medredactor@i.ua; <https://orcid.org/0000-0002-5319-7092>

Zlatozlava Shaienko, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: Zlatozlagonenko@gmail.com; phone: +380500333392; <https://orcid.org/0000-0002-8718-7589>

Iryna Dvornyk, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: medredactor@i.ua; <https://orcid.org/0000-0002-3809-8272>

**Conflicts of interests.** Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

**Authors' contribution.** Olena Horodynska — concept and design of the research, data collection, data analysis and interpretation, paper writing; Oksana Muravlova — paper editing, final approval of the paper; Zlatozlava Shaienko — data analysis and interpretation, paper editing; Iryna Dvornyk — final approval of the paper.

Горюдинська О.Ю., Муравльова О.В., Шаєнко З.О., Дворник І.А.  
Полтавський державний медичний університет, м. Полтава, Україна

### Аспекти розвитку гіпотиреоїдної кардіоміопатії на фоні хронічного системного запалення

**Резюме. Актуальність.** Серцево-судинні прояви посідають одне з перших місць у симптоматиці гіпотиреозу. Оскільки поширеність як ішемічної хвороби серця (ІХС), так і гіпотиреозу найбільша у віковій групі понад 50 років, зростає проблема поєднання цих нозологій в осіб старшого віку. **Мета дослідження:** вивчити структурно-функціональний стан міокарда лівого шлуночка при гіпотиреозі та ІХС на фоні хронічного системного запалення. **Матеріали та методи.** Відповідно до поставлених завдань було проведено рандомізоване контрольоване клінічне дослідження в паралельних групах пацієнтів із гіпотиреозом, ІХС та за умов поєднаної патології. Для формування основної групи виконано скринінговий аналіз 556 історій хвороби осіб із гіпотиреозом та ІХС протягом 2006–2015 років, що були відібрані для подальшого вивчення. **Результати.** Виявлено, що гіпертрофія міокарда розвивається в усіх групах хворих, зниження функції щитоподібної залози характеризується ремоделюванням міокарда лівого шлуночка з розвитком ексцентричної гіпертрофії, прогресуванням систолічної дисфункції в умовах коморбідності. Знайдений прямий кореляційний зв'язок зниження фракції викиду з підвищенням рівня інтерлейкіну-8. При оцінці хронічно-

го системного запалення виявлено достовірне підвищення рівня інтерлейкіну-8 у пацієнтів з ІХС, асоційованою з гіпотиреозом ( $7,66 \pm 2,18$  пг/мл;  $p < 0,05$ ). Це свідчить про те, що збереження прозапального стану в пацієнтів із поєднаною патологією є негативним прогностичним фактором розвитку серцево-судинних ускладнень. **Висновки.** При ехокардіоскопії хворих на гіпотиреоз порушення центральної гемодинаміки можна визначити за показниками діастолічної та систолічної функції серця. В осіб з ізольованим гіпотиреозом та при його поєднанні з ішемічною хворобою серця відзначається потовщення стінок міокарда лівого шлуночка, що свідчить про специфічність змін геометрії серця і призводить до розвитку ексцентричної гіпертрофії. Ці показники можна вважати маркером ураження серця при гіпотиреозі, вираженість якого може визначити тяжкість гіпотиреозу. Активізація хронічного системного запалення більш виражена за умов коморбідності, з негативним прогностичним впливом на стан серцево-судинної системи.

**Ключові слова:** щитоподібна залоза; серце; гіпотиреоз; гіпотиреоїдна кардіоміопатія; гіпертрофія міокарда; прозапальні цитокіни