УДК 616.132.2-007.61:616.447-008.61
DOI 10.17802/2306-1278-2025-14-1-15-25

ОСОБЕННОСТИ ПОРАЖЕНИЯ КОРОНАРНЫХ АРТЕРИЙ ПРИ ГИПОТИРЕОЗЕ У НАСЕЛЕНИЯ ЮЖНОЙ ИНДИИ

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ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

Основные положения

• У пациентов с ишемической болезнью сердца на фоне гипотиреоза, как манифестного, так и вновь диагностированного, наблюдается более выраженная дислипидемия, чаще выявляются диастолическая дисфункция левого желудочка и трехсосудистая коронарная болезнь. Прием заместительной гормональной терапии позволяет уменьшить выраженность дислипидемии. Количество пораженных коронарных артерий связано с уровнем тиреостимулирующего гормона. При многофакторном анализе только наличие гипотиреоза, уровень тиреоидстимулирующего гормона и частота сердечных сокращений были независимо связаны с наличием трехсосудистой коронарной недостаточности.

Цель	Изучить тяжесть ишемической болезни сердца (ИБС) у пациентов с гипотиреозом, а также оценить факторы, связанные с тяжестью коронарного атеросклероза в южноиндийском регионе.
Материалы и методы	Пациенты с ИБС (n = 240) были обследованы в клинике Института медицинских наук Кералы с проведением лабораторных анализов (общий анализ крови, биохимические исследования, оценка уровня тиреотропного гормона (ТТГ), свободного тироксина (СТ4)), инструментальных исследований – электрокардиографии (ЭКГ), эхокардиографии (ЭхоКГ) и инвазивной коронарной ангиографии (КАГ). Испытуемые были разделены на три группы: 1-я группа – пациенты с ИБС без патологии щитовидной железы (n = 150), 2-я группа – пациенты с ИБС с недавно диагностированным гипотиреозом без терапии (n = 15) и 3-я группа (n = 75) – пациенты с ИБС с гипотиреозом на фоне заместительной гормональной терапии. Группы сравнивались по исследуемым лабораторным показателям и результатам инструментального обследования.
Результаты	У больных ИБС с гипотиреозом, как без терапии, так и с терапией, выявлены статистически значимые различия в повышении концентрации глюкозы крови, общего холестерина, триглицеридов, липопротеинов низкой плотности и снижении содержания антиатерогенного липопротеина высокой плотности по сравнению с больными ИБС без гипотиреоза ($p < 0,001$). В группах пациентов с гипотиреозом, которым была оптимально подобрана заместительная гормональная терапия, а также без терапии преобладало количество пациентов с трехсосудистой ишемической болезнью сердца (66,7% и 60,0%), чем в группе пациентов с ИБС без гипотиреоза (13,3%, $p < 0,05$). Соответственно, при оценке ишемической болезни сердца с помощью SYNTAX Score пациенты с гипотиреозом в обеих группах чаще имели тяжелое поражение коронарных артерий. В исследуемой группе пациентов с ИБС выявлена статистически значимая ассоциация между уровнем ТТГ и количеством пораженных коронарных артерий ($r = 0,324$, $p < 0,001$). В модели множественной бинарной логистической регрессии следующие факторы имели значимую связь с заболеванием 3 сосудов: группа с гипотиреозом (B = 2,151; $p = 0,012$), уровень свободного Т4 (B = 0,919; $p = 0,021$) и частота сердечных сокращений (B = 0,933; $p = 0,011$).

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Заключение	Результаты настоящего исследования подчеркивают необходимость выявления гипотиреоза у пациентов с ишемической болезнью сердца. Для коррекции дислипидемии у таких пациентов необходимо дополнительно принимать заместительную гормональную терапию. Возможность улучшения прогноза за счет подобных вмешательств требует подтверждения в дальнейших исследованиях.
Ключевые слова	Ишемическая болезнь сердца • Гипотиреоз • Степень тяжести коронарного атеросклероза

Поступила в редакцию: *19.10.2024;* ***поступила после доработки:*** *22.11.2024;* ***принята к печати:*** *24.12.2024*

FEATURES OF CORONARY ARTERY LESIONS IN HYPOTHYROIDISM IN THE POPULATION IN SOUTH INDIA

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Highlights

• In patients with coronary artery disease in the presence of hypothyroidism, both manifest and newly diagnosed, more pronounced dyslipidemia is observed, left ventricle diastolic dysfunction and three-vessel coronary disease are more often detected. Taking hormone replacement therapy helps reduce the severity of dyslipidemia. The number of affected coronary arteries is associated with thyroid-stimulating hormone levels. In multivariate analysis, only the presence of hypothyroidism, thyroid-stimulating hormone levels, and heart rate were independently associated with three-vessel coronary artery disease.

Aim	To examine the severity of coronary artery disease (CAD) in patients with hypothyroidism and also to evaluate the factors associated with the severity of coronary atherosclerosis in the South Indian region.
Methods	CAD patients (n = 240) were examined at the Kerala Institute of Medical Sciences clinic with laboratory tests (general blood count, biochemical studies, assessment of thyroid hormone levels thyroid stimulating hormone (TSH), free thyroxine (FT4)), instrumental studies – electrocardiography (ECG), echocardiography (EchoCG), and invasive coronary angiography (CAG). The subjects were divided into three groups: Group 1 – CAD patients without thyroid pathology (n = 150), Group 2 – CAD patients with newly diagnosed hypothyroidism without therapy (n = 15) and Group 3 (n = 75) CAD patients with hypothyroidism with hormone replacement therapy. The groups were compared according to the studied laboratory parameters and the results of instrumental examination.
Results	In CAD patients with hypothyroidism, both without therapy and with therapy, statistically significant differences were revealed in the increase in the concentration of blood glucose, total cholesterol, triglycerides, low-density lipoproteins and a decrease in the content of anti-atherogenic high-density lipoprotein, compared with CAD patients without hypothyroidism ($p < 0.001$). In the groups of patients with hypothyroidism who had optimally selected hormone replacement therapy, as well as without therapy, the number of patients with three-vessel coronary artery disease (66.7% and 60.0%) prevailed than in the group of CAD patients without hypothyroidism (13.3%, $p < 0.05$). Accordingly, when assessing coronary artery disease using the SYNTAX Score, patients with hypothyroidism in both groups were more likely to have severe coronary artery lesion. In the study group, CAD patients showed statistically significant associations between TSH levels and the number of affected coronary arteries ($r = 0.324$, $p < 0.001$). In a multiple binary logistic regression model the following factors had a significant association with 3-vessel disease: group with hypothyroidism ($B = 2.151$; $p = 0.012$), free T4 level ($B = 0.919$; $p = 0.021$), and heart rate ($B = 0.933$; $p = 0.011$).

Conclusion The results of the present study highlight the need to identify hypothyroidism in patients with coronary artery disease. To correct dyslipidemia in such patients, it is necessary to additionally take hormone replacement therapy. The possibility of improving prognosis through such interventions requires confirmation in further studies.

Keywords Coronary artery disease • Hypothyroidism • Severity of coronary atherosclerosis

Received: *19.10.2024;* ***received in revised form:*** *22.11.2024;* ***accepted:*** *24.12.2024*

Список сокращений

A – peak velocity of late transmitral flow
CAD – coronary artery disease
CAG – coronary angiography
E – peak velocity of early transmitral flow
e' – peak early diastolic velocity at the lateral mitral annulus
ECG – electrocardiography
FT3 – free T3
FT4 – free thyroxine
LAVi – left atrial volume index
LV – left ventricular
TSH – thyroid stimulating hormone

Introduction

The development and progression of coronary artery disease (CAD) is caused by a number of known risk factors (dyslipidemia, smoking, arterial hypertension, physical inactivity, psychosocial stress, hereditary predisposition). The combination of coronary artery disease with other pathogenetic conditions can contribute to its progression and worsen the prognosis. We can recall such comorbid conditions as diabetes mellitus, chronic lung pathology, chronic kidney disease. In this series, thyroid diseases can also have adverse effects on the cardiovascular system, such as lipid profile and blood pressure. Thus, hypothyroidism has been shown to have a negative impact on factors affecting heart health, such as body mass index, lipid profile, blood pressure, endothelial function and left ventricular function [1]. Despite the fact that the role of hypothyroidism during coronary heart disease has been discussed for quite a long time, there are no recommendations for the management of such patients yet. The relevance of the study of this topic is due to the following factors: the influence of thyroid hormones on the membrane current of cardiomyocyte ions, stroke volume, morphofunctional parameters of the myocardium, and on the state of the peripheral vascular bed. Thyroid hormones are closely related to the regulation of the renin-angiotensin system [2, 3]. A controversial issue remains the influence of hypothyroidism on changes in lipid profile parameters, which play a critical role in assessing the course of coronary artery disease. However, data on the effect of hypothyroidism on the course of dyslipidemia are contradictory. According to some studies, hormone imbalance in hypothyroidism negatively changes the ratio of lipid profile fractions, and also worsens the condition of the endothelium [4–6]. There are also publications with data refuting the negative effect of thyroid hormones on the course of dyslipidemia [7].

Literary sources contain data on the negative impact of hypothyroidism on the condition of the coronary artery. According to studies, patients with primary hypothyroidism and CAD have a higher incidence of coronary artery disease compared to patients with CAD without hypothyroidism [8]. On the other hand, in subclinical hypothyroidism, non-calcified soft atherosclerotic plaques are more often observed, which does not provide a complete picture of the effect of hypothyroidism on CAD [9]. Although dyslipidemia appears to be one of the main causes of the development of coronary atherosclerosis, in hypothyroidism its pathogenetic effect on the severity of coronary atherosclerosis remains incompletely studied.

According to studies in developed Western countries, an increase in total cholesterol and triglycerides in hypothyroidism has been shown [10], however, in other countries, data on the effect of hypothyroidism on the lipid profile and other risk factors are contradictory [11–17]. This may be due to geographical, ethnic, socio-economic and hereditary factors [18]. For example, dyslipidemia is less common in black Africans with hypothyroidism [16]. Also, a study conducted in South India did not note the effect of subclinical hypothyroidism on the lipid profile of patients in a population-based study [7]. Therefore, the problem of the relationship between hypothyroidism and the state of the coronary bed (and the factors mediating their interaction) in various regions remains relevant.

This served as the basis for the present study, the **aim** of which was to examine the severity of coronary artery disease in patients with hypothyroidism and also to evaluate the factors associated with the severity of coronary atherosclerosis in the South Indian region.

Methods

Study population

In a cross-sectional study conducted at the clinic of the Kerala Institute of Medical Sciences (Trivandrum,

India) from 2015 to 2018, 1 560 patients were examined who underwent invasive coronary angiography and studied their thyroid hormone levels. Inclusion criteria were as follows: stable coronary artery disease, established diagnosis of hypothyroidism. Exclusion criteria: acute forms of coronary artery disease at the time of inclusion in the study, severe and decompensated forms of hypothyroidism, other pathologies of the thyroid gland (nodular goiter, tumors, thyrotoxicosis), chronic heart failure with functional class III–IV NYHA, atrial flutter/fibrillation, diabetes mellitus, stage III obesity, other serious illnesses, as well as refusal to participate in the study. At the stage of inclusion of patients in the study, the therapy taken for CAD was assessed. Treatment was in accordance with current recommendations of the European Society of Cardiology. Patients who, for any reason, did not take certain medications or had contraindications to them according to clinical recommendations were excluded from the study. According to the inclusion and exclusion criteria, 240 patients with stable CAD were selected (Figure 1). The study was performed in accordance with the Good Clinical Practice standards and the principles of the Declaration of Helsinki. The study protocol was approved by the Local Ethical Committee. Informed consent was obtained from all subjects involved in the study.

Data Collection

The examination plan included laboratory tests (general blood count, biochemical studies, assessment of thyroid hormone levels T4, TSH) and instrumental studies (ECG, echocardiography). All patients underwent invasive coronary angiography (CAG). Diagnosis and treatment of hypothyroidism was carried out in accordance with the American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults [19]. The subjects were divided into three groups: Group 1 – CAD patients without thyroid pathology (n = 150), Group 2 – CAD patients with newly diagnosed hypothyroidism without therapy (n = 15) and Group 3 (n = 75) – CAD patients with hypothyroidism and hormone replacement therapy (L-thyroxine with dosage varied from 25 to 100 mcg/day). The groups were compared according to the studied laboratory parameters and the results of instrumental examination. All patients who participated in the study provided prior written informed consent, taking into account the ethical principles outlined in the 2013 World Medical Association Declaration of Helsinki Revision.

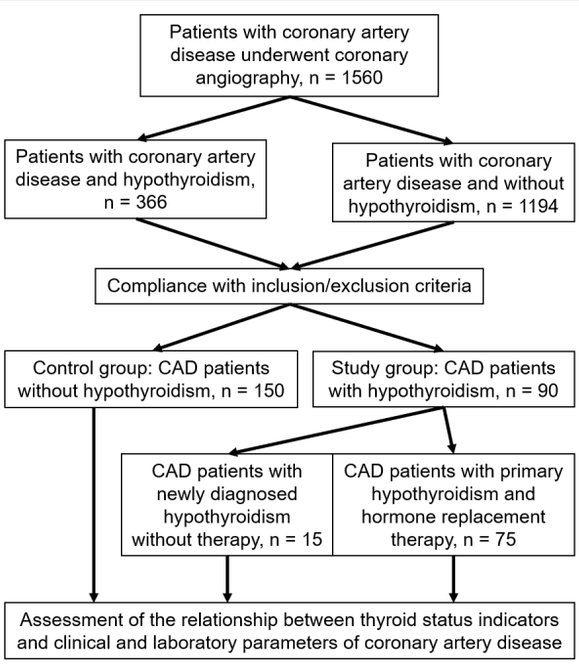

Figure 1. Flowchart of patient selection
Note: *CAD – coronary artery disease.*

Thyroid hormone determination

Before CAG, fasting venous blood tests were performed to measure cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, and cholesterol-to-low-density lipoprotein ratio. The levels of lipid profile, transaminases, bilirubin, albumin, creatinine, C-reactive protein and thyroid hormones (TSH, T4), as well as the concentrations of Na, Ca, K ions were determined using a Cobas 6 000 apparatus. The concentration of troponin T and myoglobin was studied using the apparatus Cobas e411ECLIA. The concentration of thyroid-stimulating hormone was measured in milliinternational units per liter (mIU/L), the content was considered normal 0.4–4.0 mIU/L. The level of free thyroxine in the blood was measured in picomoles per liter (pmol/L), a concentration of 10.8–24.5 pmol/L was considered normal. TSH and T4 free were determined by chemiluminescence immunoassay on microparticles (chemiluminescent immunoassay on microparticles). Blood was collected using disposable vacuum systems (BD Vacutainer) with a coagulation activator (SiCh) from the cubital vein after patients had rested for 15 minutes on an empty stomach from 8 to 9 am. Venous blood in special transport containers was delivered to the laboratory in a timely manner (delivery time did not exceed 60 minutes after blood collection). Blood serum for research was obtained by centrifuging tubes at 3,000 rpm for 10 minutes. The resulting serum was stored in disposable Eppendorf tubes at –70 °C; defrosting, if necessary, was carried out no more than once. The diagnosis of chronic kidney disease was based on KDIGO criteria [20]. Glomerular filtration rate was calculated using the CKD-EPI formula.

CAG and the severity of coronary artery lesions

Coronary angiography was performed CAG was done by the Judkins technique via radial or femoral artery using a Siemens Artiz Zee and Philips FD-20 device. CAD was defined as a greater than 70%

stenosis by visual assessment in at least one major vessel or principal side branch. The Syntax score was used to evaluate the severity of coronary artery lesions. The coronary artery lesions were divided into three categories according to Syntax scores: coronary artery mild lesions (Syntax score 0–22), coronary artery moderate lesions (Syntax score 23–32), and coronary artery severe lesions (Syntax score > 32).

Echocardiography

Echocardiography was performed using Vivid E9 and Vivid 1 (Wipro GE Medical System). The images were obtained using the long and short axes in the parasternal and apical projections and all measurements were performed according to current recommendations [21]. The dimensions of the heart chambers (left atrial dimension (LA) and volume index (LAVi), left ventricular end-diastolic and end-systolic dimensions, left ventricular end-diastolic and end-systolic volumes, regional abnormalities of left ventricular wall contraction, left ventricular ejection fraction, and the presence and degree of regurgitation were measured. Left ventricular ejection fraction was calculated according to the Simpson method. In pulsed-wave Doppler imaging, LV diastolic parameters were studied: peak velocity of early (E) and late (A) transmitral filling of LV and their ratio (E/A), and deceleration time. Tissue Doppler imaging was used to measure peak early diastolic velocity at the lateral mitral annulus (e').

The assessment of left ventricular diastolic function was carried out according to the following criteria [22]: with an E/A ratio ≤ 0.8 and a velocity E ≤ 50 cm/s, diastolic dysfunction was defined as minor (grade I / delayed relaxation). In patients with E/A ratio 0.8–2.0 and ml/m^2, the grade II of diastolic dysfunction determined based on at least two of three indicators (E/e′ > 14, LAVi ≥ 34, and peak velocity of tricuspid regurgitation > 2,8 m/s). If the E/A ratio was > 2, diastolic dysfunction was defined as severe (grade III/restriction).

Electrocardiography

ECG analysis was performed in 12 standard leads using a Mac 1 200 Marquette GE Medical System electrocardiograph. The values of the RR, PR and QT intervals, P-waves, Q-waves, the size of the ST segment, the position of the T wave were recorded. Using these parameters, the heart rate, the position of the heart axis, the presence or absence of sinus rhythm, atrial enlargement, ventricular hypertrophy, partial blockade of the conduction system. By changing the position of the T wave and/or depression of the ST segment, the presence and severity of ischemic changes in the myocardium were verified.

Statistical Analyses

Processing was carried out using application packages "Statistica 10.0 for Windows" (StatSoftInc., USA) and SPSS 10.0 (IBM, USA). The distribution of quantitative data was checked using the Shapiro-Wilk test. Considering that the distribution of all quantitative characteristics differed from normal, they are presented as a median (Me) indicating the low (LQ) and upper (UQ) quartiles. To compare groups, the Kruskal-Wallace, Mann-Whitney, and χ^2 tests were used. When the number of observations was small, Fisher's exact test with Yates' correction was used. Bonferroni correction was used to address the problem of multiple comparisons. If the data distribution was non-normal, the Spearman rank correlation method was used. We used binary logistic regression to identify factors independently associated with multivessel CAD or 3-vessel CAD (forward stepwise LR method). The critical significance level of the estimated statistical hypotheses is $p < 0.05$.

Results

The initial clinical, anamnestic and laboratory characteristics of all examined groups are presented in Table 1. There were no differences by gender in the 3 groups. CAD patients with newly diagnosed hypothyroidism without therapy were statistically significantly older ($p = 0.018$). When analyzing comorbid pathology in the studied patients, it was revealed that hypertension and dyslipidemia were statistically significantly more common in CAD patients and hypothyroidism with replacement therapy (89.3% and 65.3%) than in CAD patients without thyroid pathology (50.0% and 30.0%) and with newly diagnosed hypothyroidism without therapy (53.3% and 60.0%; $p < 0.001$). At the same time, chronic kidney disease, anemic syndrome and excess body weight were statistically significantly more often registered in patients with coronary artery disease with newly diagnosed hypothyroidism without therapy ($p < 0.05$).

A comparative analysis of basic parameters reflecting the course of hypothyroidism in CAD patients was carried out. As expected, in patients with hypothyroidism the level of thyroid hormones was statistically significantly higher than in CAD patients without hypothyroidism ($p < 0.05$). Also, in patients with hypothyroidism, both without therapy and with therapy, statistically significant differences were revealed in the increase in the concentration of blood glucose, total cholesterol, triglycerides, low-density lipoproteins and a decrease in the content of anti-atherogenic high-density lipoprotein, compared with CAD patients without hypothyroidism ($p < 0.001$).

In a comparative analysis of ECG parameters, the median heart rate values in all groups were within the normative values, however, it was statistically significantly lower in groups with hypothyroidism (without Me therapy 57 beats per minute, with Me therapy 62 beats per minute) than in the group

of patients with coronary artery disease without hypothyroidism (Me 79 beats per minute), p < 0.001. According to ECG data, signs of left ventricular myocardial hypertrophy were statistically significantly more often recorded in groups with hypothyroidism (p < 0.001). Statistically significant differences were also obtained in the duration of the PR interval and QRS amplitude (Table 2).

Table 3 presents an assessment of the structural and functional parameters of the left heart according to echocardiography data. The left ventricular wall thickness was significantly higher in the groups with hypothyroidism compared to the group without hypothyroidism (p < 0.001). The median left ventricular ejection fraction in all groups was below standard values, but it was statistically significantly higher in the group of patients with hypothyroidism and replacement therapy) than in patients without

Table 1. Basic clinical and laboratory data in groups CAD patients

	CAD without hypothyroidism (n = 150)	CAD + Hypothyroidism without therapy (n = 15)	CAD + Hypothyroidism with therapy (n = 75)	p
Men (n, %)	61 (40.7)	9 (60.0)	26 (34.7)	0.181
Age (years, Me [LQ; UQ])	57.5 [51.0; 63.0]	64.0 [59.0; 67.0]$^{+}$	59.0 [52.0; 64.0]	0.018
Body mass index (kg/m^2, Me [LQ; UQ])	26.8 [25.3; 27.4]	29.3 [27.2; 30.3]$^{+}$	27.4 [24.8; 29.7]*$^{\#}$	< 0.001
Comorbid pathology				
Arterial hypertension, (n, %)	75 (50.0)	8 (53.3)	67 (89.3)*$^{\#}$	< 0.001
Dyslipidemia, (n, %)	45 (30.0)	9 (60.0)$^{+}$	49 (65.3)*	< 0.001
Chronic kidney disease, (n, %)	39 (26.0)	8 (53.3)	14 (18.7)	0.02
Chronic obstructive pulmonary disease, (n, %)	29 (19.3)	6 (40.0)	15 (20.0)	0.167
Anemia, (n, %)	22 (14.7)	6 (40.0)$^{+}$	9 (12.0)$^{\#}$	0.02
Laboratory indicators				
FT4, pmol/L, Me [LQ; UQ]	12.91 [12.39; 17.00]	9.5 [8.03; 10,1]$^{+}$	15.34 [12.78; 16.61] *	< 0.001
TSH, mIU/L, Me [LQ; UQ]	1.9 [1.1; 2.3]	11.0 [5.5; 15.5]$^{+}$	4.2 [2.06; 11.2]*	< 0.001
Troponin T, pg/mL; Me [LQ; UQ]	31.5 [12.2; 672.0]	292.0 [29.0; 800.0]	27.0 [12.0; 324.0]	0.07
CK MB, ng/mL; Me [LQ; UQ]	4.03 [2.8; 32.9]	10.7 [4.9; 29.0]	5.0 [3.4; 10.0]	0.14
Glucose, mg/dl, Me [LQ; UQ]	171.19 [117.13; 196,42]	261.19 [250.48; 272.10]$^{+}$	216.24 [86.45; 250.48]$^{\#}$	< 0.001
HbA1C, %; Me [LQ; UQ]	7.7 [6.1; 8.7]	10.4 [10.1; 10.8]$^{+}$	9.2 [5.7; 10.0]*$^{\#}$	< 0.001
Cholesterol, mmol/L; Me [LQ; UQ]	4.6 [4.3; 4.9]	5.7 [5.1; 7.5]$^{+}$	5.5 [5.2; 7.0]*	< 0.001
Triglycerides, mmol/L, Me [LQ; UQ]	1.1 [0.98; 1.2]	1.9 [0.9; 3.3]$^{+}$	1.5 [1.0; 2.1]*	< 0.001
HDL, mmol/L; Me [LQ; UQ]	1.1 [1.04; 1.2]	0.99 [0.83; 1.09]$^{+}$	1.1 [0.9; 1.3]	0.006
LDL, mmol/L; Me [LQ; UQ]	2.9 [2.7; 3.3]	4.03 [3.8; 5.3]$^{+}$	3.7 [3.6; 4.9]*	< 0.001
VLDL, mmol/L; Me [LQ; UQ]	0.49 [0.44; 0.52]	0.88 [0.4; 1.5]$^{+}$	0.7 [0.5; 1.0]*	< 0.001
Atherogenic coefficient, Me [LQ; UQ]	4.0 [3.7; 4.4]	7.2 [4.8; 8.0]$^{+}$	5.6 [4.2; 7.0]*$^{\#}$	< 0.001
GFR (mL/min/1.73 m^2), Me [LQ; UQ]	95.7 [93.2; 99.2]	80.3 [78.2; 88.0]$^{+}$	88.7[82.1; 97.2]*$^{\#}$	< 0.001

Note: *$^{+}$ p < 0.05 when compared groups 1 and 2; * p < 0.05 when compared groups 1 and 3; $^{\#}$ p < 0.05 when compared groups 2 and 3; CAD – coronary artery disease; CK MB – creatine phosphokinase MB; GFR – glomerular filtration rate; HbA1C – glycated hemoglobin; HDL – high density lipoproteins; LDL – low density lipoproteins; T4 – thyroxine; TSH – thyroid-stimulating hormone; VLDL – very low-density lipoproteins.*

Table 2. Basic data of electrocardiography in groups CAD patients

	CAD without hypothyroidism (n = 150)	CAD + Hypothyroidism without therapy (n = 15)	CAD + Hypothyroidism with therapy (n = 75)	p
Heart rate, beats/minute, Me [LQ; UQ]	79.0 [73.0; 86.0]	57.0 [56.0; 63.0]$^{+}$	62.0 [56.0; 63.0]*	< 0.001
QRS amplitude (thoracic lead), mm, Me [LQ; UQ]	9.0 [8.0; 10.0]	3.0 [3.0; 4.0]$^{+}$	3.0 [3.0; 4.0]*	< 0.001
QRS amplitude (enhanced limb leads), mmMe [LQ; UQ]	15.0 [15.0; 17.0]	8.0 [7.0; 9.0]$^{+}$	8.0 [7.0; 9.0]*	< 0.001
PR interval, ms, Me [LQ; UQ]	116.0 [112.0; 118.0]	196.0 [189.0; 216.0]$^{+}$	196.0 [189.0; 210.0]*	< 0.001
QT interval, ms, Me [LQ; UQ]	425.0 [422.0; 430.0]	425.0 [418.0; 468.0]	425.0 [422.0; 435.0]	0.513
Left ventricular hypertrophy (S1+RV4 or V5) > 35 mm, Me [LQ; UQ]	37.0 [28.0; 39.0]	41.0 [36.0; 51.0]$^{+}$	38.0 [36,0; 51.0]*	< 0.001

Note: *$^{+}$ p < 0.05 when compared groups 1 and 2; * p < 0.05 when compared groups 1 and 3; $^{\#}$ p < 0.05 when compared groups 2 and 3; CAD – coronary artery disease.*

hypothyroidism (57.0% and 49%, p = 0.011). When assessing the indicators of LV diastolic function, statistically significant differences were obtained between the E/e' ratio in patients in the CAD group with newly diagnosed hypothyroidism and hypothyroidism with therapy and the indicator in CAD patients without hypothyroidism (p < 0.001).

The severity of coronary artery disease was analyzed in the study groups. Thus, in the groups of patients with hypothyroidism who had optimally selected hormone replacement therapy, as well as without therapy, the number of patients with three-vessel coronary artery disease (66.7% and 60.0%) prevailed than in the group of CAD patients without hypothyroidism (13.3%, p < 0.05) (Figure 2). Accordingly, when assessing coronary artery disease using the SYNTAX Score, patients with hypothyroidism in both groups were more likely to have severe coronary artery lesion.

During the observation period, in 62.5% of patients underwent myocardial revascularization (Figure 3). Percutaneous coronary intervention was performed statistically significantly more often in patients in the CAD group with newly diagnosed hypothyroidism (53.3%) and hypothyroidism with replacement therapy (38.7%) than in the group of patients with coronary artery disease without hypothyroidism (22.0%; p = 0.003). The opposite trend was observed for coronary artery bypass grafting; in the group of CAD patients with without hypothyroidism, the operation was performed in 38.0% of cases, in the group of CAD patients with newly diagnosed hypothyroidism in 20.0%, and in the group with hypothyroidism and replacement therapy in 21.3% (p = 0.014). In other cases, the tactics of optimal medical therapy were chosen, without a statistically significant difference in all groups.

A correlation analysis of possible associations of the frequency of coronary artery lesions with the levels of thyroid hormones (FT4, TSH) in the study groups was carried out (Table 3). The TSH level inversely correlated with single-vessel disease (p < 0.001), directly correlated with three-vessel disease and damage to 2 or more coronary arteries (p < 0.001 in both cases, Table 4). Free T4 directly correlated with damage to 2 coronary arteries (p = 0.027) and multivessel disease (2 or more vessels, p = 0.011).

In a multiple binary logistic regression model (forward LR method), the following factors had a significant association ($\chi^2(3) = 67.502$; p < 0.001) with multivessel disease: group of hypothyroidism (B = 2.558; p = 0.001), and heart rate (B = 0.961; p = 0.047). This model explained only 34.4% (Nagelkerke R2) of the variance and correctly classified 73.0% of cases (Table 5). A significant association ($\chi 2(3) = 75.529$; p < 0.001) with 3-vessel disease was identified for the following indicators: group of hypothyroidism (B = 2.151; p = 0.012), free T4 level (B = 0.919; p = 0.021) and heart rate (B = 0.933; p = 0.011). For this model, the Nagelkerke R2 indicator was 0.397, 81% cases were correctly classified.

Table 3. Correlation between thyroid hormones and the number of affected coronary arteries in CAD patients

	TSH		FT4	
	Spearman R	p-value	Spearman R	p-value
1-vessel disease	–0.300	< 0.001	–0.169	0.011
2-vessel disease	0.003	0.968	0.147	0.027
3-vessel disease	0.319	< 0.001	0.053	0.421
Multi-vessel lesion (2 or more coronary arteries)	0.302	< 0.001	0.167	0.012
Number of coronary arteries	0.324	< 0.001	–0.039	0.541

Note: *FT4 – free thyroxine; TSH – thyroid-stimulating hormone.*

Discussion

The present study showed that three-vessel coronary disease was more often detected in patients with coronary artery disease in the presence of

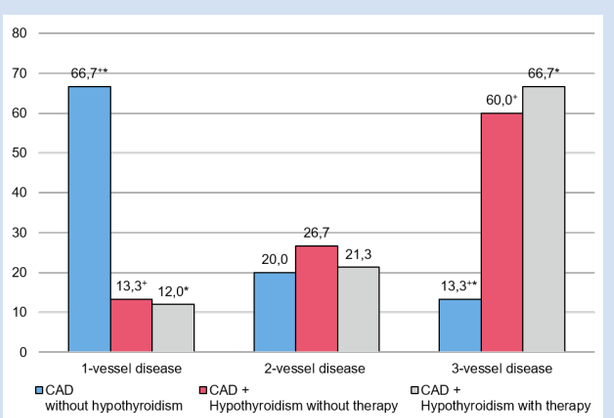

Figure 2. Results of coronary angiography in groups of CAD patients

Note: *+ p < 0.05 when compared groups 1 and 2; * p < 0.05 when compared groups 1 and 3; # p < 0.05 when compared groups 2 and 3; CAD – coronary artery disease.*

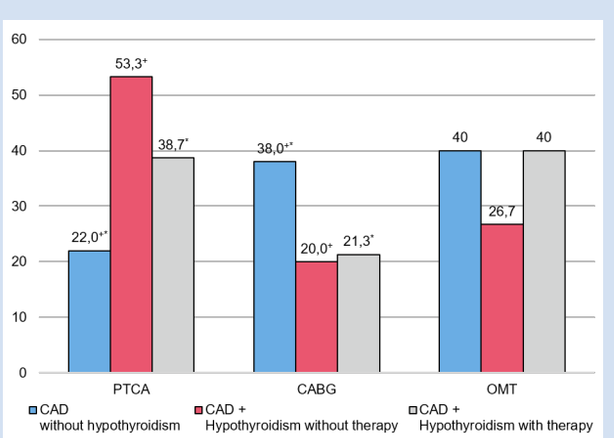

Figure 3. Results of revascularization in groups of CAD patients

Note: *+ p < 0.05 when compared groups 1 and 2; * p < 0.05 when compared groups 1 and 3; # p < 0.05 when compared groups 2 and 3; CABG – coronary artery bypass grafting; CAD – coronary artery disease; OMT – optimal medical therapy; PTCA – percutaneous transluminal coronary angioplasty.*

hypothyroidism, both manifest and newly diagnosed. Although groups with hypothyroidism compared with patients with coronary artery disease with euthyroidism more often had dyslipidemia, among the independent predictors of the presence of three-vessel coronary artery disease were only heart rate and assignment to the group with hypothyroidism.

Previous studies also showed an association between the severity of coronary atherosclerosis and the presence of hypothyroidism in patients with coronary artery disease. In addition, when assessing the level of thyroid hormones in patients with stable coronary artery disease and euthyroidism, it was shown that in the group with three-vessel disease, the mean FT3 values were significantly lower than in the group with normal coronary arteries than in the group ($p = 0.004$), and the levels FT3 showed an inverse relationship with the Gensini index ($r = –0.30$; $p = 0.002$). Free T3 level ≤ 2.7 predicted CAD severity with a sensitivity of 70% and specificity of 60% (area under the curve (AUC): 0.755, $p = 0.001$). That is, the dependence of the severity of coronary atherosclerosis on the level of thyroid hormones can also manifest itself when their level is within standard values [23]. Subsequently, it was shown that among euthyroid patients with coronary artery disease, an inverse relationship between the Gensini index and the level of free T3 is typical for men and young people, but not for older age groups [24]. A recent work by Yu N et al [25] further showed that the FT3/FT4 ratio was significantly correlated with the prevalence of CAD in the euthyroid population. In this work, we studied the severity of coronary atherosclerosis in patients with manifest hypothyroidism, including those receiving replacement therapy. Consequently, it was possible to identify the dependence of the number of affected coronary arteries only on the TSH level. Also, in the study by Bai MF et al [8] it was shown that the severity of coronary artery damage was equally pronounced both in patients with an isolated decrease in free T3 (Low T3 syndrome) and in patients with laboratory signs of hypothyroidism. At the same time, the presence of Low T3 syndrome was an independent predictor of severe coronary artery damage (according to the Gensini index). Using CT coronary angiography, it was found that severe subclinical hypothyroidism was associated with the presence of non-calcified plaques [9]. In optical coherence tomography, CAD patients with subclinical hypothyroidism showed a higher content of lipid-rich plaques and a larger lipid arc compared with patients with euthyroidism [26]. This makes us wonder to what extent the severity of

Table 4. Basic data of echocardiography in groups of CAD patients

	CAD without hypothyroidism (n = 150)	CAD + Hypothyroidism without therapy (n = 15)	CAD + Hypothyroidism with therapy (n = 75)	p
Structural indicators and systolic function indicators of left ventricular				
LA, mm, Me [LQ; UQ]	3.9 [3.8; 4.0]	3.8 [3.6; 4.1]	3.8 [3.6; 4.0]*	0.007
LV EDR, mm, Me [LQ; UQ]	5.1 [4.7; 5.7]	5.4 [4.8; 5.5]	4.8 [4.7; 5.4]$^{\#}$	0.128
LV ESD, mm, Me [LQ; UQ]	3.9 [3.1; 4.5]	3.8 [2.9; 4.7]	3.4 [2.5; 3.8]*	0.001
LV EDV, mL, ME [LQ; UQ]	124.0 [104.0; 159.0]	139.0 [105.0; 150.0]	105.0 [104.0; 141.0]$^{\#}$	0.135
LV ESV, mL, ME [LQ; UQ]	56.0 [38.0; 91.0]	63.0 [32.0; 101.0]	48.0 [23.0; 63.0]*	0.002
LVEF, %, ME [LQ; UQ]	49.0 [44.0; 63.0]	48.0 [32.0; 74.0]	57.0 [45.0; 77.0]*	0.011
SV, mL, Me [LQ; UQ]	67.0 [61.0; 72.0]	57.0 [48.0; 78.0]	71.0 [54.0; 85.0]*	0.012
IVSD, cm, ME [LQ; UQ]	1.2 [0.8; 1.3]	1.5 [1.4; 1.8]$^{+}$	1.6 [1.4; 1.7]*	< 0.001
TPWD, cm, ME [LQ; UQ]	1.2 [0.8; 1.3]	1.6 [1.5; 1.8]$^{+}$	1.6 [1.4; 1.7]*	< 0.001
Indicators of LV diastolic function				
E, cm/sec, Me [LQ; UQ]	0.99 [0.91; 1.8]	1.05 [0.64; 1.09]	0.99 [0.66; 1.8]	0.656
A, cm/sec, ME [LQ; UQ]	1.0 [0.68; 1.21]	1.03 [0.5; 1.21]	1.03 [0.76; 1.21]	0.165
E/A, Me [LQ; UQ]	1.42 [1.33; 1.49]	1.3 [0.6; 2.1]	1.31 [0.64; 1.42]	0.106
E/e', ME [LQ; UQ]	9.0 [7.0; 11.0]	11.0 [9.0; 18.0]$^{+}$	9.0 [9.0; 12.0]*	< 0.001
DT, mm/s, Me [LQ; UQ]	181.0 [174.0; 201.0]	179.0 [126.0; 212.0]	186.0 [174.0; 216.0]	0.184
LV DD type 1, (n, %)	38 (25.3)	7 (46.7)	32 (42.7)	0.014
LV DD type 2, (n, %)	43 (28.7)	3 (20.0)	23 (30.7)	0.71
LV DD type 3, (n, %)	1 (0.67)	5 (33.3)	8 (10.7)	< 0.001

Note: *$^{+}$ $p < 0.05$ when compared groups 1 and 2; * $p < 0.05$ when compared groups 1 and 3; $^{\#}$ $p < 0.05$ when compared groups 2 and 3; A – rate of late diastolic filling of the left ventricle; CAD – coronary artery disease; DT – deceleration time; E – rate of early diastolic filling of the left ventricle; E/A – ratio of early and late diastolic transmitral flow; E/e' – ratio of the flow velocity of early filling of the left ventricle to the speed of early diastolic movement of the mitral valve ring; IVSD – thickness of the interventricular septum in diastole; LA – left atrium diameter; LV – left ventricle; LV EDR – end diastolic size of the left ventricle; LV EDV – left ventricular end-diastolic volume; LV ESD – end systolic size of the left ventricle; LV ESV – end systolic volume of the left ventricle; LVDD – diastolic dysfunction of the left ventricle; LVEF – left ventricular ejection fraction; SV – left ventricular stroke volume; TPWD – thickness of the posterior wall of the left ventricle in diastole.*

coronary artery damage in hypothyroidism is due to the direct influence of hormonal dysfunction, or to the development of concomitant dyslipidemia?

Accordingly, the question remains unclear: on what factors does the severity of coronary artery damage in patients with hypothyroidism depend? When comparing lipid profile parameters in groups of patients with hypothyroidism, dyslipidemia was more pronounced than in patients with coronary artery disease without hypothyroidism. In the same state of India, a study was conducted that showed that subclinical hypothyroidism, especially with TSH < 10 μIU/mL, does not make a significant contribution to cardiovascular risk [7]. Nair S.N. et al. demonstrated a small effect of subclinical hypothyroidism on the lipid profile, and the authors considered it to be clinically insignificant [7]. The results of the present study show that dyslipidemia in patients with overt hypothyroidism is more pronounced and can serve as a therapeutic target when combined with coronary artery disease.

Noteworthy is the large number of publications on subclinical hypothyroidism conducted in various regions of India and South Asia [7, 13, 14, 18, 23, 27, 28]. The increased attention of researchers to this issue is explained by the high frequency of detection of hypothyroidism in these countries. For example, the state of Kerala in southern India has a much higher prevalence of thyroid disease than other regions (about 10%), despite being an iodine-sufficient population [26]. If we remember the opinion that the prevalence of subclinical hypothyroidism is 5–10 times higher than the prevalence of manifest hypothyroidism [29], then the attention to this issue of researchers in this region is understandable. Reasons for this phenomenon include high background radiation due to thorium-containing monazite sands or high consumption of cyanogenic glycosides found in local tapioca crops [7]. The combination of the uniquely high rate of thyroid disease in Kerala and the apparent genetic predisposition to CAD in the South Asian population [18] underscores the great clinical significance of studies of patients with a combination of CAD and hypothyroidism.

Table 5. Factors associated with the presence of multivessel or three-vessel disease according to binary logistic regression analysis (Forward Stepwise LR method)

		B	S.E.	Wald	df	Sig.	Exp(B)
Multivessel disease							
Step 1	Group of patients with hypothyroidism	1.355	0.204	44.312	1	< 0.001	3.878
	Constant	–2.018	0.321	39.460	1	< 0.001	0.133
Step 2	Heart rate	–0.040	0.020	3.946	1	0.047	0.961
	Group of patients with hypothyroidism	0.939	0.283	11.024	1	0.001	2.558
	Constant	1.598	1.827	0.65	1	0.382	4.942
Three-vessel disease							
Step 1	Group of patients with hypothyroidism	1.257	0.173	52.811	1	< 0.001	3.516
	Constant	–3.006	0.370	66.159	1	< 0.001	0.049
Step 2	Heart rate	–0.072	0.027	6.996	1	0.008	0.931
	Group of patients with hypothyroidism	0.593	0.287	4.251	1	0.039	1.809
	Constant	3.273	2.342	1.953	1	0.162	26.404
Step 3	Heart rate	–0.070	0.028	6.388	1	0.011	0.933
	Group of patients with hypothyroidism	0.766	0.304	6.338	1	0.012	2.151
	FT4	–0.085	0.037	5.288	1	0.021	0.919
	Constant	4.081	2.425	2.834	1	0.092	59.233

Note: *FT4 – free thyroxine.*

Although dyslipidemia due to hypothyroidism did not increase cardiovascular risk in a population-based study in southern India, it was associated with a higher prevalence of coronary atherosclerosis among patients with coronary artery disease. This shows that in this region it is necessary to actively identify hypothyroidism in patients with coronary artery disease, followed by more active lipid-lowering therapy. Also important is the fact that in the hypothyroidism group during replacement therapy, the severity of dyslipidemia was less than in manifest hypothyroidism. This emphasizes the importance of its timely administration for the correction of dyslipidemia in patients with hypothyroidism. However, there were no differences in the number of affected coronary arteries in the hypothyroidism groups, so it remains unclear whether replacement therapy for hypothyroidism can affect the prevalence of coronary atherosclerosis during prospective follow-up.

In the present study, we were unable to avoid limitations. First, this is a single-center study with a limited sample size. Therefore, our results need to be verified in a multicenter study with a larger sample size. Secondly, the study was conducted in a region with a high incidence of hypothyroidism and a high susceptibility to coronary artery disease. It is possible that the identified patterns may not appear in other regions. Third, this study was cross-sectional, so cause-and-effect relationships could not be determined; further prospective research is needed to determine them.

Conclusion

The present study showed that in patients with coronary artery disease in the presence of hypothyroidism, both manifest and newly diagnosed, more pronounced dyslipidemia is observed, left ventricle diastolic dysfunction and three-vessel coronary disease are more often detected. Taking hormone replacement therapy helps reduce the severity of dyslipidemia. The number of affected coronary arteries is associated with TSH levels. In multivariate analysis, only the presence of hypothyroidism, TSH levels, and heart rate were

independently associated with three-vessel coronary artery disease. The results of this study emphasize the need to identify hypothyroidism in patients with coronary artery disease; to correct dyslipidemia in such patients, it is necessary to additionally take hormone replacement therapy. The possibility of improving prognosis through such interventions requires confirmation in further studies.

Conflict of interest

M.A. Rahman declares no conflict of interest. A.N. Sumin A.N. Sumin is the scientific editor of the journal "Complex Issues of Cardiovascular Diseases". A.V. Shcheglova declares no conflict of interest. N.A. Bezdenezhnykh declares no conflict of interest. A.S. Ankudinov declares no conflict of interest. A.N. Kalyagin declares no conflict of interest. G. Vijayaraghavan is the Editorial Board member of the journal "Complex Issues of Cardiovascular Diseases".

Financial

This study was supported by the Complex Program of Basic Research under the Siberian Branch of the Russian Academy of Sciences within the Basic Research Topic of Research Institute for Complex Issues of Cardiovascular Diseases No. 0419-2022-0002.

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Для цитирования: *Муниир А.Р., Сумин А.Н., Щеглова А.В., Безденежных Н.А., Анкудинов А.С., Калягин А.Н., Виджаярагхаван Г. Особенности поражения коронарных артерий при гипотиреозе у населения Южной Индии. Комплексные проблемы сердечно-сосудистых заболеваний. 2025;14(1): 15-25. DOI: 10.17802/2306-1278-2025-14-1-15-25*

To cite: *Muneer A.R., Sumin A.N., Shcheglova A.V., Bezdenezhnykh N.A., Ankudinov A.S., Kalyagin A.N., Vijayaraghavan G. Features of coronary artery lesions in hypothyroidism in the population in South India. Complex Issues of Cardiovascular Diseases. 2025;14(1): 15-25. DOI: 10.17802/2306-1278-2025-14-1-15-25*