

Comparative effect of dyslipidemia and hypothyroidism on the morphofunctional condition of the heart in coronary heart disease

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Abstract. Dyslipidemia and hypothyroidism are important risk factors for coronary heart disease. **Aim:** comparative assessment of the effect of dyslipidemia and hypothyroidism on the morphofunctional condition of the heart. **Material and methods.** The study included the results of examinations of 63 patients, 42 men and 21 women. All patients had coronary heart disease and were divided into two groups: dyslipidemia — 47 (75%) and hypothyroidism — 16 (25%) patients. Anamnestic data were collected from all patients, biochemical analysis of blood (lipid profile, blood sugar), electrocardiogram, echocardiogram were performed, and the results of coronary angiography were evaluated by SYNTAX score. These indicators were evaluated and compared in the initial and 1-year follow-up period after basic treatment in accordance with international classifications. The obtained results were developed in IBM Statistics SPSS-26 program; $p < 0.05$ was considered statistically accurate. **Results.** Dyslipidemia causes more damage to the coronary arteries than hypothyroidism. Thus, the number of localizations in the coronary arteries with more than 50% of the damage and the number of damaged vessels was higher in the dyslipidemia group than in the hypothyroidism group. Dyslipidemia can be considered a more dangerous risk factor than hypothyroidism.

Key words: dyslipidemia, hypothyroidism, coronary heart disease, myocardial infarction, angina pectoris, heart failure, coronary angiography.

Introduction

Coronary heart disease (CHD) has been identified as the leading cause of death worldwide. Dyslipidemia is accompanied by an increase in blood cholesterol, triglycerides, low-density lipoprotein (LDL), a decrease in high-density lipoprotein (HDL) and is a strong risk factor for CHD. It is known that with age, the amount of cholesterol, triglycerides, LDL in the blood increases. According to the National Health and Nutrition Examination Survey (NHANES), an increase in LDL is 11.7% between the ages of 20–39 and 41.2% between the ages of 40–64 [2]. Decreased total cholesterol levels have been found to reduce mortality and reduce the need for revascularization in patients with CHD [3]. There is a strong correlation between the amount of total cholesterol in the blood, LDL and the risk of cardiovascular disease. Meta-analyses of numerous studies have shown that a decrease in LDL leads to a reduction in cardiovascular risk. A drop in LDL of 1 mmol/L results in a 20–25% reduction in cardiovascular disease mortality [4].

It has been established that thyroid dysfunction affects the ability of the heart to contract, peripheral vascular resistance and blood pressure. Subclinical hypothyroidism may be an independent risk factor for CHD [5]. The results of several studies in patients with coronary angiography have shown that the incidence of CHD is inversely proportional to the level of free thyroxine (T_4) or triiodothyronine (T_3) in the blood and directly proportional to the level of thyrostimulating hormone [6–8].

Individual data on 55,287 participants between 1972 and 2007 were obtained from 11 prospective cohorts in the United States, Europe, Australia, Brazil, and Japan. According to available data, the risk of developing CHD was studied in 25,977 participants from 7 cohorts. Euthyroidism was defined as a thyroid-stimulating hormone (TSH) level of 0.50 to 4.49 mIU/L. Subclinical hypothyroidism was defined as a TSH level of 4.5 to 19.9 mIU/L with normal thyroxine concentrations. An increase in the risk of death from CHD and CHD has been observed in individuals with higher TSH levels in the blood, especially those with a TSH concentration of 10 mIU/L and above [9].

The purpose of the study is a comparative assessment of the impact of risk factors such as dyslipidemia and hypothyroidism on the course and complications of the disease separately in CHD.

Materials and methods

The research was conducted at the Scientific Research Institute of Cardiology. The study included patients diagnosed with CHD in accordance with generally accepted diagnostic criteria and the recommendations of the European Society of Cardiology (2019), with only one of the risk factors, such as dyslipidemia and hypothyroidism.

During the study, the results of 63 patients, regardless of gender and age, were analyzed, of which 42 (67%) were men and 21 (33%) women. In order to achieve the set goal, the persons aged 44–85 years (average age 64.1 ± 1.1) were examined. Anamnestic data were collected from all patients, biochemical analysis of blood: lipid profile, blood sugar, 12-lead electrocardiogram (ECG), transthoracic echocardiogram (echoCG) and coronary angiography were evaluated by SYNTAX score.

The collected data were divided into quantitative and qualitative characteristics. Quantitative indicators include age, systolic blood pressure, diastolic blood pressure, blood sugar, lipid profile, end-diastolic measurement (EDM), end-systolic measurement (ESM), left atrium (LA), ejection fraction (EF), SYNTAX score index, refers to the number of Q-wave and QS to determine the depth of the infarction on the ECG. Qualitative indicators include determination of functional classes of stable angina (SA) by the Canadian classification, determination of functional class (FC) of heart failure (HF) by NYHA classification, dynamics of the ST segment, T-wave on the ECG.

Patients' risk factors, number, sex, and age are shown in Table 1. The patients included in the study were divided into two groups: 47 (75%) patients (38 men and 9 women) in the dyslipidemia group. There were 16 (25%) patients (4 men and 12 women) in the hypothyroidism group. The dyslipidemia group included only patients with dyslipidemia, cholesterol above 5.2, triglycerides above 2.3, and HDLs above 3.0 mmol/L. The hypothyroidism group included patients without other risk factors with blood TSH > 4 mIU/L. The main diagnosis in both groups of patients was CHD. The dyslipidemia group was between the ages of 44–79 (average age 63.7 ± 1.3), and the hypothyroidism group was between the ages of 48–85 (average age 65.3 ± 2.3). There was no difference in the age of the patients between the groups.

Patients received basic treatment and were monitored for 1 year according to international classifications. Patients were re-examined

Table 1 Distribution of patients by risk factor, number, gender and age

Indicators	Risk factors	
	Dyslipidemia (n=47)	Hypothyroidism (n=16)
	n (%)	n (%)
Men	38 (81)	4 (25)*
Women	9 (19)	12 (75)*
Age	63.7±1.3	65.3±2.3

*Statistical accuracy of the difference between the dyslipidemia and hypothyroidism groups ($p<0.05$).

Table 2 Comparison of MI, number of QS and Q-wave, assessment of atherosclerotic vascular damage on the SYNTAX score scale between groups

Indicators	Dyslipidemia (n=47)	Hypothyroidism (n=16)
	n (%)	n (%)
MI	24 (55.8)	8 (50.0)
QS	10 (21.3)	5 (31.3)
Q	11 (23.4)	0 (0)*
SYNTAX score	light	4 (100)
	average	0 (0)
	heavy	0 (0)

*The accuracy of the difference between the dyslipidemia and hypothyroidism groups ($p\chi^2=0.033$).

every 6 months. ECG indicators, ECG results, FC of SA, THC were determined and compared. The presence of Q and QS myocardial infarction (MI) on the ECG, the dynamics of ST segment depression were taken as diagnostic important criteria. Patients were compared between EDM, ESM, LA, EF. Based on NYHA classifications, they were assessed every 6 months, divided into FC. The FC of SA was determined and dynamics were monitored. The results of coronary angiography were evaluated by SYNTAX score and divided into light (<22), medium (23–32) and heavy (>32) groups [10, 11].

The obtained results were developed by IBM Statistics SPSS-26 program, statistical analyzes: discriminant analysis (χ^2 -Pearson), variance analysis (F-Fisher), variation analysis (z-Kolmogorov — Smirnov; H-Kruskal — Wallis, U-Mann — Whitney) was conducted. If the difference between the groups is $p<0.05$, it is considered valid.

Results and Discussion

Dyslipidemia is a more damaging factor than hypothyroidism. Coronary arteries are more damaged in the dyslipidemia group, the ejection fraction decreases in more patients, FC III–IV of the HF is more common than in the hypothyroid group.

In total, MI was detected in 32 (50.8%) of 63 patients. Of these, 11 (34.4%) patients had Q-wave infarction and 15 (46.8%) patients had Q-wave infarction. Angina pectoris was found in 40 (63.5%) patients. Of these, 3 (7.5%) patients had unstable angina pectoris, 37 (92.5%) patients had stable angina pectoris: I FC — 8 (21.6%), II — 10 (27%), III — 15 (40.5%), IV — 4 (10.8%). In 27 (42.9%) patients, EF was <50%. There was no difference in the incidence (55.8% and 50.0%, $p\chi^2=0.690$, respectively). In 10 (21.3%) patients in the dyslipidemia group, 33 QS-wave and QS/N coefficient were 3.3, 11 (23.4%) patients had 29 Q-wave and a Q/N coefficient of 2.6. In the hypothyroidism group, 5 (31.3%) patients had 19 QS-wave and a QS/N coefficient of 3.8, no Q-wave infarction. The incidence of QS infarction did not differ statistically significantly between the dyslipidemia and hypothyroidism groups ($21.3\pm6\%$ and $31.3\pm11.6\%$, respectively; $p\chi^2=0.419$). Q-wave infarction was statistically significantly higher in the dyslipidemia group than in the hypothyroidism group ($23.4\pm6.2\%$ and 0; $p\chi^2=0.033$).

There was no statistically significant difference between the dyslipidemia and hypothyroidism groups in the degree of vascular damage on the SYNTAX score scale (18.4 ± 2.9 and 10.0 ± 3.7 ; $p\chi^2=0.160$,

respectively). In the dyslipidemia group, 9 (60.0%) patients had mild, 5 (33.3%) — moderate and 1 (6.7%) — severe damage. In the hypothyroidism group, 4 (100%) patients had mild lesions and no moderate or severe lesions ($p\chi^2=0.311$) (Table 2).

A retrospective analysis of coronary angiography protocols with a study of the frequency of revascularization previously performed and the severity of coronary atherosclerosis in patients with CHD with dyslipidemia and hypothyroidism is shown in Table 3. The results of the analysis showed that 4 (8.5%) out of 47 patients in the dyslipidemia group underwent ultrasound surgery, in the hypothyroidism group, 1 (6.3%) patient ($p\chi^2=0.773$). Coronary stenting was performed in 6 (12.8%) patients in the dyslipidemia group and in 2 (12.5%) patients in the hypothyroidism group ($p\chi^2=0.978$). The mean number of local coronary lesions was statistically significantly higher in the dyslipidemia group than in the hypothyroidism group (4.20 ± 0.52 and 1.50 ± 0.12 ; $p\chi^2=0.048$, respectively). There was no statistically significant difference between the dyslipidemia and hypothyroidism groups in the mean number of damaged coronary arteries (2.27 ± 0.23 and 1.50 ± 0.12 , respectively; $p\chi^2=0$).

Changes in the ECG during the observation period were assessed as: ST depression/elevation, negative T-wave formation, negative dynamics, reduction and normalization of ST depression/elevation, negative T-wave shrinkage, positive T-wave formation as positive dynamics (Table 4). After 1 year of treatment, the dynamics were positive in 14 (29.8%) patients in the dyslipidemia group, negative in 2 (4.3%) patients, and no dynamics in 31 (66.0%) patients. In the hypothyroidism group, 7 (43.8%) patients had positive dynamics, 3 (18.8%) patients had negative dynamics and 6 (37.5%) patients had no dynamics ($p\chi^2=0.028$).

Patients' echoCG was also compared at the beginning of the observation and 1 year later (Table 5).

Patients' echoCG was also compared. Thus, the mean values of EDM and ESM did not differ between dyslipidemia and hypothyroidism groups (5.54 ± 0.12 and 5.52 ± 0.23 ; $pF=0.913$, respectively) and (4.17 ± 0.13 and 4.07 ± 0.32 ; $pF=0.723$, respectively). EDM was above normal in 19 (40.4%) patients in the dyslipidemia group and 6 (37.5%) in the hypothyroidism group ($p\chi^2=0.836$). ESM was above normal in 20 (42.6%) patients in the dyslipidemia group and in 7 (43.8%) patients in the hypothyroidism group ($p\chi^2=0.933$). The mean LA measurement was statistically significant between the dyslipidemia and hypothyroidism groups (3.83 ± 0.07 and 4.26 ± 0.23 ; $pF=0.019$, respectively). Left ventricular EF was normal in 26 (55.3%) and low in 21 (44.7%) patients in the dyslipidemia group. In the hypothyroidism group, 7 (43.8%) patients were normal and 9 (56.3%) were low ($p\chi^2=0.424$). After 1 year of observation in groups EDM, ESM, changes in LA measurements were not statistically significant ($p>0.05$). EF was statistically significant in 76% of patients in the dyslipidemia group, increased in 24% of patients ($p\chi^2=0.028$),

Table 3 Frequency of revascularization and severity of coronary atherosclerosis in dyslipidemia and hypothyroidism groups

Severity of coronary atherosclerosis	Risk factors	
	Dyslipidemia (n=47)	Hypothyroidism (n=16)
Number of damaged coronary arteries	2.27±0.23	1.50±0.12
Severity of coronary atherosclerosis (score)	18.4±2.9	10.0±3.7
Number of localizations of vascular damage	4.20±0.52	1.50±0.12*

*The accuracy of the difference between the dyslipidemia and hypothyroidism groups ($p\chi^2=0.048$).

Table 4 Post-treatment dynamics of ECG

Indicators		Dyslipidemia (n=47)	Hypothyroidism (n=16)
ECG dynamics		n (%)	n (%)
ECG	No dynamics	31 (66)	6 (37.5)*
1 year later	Positive dynamics	14 (29.8)	7 (43.8)*
	Negative dynamics	2 (4.3)	3 (18.8)*

*The accuracy of the difference between the dyslipidemia and hypothyroidism groups ($p\chi^2<0.05$).

Table 5 Initial echoCG of the left ventricle and after 1 year

Patient groups		Dyslipidemia (n=47)	Hypothyroidism (n=16)
Time	EchoCG indicators		
Initial	EDM (sm)	5.54±0.12	5.52±0.23
	ESM (sm)	4.17±0.13	4.07±0.32
	LA (sm)	3.83±0.07	4.26±0.23*
	EF (%)	50.4±1.7	44.2±3.7
1 year later	EDM (sm)	5.65±0.23	5.60±0.32
	ESM (sm)	4.38±0.23	4.40±0.47
	LA (sm)	4.14±0.16	4.30±0.20
	EF (%)	42.4±3.2^	46.0±5.7

^An honest difference between the initial and 1-year indicators, *the accuracy of the difference between the dyslipidemia and hypothyroidism groups ($p=0.019$).

Table 6 Frequency of SA onset and post-treatment prevalence depending on FC

Indicator		Dyslipidemia (n=47)	Hypothyroidism (n=16)
		n (%)	n (%)
SA first	Yes	32 (68.1)	8 (50)
SA next	Yes	20 (42.5)^	6 (28.1)

^Difference between initial and 1 year later ($p=0.013$).

Table 7 Frequency of initial and post-treatment transmission of HF depending on FC

Patient groups		Dyslipidemia (n=47)	Hypothyroidism (n=16)
FC		n (%)	n (%)
Initial	No	27 (57.4)	9 (56.3)
	I–II FC	14 (29.8)	1 (6.25)*
	III–IV FC	6 (12.8)	6 (37.5)*
A year later	No	33 (70.2)	10 (62.5)
	I–II FC	13 (27.7)	5 (31.25)
	III–IV FC	1 (2.1)^	1 (6.25)^

*The accuracy of the difference between the dyslipidemia and hypothyroidism groups ($p<0.05$),

^difference between initial and 1 year later ($p<0.05$).

decreased in 29% of patients in the hypothyroidism group, and increased in 57% of patients ($p=0.293$).

Table 6 shows the incidence of SA in groups, initially and after 1 year. As shown in the **Table 6**, the incidence of SA in the dyslipidemia group after 1 year of observation decreased statistically correct by 42.5% ($p=0.013$). There was no statistically significant difference in the frequency of occurrence of individual FC of SA between the groups. In the follow-up, 26 (55%) patients in the dyslipidemia group had a decrease in FC of SA, 1 (2%) had an increase, and 20 (42%) had no change ($p=0.013$). In the hypothyroidism group, the FC of SA decreased in 4 (25%), increased in 2 (12.5%) and remained unchanged in 10 (62.5%) patients ($p=0.114$).

As shown in **Table 7**, in the initial patient response, I–II FC was statistically more common in the dyslipidemia group than in the hypothyroidism group (29.8 and 12.8%, respectively; $p=0.036$). III–IV FC were statistically less common in the dyslipidemia group than in the hypothyroidism group (12.8 and 37.5%; $p=0.030$). After 1 year of baseline treatment, FC in all three groups of patients was statistically significantly reduced. This showed that both groups responded well to treatment. Thus, in the dyslipidemia and hypothyroidism groups, the incidence of III–IV FC was statistically significantly reduced (12.8 and 2.1%, respectively; $p=0.04$; 37.5 and 6.25%, respectively; $p=0.026$).

In the dyslipidemia group, 4 (8.5%) patients and in the hypothyroidism group, 1 (6.3%) patients were treated ($p=0.773$). 6 (12.8%) patients in the dyslipidemia group and 3 (18.75%) in the hypothyroidism group had coronary stenting ($p=0.565$). However, the differences between the groups were not statistically significant.

Hypothyroidism was found to be more common in women with CHD than in men, and women had higher cholesterol and HDL levels during hypothyroidism, but there was no association between hypothyroidism and cholesterol increase in men [12]. In our study, hypothyroidism was 3 times more common in women than in men, but cholesterol and HDL levels in the hypothyroidism group were normal in both sexes.

Some other studies have found high levels of cholesterol and HDL in patients with hypothyroidism. Decreased lipoprotein catabolism and lipoprotein receptor expression have been shown to cause hypercholesterolemia during hypothyroidism [13].

In a study of 863 patients with CHD, all patients underwent coronary angiography, and patients with TSH levels above 4.0 mU/L had more vascular damage than normal, with 74.3% of male patients and 42 of women. 6% had a history of MI. The study found that the number of coronary vasoconstrictions also increased in patients with elevated TSH levels. However, in this study, risk factors such as arterial hypertension, diabetes mellitus and hypertriglyceridemia were also present in patients [14]. In our hypothyroidism group, patients did not have concomitant risk factors.

Conclusion

Dyslipidemia causes more damage to the coronary arteries than hypothyroidism. Thus, the number of localizations in the coronary arteries with more than 50% of the damage and the number of damaged vessels was higher in the dyslipidemia group than in the hypothyroidism group. Q-wave infarction was statistically more common in the dyslipidemia group than in hypothyroidism. In echoCG, LA grew more in the hypothyroidism group. ECG changes were positive in both groups after treatment. EF changed after treatment in the hypothyroidism group, and in the dyslipidemia group, EF decreased statistically despite treatment. HF of III–IV FC was more common during hypothyroidism than dyslipidemia. One year after treatment, a decrease in FC of all three groups was observed in both groups.

References

- Murray C.J., Lopez A.D. (1997) Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*, 349: 1269–1276.
- Pencina M.J., Navar-Boggan A.M., D'Agostino R.B. et al. (2014) Application of new cholesterol guidelines to a population-based sample. *N. Engl. J. Med.*, 370: 1422–1431. doi: 10.1056/NEJMoa1315665.
- Rohold A., Haastrup B., Larsen S. et al. (1996) Prevalence and Treatment in Patients Referred for Coronary Arteriography. *Cardiology*, 87: 497–501. DOI:10.1159/000177145.
- Cholesterol Treatment Trialists' Collaboration, Mihaylova B., Emberson J., Blackwell L. et al. (2012) The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*, 380(9841): 581–590. doi: 10.1016/S0140-6736(12)60367-5.
- Walsh J.P., Bremner A.P., Bulsara M.K. et al. (2005) Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch. Intern. Med.*, 165(21): 2467–2472. doi: 10.1001/archinte.165.21.2467.
- Kim E.S., Shin J.A., Shin J.Y. et al. (2012) Association between low serum free thyroxine concentrations and coronary artery calcification in healthy euthyroid subjects. *Thyroid*, 22(9): 870–876.
- Ertaş F., Kaya H., Soyduñ M.S. (2012) Low serum free triiodothyronine levels are associated with the presence and severity of coronary artery disease in the euthyroid patients: an observational study. *Anadolu Kardiyol. Derg.*, 12(7): 591–596.
- Yang L., Zou J., Zhang M. et al. (2013) The relationship between thyroid stimulating hormone within the reference range and coronary artery disease: impact of age. *Endocrine J.*, 60(6): 773–779.
- Rodondi N., den Elzen W.P.J., Bauer D.C.; Thyroid Studies Collaboration et al. (2010) Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*, 304(12): 1365–1374. doi: 10.1001/jama.2010.1361.
- Franzone A., Taniwaki M., Rigamonti F. et al. (2016) Angiographic complexity of coronary artery disease according to SYNTAX score and clinical outcomes after revascularisation with newer-generation drug-eluting stents: a substudy of the BIOSCIENCE trial. *EuroIntervention*, 12(5): e595–e604. DOI: 10.4244/EIJV12I5A99.
- Esper R.B., Farkouh M.E., Ribeiro E.E. et al. (2018) SYNTAX score in patients with diabetes undergoing coronary revascularization in the FREEDOM trial. *J. Am. Coll. Cardiol.*, 72(23 Pt. A): 2826–2837. DOI: 10.1016/j.jacc.09.046.

12. Mayer O.Jr., Simon J., Hrbkova J. et al. (2005) Epidemiological study of hypothyroidism as cardiovascular risk in the population. *Cas Lek Cesk*, 144: 459–464. doi:10.2147/vhrm.2006.2.4.499.
13. Scabbottolo L., Trezze E., Roma P. et al. (1986) Experimental hypothyroidism modulates the expression of the low density lipoprotein receptor by the liver. *Atherosclerosis*, 59: 329–333.
14. Волкова А.Р., Дора С.В., Бадмаева М.И. и др. (2008) Функциональное состояние щитовидной железы у больных ишемической болезнью сердца жителей Санкт-Петербурга. *Вест. Санкт-Петербургского ун-та*, 11(4): 46–51.

Порівняльний вплив дисліпідемії та гіпотиреозу на морфофункціональний стан серця при ішемічній хворобі серця

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Анотація. Дисліпідемія та гіпотиреоз є важливими факторами ризику ішемічної хвороби серця. **Мета:** порівняльна оцінка впли-

ву дисліпідемії та гіпотиреозу на морфофункціональний стан серця. **Об'єкт і методи дослідження.** Дослідження включало результати обстежень 63 пацієнтів, 42 чоловіків і 21 жінки. Усі хворі мали ішемічну хворобу серця і були розподілені на дві групи: з дисліпідемією — 47 (75%) та з гіпотиреозом — у 16 (25%) пацієнтів. У всіх хворих зібрано анамнестичні дані, проведено біохімічний аналіз крові (ліпідний профіль, рівень глюкози в крові), електрокардіограму, ехокардіограму, оцінку результатів коронароангіографії за шкалою SYNTAX. Ці показники оцінювали та порівнювали при початковому рівні та після 1 року спостереження після базисного лікування відповідно до міжнародних класифікацій. Отримані результати оброблено в програмі IBM Statistics SPSS-26; $p < 0,05$ вважали статистично значущим. **Результати.** Дисліпідемія викликає більше ураження коронарних артерій, ніж гіпотиреоз. Таким чином, кількість локалізацій у коронарних артеріях з більше ніж 50% пошкодженням та пошкоджених судин у групі з дисліпідемією була більшою, ніж у групі з гіпотиреозом. Дисліпідемію можна вважати більш небезпечним фактором ризику, ніж гіпотиреоз.

Ключові слова: дисліпідемія, гіпотиреоз, ішемічна хвороба серця, інфаркт міокарда, стенокардія, серцева недостатність, коронарна ангіографія.

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Received: 08.04.2022

Accepted: 25.04.2022