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SECONDARY DYSLIPIDEMIA AND ARTERIAL STIFFNESS IN ASYMPTOMIC PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM AND CAROTID ATHEROSCLEROSIS

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Secondary dyslipidemia accounts for 30–40% of all dyslipidemias and is a well-established risk factor for the development of atherosclerosis and its complications. The study of the contribution of endocrine pathology to cardiovascular risks and opportunities for prevention of cardiovascular complications is among the priority areas of healthcare worldwide. According to the World Health Organization, thyroid diseases hold one of the leading positions in the list of endocrine pathologies. Despite the high morbidity and mortality of patients worldwide due to cardiovascular diseases and considering the known success of healthcare in the prevention of the complications of atherothrombosis, there are still no clear therapeutic, diagnostic, and preventive guidelines in asymptomatic patients with concomitant endocrine pathology.

Purpose of the study: to evaluate the relationship of cardiac-ankle vascular index (CAVI), ankle-brachial index (ABI) and brachiocephalic artery ultrasound findings and lipid profile in asymptomatic working-age patients with subclinical hypothyroidism.

The design of the study. A cross-sectional cohort study analyzing data from 70 patients of working age with different thyroid hormonal status without clinical signs of chronic insufficiency of cerebral circulation.

Materials and methods. The study included 70 persons of working-age without clinical signs of chronic insufficiency of cerebral circulation: 46 with laboratory-confirmed subclinical hypothyroidism (thyroid stimulating hormone (TSH) level > 4.0 mIU/L with normal thyroid hormone free fractions) and 24 patients without thyroid dysfunction. The groups were comparable in terms of age, sex, smoking, arterial hypertension. All patients underwent comparative analysis of lipid spectrum parameters (Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C), Low- and High-Density Apolipoproteins) and ultrasound examination of carotid arteries. One of the used methods of preclinical diagnostics of atherosclerosis – volumetric sphygmography with assessment of cardiac-ankle vascular index (CAVI) and ankle-brachial index (ABI) – is described in detail in the article.

Results. Patients with subclinical hypothyroidism exhibited significantly higher levels of TC, LDL-C, ApoB, ApoB/ApoA1 ratio, and atherogenic coefficient, and lower levels of HDL-C compared to patients without thyroid dysfunction. Additionally, a higher proportion of patients with subclinical hypothyroidism had elevated total cholesterol and LDL-C levels. Our data indicate that a significantly higher proportion of patients with subclinical hypothyroidism have atherogenic types of hyperlipidemia compared to those without thyroid dysfunction. Specifically, Type IIa hyperlipidemia was more prevalent in the subclinical hypothyroidism group. A direct, moderately strong association between elevated TSH level and atherogenic type of hyperlipidemia ($r = 0.60$; $p < 0.01$), atherosclerotic ($r = 0.58$; $p < 0.01$), multivessel ($r = 0.54$; $p < 0.05$) lesion of brachiocephalic arteries, presence of signs of atherosclerotic plaque instability ($r = 0.64$; $p < 0.01$) were found. In the group of patients with subclinical hypothyroidism, the proportion with low ABI was significantly higher: 34.7% (n = 16) vs 12.5% (n = 3) ($F = 0.057$; $p < 0.05$). A direct association between the reduced ABI value and the presence of ultrasound signs of multivessel atherosclerotic lesion of brachiocephalic arteries ($r = 0.337$, $p < 0.001$), and a negative association between ABI < 1.00 and atherogenic hyperlipidemia type IIa ($r = 0.43$; $p < 0.05$) were established.

Conclusion. In clinically healthy working-age patients with subclinical hypothyroidism compared to those with normal thyroid function, there is a higher proportion of individuals with atherosclerotic multivessel lesions of the precerebral basin (32.6% (n = 15) vs. 8.3% (n = 2), $\chi^2 = 5.05$; $p < 0.05$). The disease progression is associated with a background of atherogenic type 2a hyperlipidemia (93.5% (n = 43) vs. 70.8% (n = 17), $\chi^2 = 6.60$; $p < 0.05$) combined with a deficiency of antiatherogenic high-density lipoproteins (HDL-C) (1.0±0.09 mmol/L vs. 1.3±0.06 mmol/L; $p < 0.05$).The etiopathogenetic mechanisms of "early vascular aging", the criteria for stratification of risk groups for atherosclerosis-associated cardiovascular diseases, the selection of diagnostic algorithms for visualizing preclinical stages of atherogenesis, and timely antiatherogenic strategies in asymptomatic patients with comorbid thyroid pathology require further exploration. Active implementation in practical healthcare of the assessment of regional (segmental) vascular stiffness using volumetric sphygmography based on the characteristics of the main (CAVI) and peripheral (ABI) blood flow can be proposed for diagnosing preclinical stages of atherogenesis in comorbid patients with endocrinopathies. Verification of a stenosing hemodynamically significant or non-hemodynamically significant atherosclerotic lesion of the coronary arteries, irrespective of the clinical component, is a factor of high cardiovascular risk necessitating immediate correction of hyperlipidemia.

ВТОРИЧНАЯ ДИСЛИПИДЕМИЯ И ПОКАЗАТЕЛИ АРТЕРИАЛЬНОЙ ЖЕСТКОСТИ У БЕССИМПТОМНЫХ ПАЦИЕНТОВ С СУБКЛИНИЧЕСКИМ ГИПОТИРЕОЗОМ И АТЕРОСКЛЕРОЗОМ ПРЕЦЕРЕБРАЛЬНЫХ АРТЕРИЙ

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ДЛЯ ЦИТИРОВАНИЯ. Е.Б. Петрова, О.Н. Шишко, М.Г. Колядко, Т.В. Статкевич, С.В. Черняк, О.Н. Попель, Н. Ганаатпишесанани, А.А. Плешко, Н.П. Митьковская. Вторичная дислипидемия и показатели артериальной жесткости у бессимптомных пациентов с субклиническим гипотиреозом и атеросклерозом прецеребральных артерий. *Неотложная кардиология и кардиоваскулярные риски*, 2024, Т. 8, № 1, С. 2125–2136.

Вторичная дислипидемия составляет 30–40% всех дислипидемий и является общепризнанным фактором риска развития атеросклероза и его осложнений. Изучение вклада эндокринной патологии в формирование сердечно-сосудистых рисков и возможностей профилактики кардиоваскулярных осложнений относится к приоритетным направлениям по охране здоровья во всем мире. По данным Всемирной организации здравоохранения, заболевания щитовидной железы занимают одну из лидирующих позиций в списке эндокринных заболеваний. Несмотря на высокую заболеваемость и смертность пациентов во всем мире по причине болезней системы кровообращения, успехи мирового здравоохранения в профилактике последствий атеротромбоза, не существует четких лечебно-диагностических и профилактических регламентов у бессимптомных пациентов ссопутствующей эндокринной патологией.

Цель исследования: оценить взаимосвязь сердечно-лодыжечного сосудистого индекса (CAVI), лодыжечно-плечевого индекса (ABI) и результатов ультразвукового исследования брахиоцефальных артерий, липидного профиля у бессимптомных пациентов трудоспособного возраста с субклиническим гипотиреозом.

Дизайн исследования. Поперечное когортное исследование с анализом данных 70 пациентов трудоспособного возраста с различным гормональным статусом щитовидной железы (ЩЖ) без клинических признаков хронической недостаточности мозгового кровообращения.

Материалы и методы. В исследование включено 70 лиц трудоспособного возраста без клинических признаков хронической недостаточности мозгового кровообращения: 46 – с лабораторно подтвержденным субклиническим гипотиреозом (уровень тиреотропного гормона (ТТГ) > 4,0 мМЕ/л при нормальных характеристиках свободных фракций тиреоидных гормонов) и 24 пациента без дисфункции ЩЖ. Группы сопоставимы по возрасту, полу, причастности к курению и наличию артериальной гипертензии. Всем пациентам проводился сравнительный анализ показателей липидного спектра и ультразвуковое исследование сонных артерий. В статье подробно описан одного из использованных методов доклинической диагностики атеросклероза – объемной сфигмографии с оценкойсердечно-лодыжечного сосудистого индекса (CAVI) и лодыжечно-плечевого индекса (ABI).

Результаты. Установлена прямая, умеренно сильная взаимосвязь между повышением уровня ТТГ и атерогенным типом гиперлипидемии ($r = 0,60$; $p < 0,01$), атеросклеротическим ($r = 0,58$; $p < 0,01$), многососудистым ($r = 0,54$; $p < 0,05$) поражением брахиоцефальных артерий, наличием признаков нестабильности атеросклеротической бляшки ($r = 0,64$; $p < 0,01$). В группе пациентов с субклиническим гипотиреозом доля с низким ABI была достоверно выше: 34,7% ($n = 16$) против 12,5% ($n = 3$) ($F = 0,057$; $p < 0,05$). Установлена прямая корреляционная связь между сниженным значением ABI и наличием ультразвуковых признаков многососудистого атеросклеротического поражения брахиоцефальных артерий ($r = 0,337$, $p < 0,001$), отрицательная корреляционная взаимосвязь между снижением индекса ABI < 1,00 и атерогенной гиперлипидемией IIa типа ($r = 0,43$; $p < 0,05$).

Заключение. У клинически здоровых пациентов трудоспособного возраста с субклиническим гипотиреозом в сравнении нормальной функцией щитовидной железы выше доля лиц с атеросклеротическим многососудистым поражением прецеребрального бассейна (32,6% ($n = 15$) против 8,3% ($n = 2$) ($\chi2 = 5,05$; $p < 0,05$), а заболевание протекает на фоне атерогенного 2а типа гиперлипидемии (93,5% ($n = 43$) против 70,8 % ($n = 17$) ($\chi2 = 6,60$; $p < 0,05$) в сочетании с недостаточностью проатерогенных липопротеидов высокой плотности (1,0±0,09 ммоль/л против 1,3±0,06 ммоль/л; $p < 0,05$). Этиопатогенетические механизмы «раннего сосудистого старения», критерии стратификации групп риска атеросклероз-ассоциированных заболеваний, выбор диагностических алгоритмов визуализации доклинических стадий атерогенеза и своевременная антиатерогенная тактика у бессимптомных пациентов с коморбидной патологией щитовидной железы требуют дальнейшего изучения. Для диагностики доклинических стадий атерогенеза можнопредложить активное внедрение в практическое здравоохранение метода оценки региональной (сегментарной) сосудистой жесткости методом объемной сфигмографии с обязательным комбинированным анализомсердечно-лодыжечного сосудистого индекса (CAVI) и лодыжечно-плечевого индекса (ABI). Верификация атеросклеротического поражения артериального русла, независимо от клинического компонента, является фактором высокого сердечно-сосудистого риска, требующего немедленной коррекции гиперлипидемии.

Introduction

Despite significant advancements in both national and international healthcare systems, cardiovascular diseases (CVDs) associated with atherosclerosis continue to exert a profound impact on global disability and mortality rates. Atherosclerosis, the principal pathological process underpinning the majority of CVDs, can initiate early in life and remain clinically silent for prolonged periods before advancing to more severe stages [1, 2]. In the post-war period of the 20th century, over 300 million individuals in the USA and Europe succumbed to complications related to atherosclerosis, a figure that surpasses the combined fatalities of all wars during that century. CVDs, especially coronary artery disease (atherosclerosis affecting the coronary arteries) and stroke (atherosclerosis affecting the cerebral arteries), are responsible for nearly 9 million deaths annually. Consequently, atherosclerosis is the foremost cause of mortality on a global scale (Figure 1) [3]. Projections by the World Health Organization (WHO) suggest that by the year 2030, approximately 23.6 million individuals will succumb to CVDs each year [1].

Atherosclerosis has emerged as a significant global health concern, with its risk extending beyond the older population and increasingly affecting younger individuals as well [1–3]. This issue is not restricted to developed nations alone, it has also become a considerable burden for low-income countries worldwide.

CVDs are significant cause of mortality globally, particularly in the United States and Europe. In the United States, approximately 610,000 people die from heart diseases each year, accounting for 1 in every 4 deaths. Coronary heart disease (CHD) is the leading cause of death in the Western world, responsible for over 370,000 deaths annually. Additionally, there are about 735,000 heart attacks in the United States each year, with 525,000 being initial attacks and 210,000 being recurrent attacks [4].Atherosclerosis has been identified as the primary cause of CVDs in the United States, affecting around 16.5 million Americans aged 20 and above [5]. In Europe, CVDs remain the leading cause of mortality, causing approximately 4.1 million deaths per year, which accounts for 46% of all deaths in the region. Of these deaths, 20% are attributed to CHD and 12% to stroke. It is worth noting that cardiovascular disease causes a higher proportion of deaths among women (51%) than men (42%), and these deaths in women are more likely to occur in old age [3].

In Belarus, despite the potential underreporting of the prevalence and impact of atherosclerosis, CVDs closely associated with atherosclerosis are recognized as leading causes of mortality in the country [6]. The disability rate among the working-age population due to atherosclerosis-related conditions is notably high, affecting more than 50 individuals per 10,000. The severity of initial disability, categorized by the number of individuals within various disability groups, is approximately 7 individuals per 10,000 working-age population in group I and exceeds 40 individuals per 10,000 in groups II and III [7]. These statistics underscore the substantial burden of atherosclerosis-related conditions in Belarus.

Health patterns across Asia exhibit considerable diversity due to the continent's vast size and heterogeneous population. Nevertheless, atherosclerotic cardiovascular disease (ASCVD) has become a major public health concern throughout the region, with case numbers escalating rapidly [8, 9]. In Iran, CVDs account for nearly half of all deaths, underscoring a critical public health issue. Similarly, in India, the prevalence of ASCVD is increasing, largely due to lifestyle changes and the growing adoption of Western dietary habits [10].

Lipid metabolism disorders are pivotal in the development of atherogenesis. Cholesterol is typically categorized into three types: low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and very low-density lipoprotein (VLDL). Beyond these classical classifications, other lipid spectrum components also play significant roles in the pathogenesis

Figure 1.
Leading causes of death globally (according to WHO data) [3]

Рисунок 1.
Основные причины смертности в мире (по данным ВОЗ) [3]

*Источник: Данные ВОЗ /WHO data**

Примечания/Note: * – [https://www.who.int/ru]

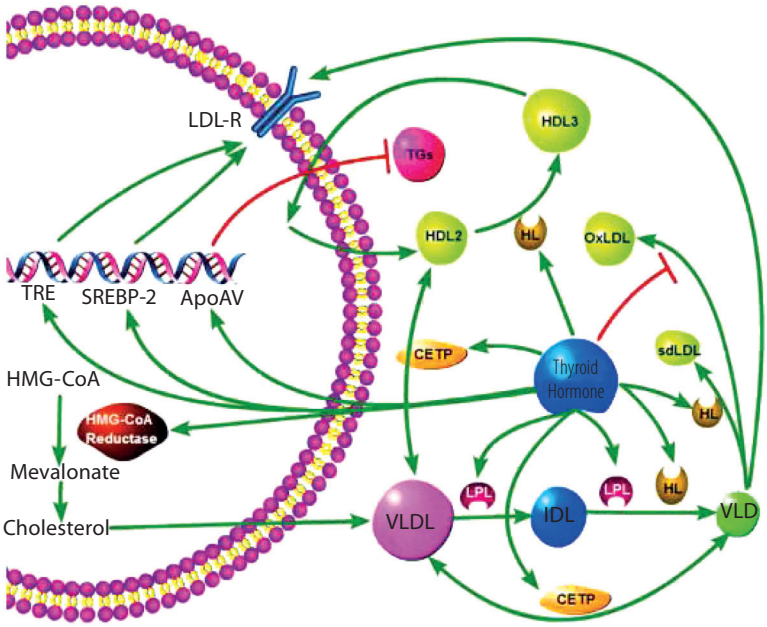

Figure 2. Regulation of Lipid Metabolic Parameters by Thyroid Function (adapted from Shin D.J et al., 2003 [25])

Рисунок 2. Регуляция параметров липидного обмена гормонами щитовидной железы (адаптировано из Shin D.J et al., 2003 [25])

Note: thyroid hormones induce the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the first step in cholesterol biosynthesis. Moreover, triiodothyronine (T3) upregulates low-density lipoprotein (LDL-C) receptors by controlling the LDL-C receptor gene activation. This T3-mediated gene activation is done by the direct binding of T3 to specific thyroid hormone responsive elements (TREs). Furthermore, T3 controls the sterol regulatory element-binding protein-2 (SREBP-2), which in turn regulates LDL-C receptor's gene expression. T3 has also been associated with protecting LDL-C from oxidation. Thyroid hormones can influence HDL-C metabolism by increasing cholesteryl ester transfer protein (CETP) activity, which exchanges cholesteryl esters from HDL2 to the very low-density lipoproteins (VLDL-C) and TGs to the opposite direction. In addition, thyroid hormones stimulate the lipoprotein lipase (LPL), which catabolizes the TG-rich lipoproteins, and the hepatic lipase (HL), which hydrolyzes HDL2 to HDL3 and contributes to the conversion of intermediate-density lipoproteins (IDL-C) to LDL-C and in turn LDL-C to small dense LDL-C (sdLDL). Another effect of T3 is the up-regulation of apolipoprotein AV (ApoAV), which plays a major role in TG regulation. Indeed, increased levels of ApoAV have been associated with decreased levels of TGs. Proposed mechanisms for this effect include the decrease of hepatic VLDL-TG production and the increase of plasma LPL levels and activity, resulting in increase of lipoprotein remnant generation due to enhanced LPL-mediated lipolysis of VLDL-TG. Moreover, a greater clearance of lipoprotein core remnants, caused by increased hepatic uptake due to an enhanced affinity for the LDL-C receptor, has also been ascribed to ApoAV.

Примечание: тиреоидные гормоны индуцируют 3-гидрокси-3-метилглутарил-коэнзим А (HMG-CoA) редуктазу, которая является первым этапом в биосинтезе холестерина. Кроме того, трийодтиронин (Т3) увеличивает количество рецепторов липопротеинов низкой плотности (LDL-C), контролируя активацию гена рецептора LDL-C. Эта активация гена, опосредованная Т3, осуществляется путем прямого связывания Т3 с определенными элементами, реагирующими на тиреоидные гормоны (TREs). Т3 контролирует белок-2, связывающий стерольные регуляторные элементы (SREBP-2), который, в свою очередь, регулирует экспрессию гена рецептора LDL-C. Т3 также связан с защитой LDL-C от окисления. Тиреоидные гормоны могут влиять на метаболизм HDL-C, увеличивая активность белка, переносящего эфиры холестерина (CETP). Также тиреоидные гормоны стимулируют липопротеиновую липазу (LPL), которая катаболизирует липопротеины, богатые TG, и печеночную липазу (HL), которая гидролизует HDL2 до HDL3 и способствует превращению липопротеинов промежуточной плотности (IDL-C) в LDL-C, а затем LDL-C в мелкие плотные LDL-C (sdLDL). Другим эффектом Т3 является увеличение аполипопротеина AV (ApoAV), который играет важную роль в регуляции TG. Повышенные уровни ApoAV ассоциируются со снижением уровней TG. Предлагаемые механизмы этого эффекта включают уменьшение продукции VLDL-TG в печени и увеличение уровней и активности LPL в плазме, что приводит к увеличению генерации остатков липопротеинов благодаря усиленному липолизу VLDL-TG, опосредованному LPL. Кроме того, более активное выведение остатков липопротеиновых ядер, вызванное увеличением печеночного захвата благодаря повышенной аффинности к рецептору LDL-C, также приписывается ApoAV.

of atherosclerosis. For instance, hypertriglyceridemia and the concentration of atherogenic lipoprotein particle Lp(a) in human blood have been directly linked to the severity of atherosclerosis in coronary, carotid, and peripheral arteries [11]. Additionally, the balance between low- and high-density apolipoproteins (ApoB/ApoA) serves as an indicator of cardiovascular risk, independent of cholesterol-related lipid levels, even when LDL-C levels are normal or low [12].

Dyslipidemia is classified into primary and secondary types. Primary dyslipidemia is inherited and caused by single or multiple gene mutations that result in either the overproduction or defective clearance of triglycerides and cholesterol [12, 13]. Secondary dyslipidemia is caused by unhealthy lifestyle factors and acquired medical conditions including underlying diseases and the use of certain medications. Secondary dyslipidemia accounts for 30–40% of all dyslipidemia cases. A large number of scientists around the world are studying the contribution of comorbid pathologies to the mechanisms of atherogenesis. Many publications are devoted to the study of atherogenesis in various functional conditions of the thyroid gland [2, 14–22].

Thyroid hormones (THs) perform crucial functions, such as the regulation of nutrient metabolism, blood glucose, dyslipidemia, have their role in menstruation and pregnancy, could be involved in heart rhythm disturbances, cardiac remodeling and development of heart failure [14]. Uncompensated hypothyroidism is characterized by a deterioration in the quality of life and serious cardiometabolic disorders. The relationship between thyroid dysfunction, particularly manifest hypothyroidism (HT), and abnormal lipid metabolism, as well as the development and progression of atherosclerosis, has been recognized by medical professionals over the years (Figure 2) [7, 22–25].

According to a number of studies, underactivity of the thyroid gland promote dyslipidemia – a high level of cholesterol and/or triglycerides or a low level of HDL [12, 24, 26]. Elevated TC and LDL-C can lead to progressive lipid accumulation, plaque formation in the arteries and increase the risk of CVDs – of the leading cause of disability and death worldwide [27]. On the other hand, hyperthyroidism could cause increased heart rate, cardiac remodeling, and elevated pulse pressure. Pulse pressure may become an independent predictor of the phenomenon of early vascular aging [7, 28].

Subclinical hypothyroidism is observed in 4–10% of patients with dyslipidemia. However, the connection between subclinical hypothyroidism and atherosclerotic lesions has not been fully established. There are conflicting data on this issue in the literature. A number of studies, including one of the first cross-sectional cohort studies conducted in 1977 in the UK by Tunbridge et al., deny the connection between subclinical hypothyroidism and CVDs [29]. In a meta-analysis which studied the effect of dyslipidemia due to subclinical hypothyroidism on carotid artery intima-media thickness (cIMT), subclinical hypothyroidism with TSH ≥ 10 μU/mL was associated with elevations of TC, LDL-C, TG, and cIMT [30]. Kim H. et al.

found no connection between atherosclerotic lesions of the carotid arteries and subclinical hypothyroidism in a 5-year follow-up study [31]. At the same time, they showed a strong association between the severity of precerebral atherosclerosis and such markers as gender, Body Mass Index (BMI), cholesterol, and LDL-C levels.

There is currently no such evidence showing that thyroid hormone replacement therapy reduces cardiovascular events [32]. A number of studies demonstrate that levothyroxine treatment and thyroid mimetics have been found beneficial for patients with subclinical hypothyroidism due to the reduction of both serum total cholesterol and LDL-C [33–35]. Furthermore, thyroid hormone replacement therapy reduced cIMT in patients with subclinical hypothyroidism [35, 36]. Probably, all conflicting data are due to factors such as differences in the selection of study groups and lack of control of thyroid status to exclude the transient nature of changes in thyroid hormones.

The complexities of dyslipidemia and premature vascular aging in individuals with thyroid dysfunction represent a multifaceted, interdisciplinary challenge necessitating comprehensive investigation. The pursuit of optimal protocols for the preclinical diagnosis of atherosclerosis and the development of strategies to correct secondary dyslipidemia hold the potential to yield more compelling clinical outcomes compared to conventional approaches. Such advancements are crucial for the effective prevention of atherosclerosis-associated CVDs in this patient population.

Early detection and diagnosis of atherosclerosis are critical for effective treatment and the prevention of complications. However, the early diagnosis of atherosclerosis remains challenging due to the lack of specific and sensitive diagnostic tests. Traditionally, atherosclerosis has been diagnosed through methods such as electrocardiogram (ECG) evaluation both at rest and during physical activity. However, exercise tests are not feasible or informative for certain patient categories. The gold standard for diagnosis is invasive angiography [2], which, despite its accuracy, is invasive, costly, and unsuitable for screening asymptomatic individuals. Currently, non-invasive imaging techniques have made it possible to visualize atherosclerotic plaques. These methods include ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) (nuclear imaging techniques) [35].

Visualization methods vary, and a specific technique is selected based on the stage of plaque development. For instance, endothelial dysfunction at an early stage can be diagnosed by functional measurements such as peripheral arterial tonometry (PAT) and visualized using PET and CT scans. More advanced lesions with lipid build-up can be detected using coronary intravascular ultrasound, MRI, and coronary CT. Expanded plaques are identifiable with electron beam computed tomography [35, 37, 38]. One of the major challenges in diagnosing early-stage atherosclerosis is the absence of symptoms. Consequently, atherosclerosis often remains undetected until it has progressed to a more advanced stage, thereby increasing the risk of complications. This underscores the necessity for non-invasive, cost-effective, and sensitive diagnostic tests capable of detecting atherosclerosis before the onset of symptoms.

Sphygmography encompassing metrics such as the Cardio-Ankle Vascular Index (CAVI) and the Ankle-Brachial Index (ABI) is gaining recognition for its utility in the early detection of atherosclerosis [40].

The Cardio-Ankle Vascular Index (CAVI) is an index that measures the overall stiffness of the artery from the origin of the aorta to the ankle [39, 40]. It was developed to obtain an arterial stiffness index that is not influenced by blood pressure at the time of measurement and which reflects the stiffness of a significant length of the artery [40]. CAVI reflects the stiffness of the entire arterial segment, including the aorta, femoral artery, and tibial artery (Figure 3) [40, 41].

CAVI can be calculated from the Pulse Wave Velocity (PWV) at the origin of the aorta to the ankle portion of the tibial artery, along with systolic and diastolic blood pressures measured at the upper brachial artery. This index was originally derived from the stiffness parameter β proposed by Hayashi [41–43] and Kawasaki et al., with the application of Bramwell-Hill's equation [40] (the principle of the CAVI formula is described briefly in Figure 4):

$$CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)\ PWV2\}+b$$

Where Ps – systolic blood pressure, Pd – diastolic blood pressure, PWV – pulse wave velocity from the origin of the aorta to tibial artery at the ankle through the femoral artery, ΔP (pulse pressure) – difference Ps-Pd, ρ – blood density, a and b – constants.

The derivation of the aforementioned equation is as follows: CAVI is fundamentally represented by β, where β is defined as $\beta = \ln(Ps/Pd) \times (D/\Delta D)$. In this equation, D signifies the arterial diameter, and ΔD denotes the variation in the arterial diameter in response to changes in pressure [42].

D/ΔD can be obtained from a modification of The Bramwell-Hill's equation (Figure 4) [40]:

$$PWV^2 = \Delta P/\rho \cdot V/\Delta V$$

CAVI is designed to represent the overall stiffness of the aorta, femoral artery, and ti-

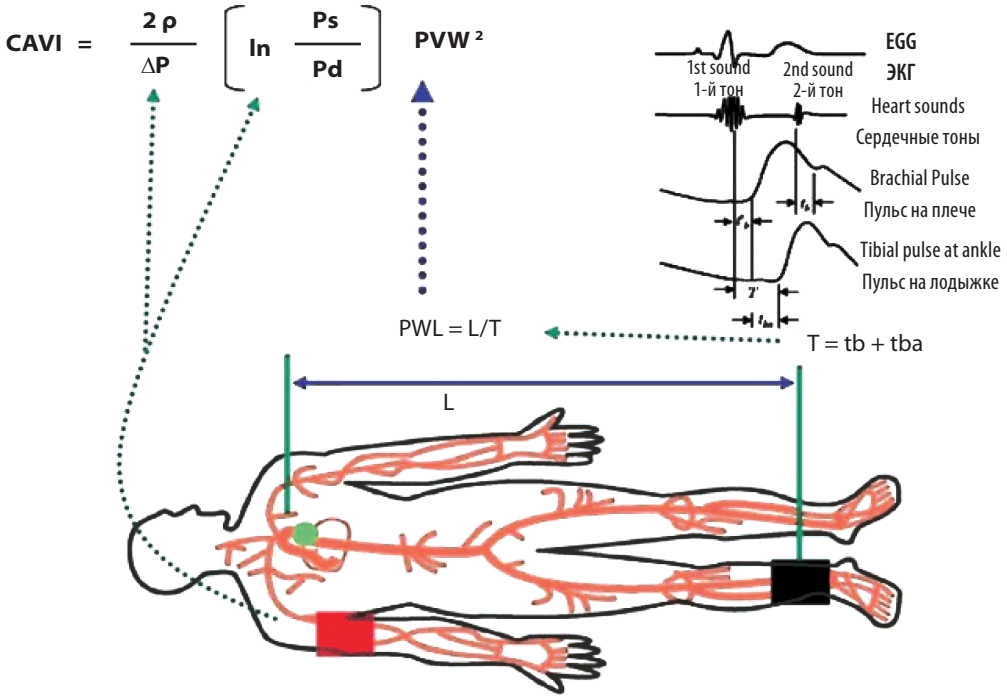

Figure 3.
Cardio-Ankle Vascular Index (CAVI) and its measurement (adapted from Sumin A.N. et al., 2021 [40], Saiki A. et al., 2020 [41])

Рисунок 3.
Сердечно-лодыжечный сосудистый индекс (CAVI) и его измерение (адаптировано из Sumin A.N. et al., 2021 [40], Saiki A. et al., 2020 [41])

N o t e: Ps – systolic blood pressure, Pd – diastolic blood pressure, PWV – pulse wave velocity, ΔP –pulse pressure, difference Ps-Pd, ρ – blood density, L – length from the origin of the aorta to the ankle, T – time taken for the pulse wave to propagate from the aortic valve to the ankle, tba – time between the rise of brachial pulse wave and the rise of ankle pulse wave, tb – time between aortic valve closing sound and the notch of brachial pulse wave, t'b – time between aortic valve opening sound and the rise of brachial pulse wave, ECG – electrocardiogram. With the patient lying supine, an ECG and heart sounds are monitored. PWV from the heart to the ankle is obtained by measuring the length from the origin of the aorta to the ankle, and by calculating T = tb + tba. Blood pressure is measured at the brachial artery.

П р и м е ч а н и е: Ps – систолическое артериальное давление, Pd – диастолическое артериальное давление, PWV – скорость пульсовой волны, P – пульсовое давление, разница Ps-Pd, ρ – плотность крови, L – длина от корня аорты до лодыжки, T – время, за которое пульсовая волна проходит расстояние от аортального клапана до лодыжки, tba – время между началом прироста плечевого пульса и лодыжечного пульса, tb – время между тоном закрытия аортального клапана и зазубриной плечевой пульсовой волны, t'b – время между тоном открытия аортального клапана и ростом плечевой пульсовой волны, ЭКГ – электрокардиограмма. При положении пациента лёжа на спине, мониторируются ЭКГ и сердечные тоны, скорость пульсовой волны (PWV) от сердца до лодыжки определяется измерением длины от начала аорты до лодыжки и расчётом T = tb + tba, артериальное давление измеряется на плечевой артерии.

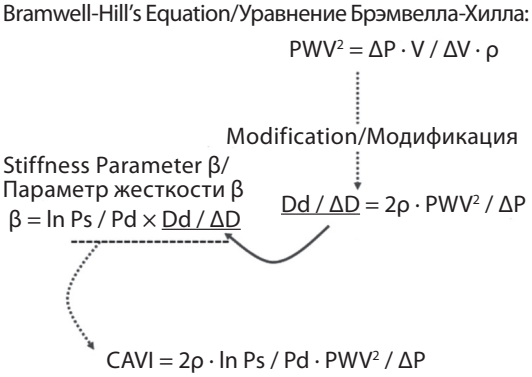

Figure 4.
The principle of the cardio-ankle vascular index (CAVI) formula (adapted from Sumin A.N. et al., 2021 [40])

Рисунок 4.
Суть формулы расчета сердечно-лодыжечного сосудистого индекса (CAVI) (адаптировано из Sumin A.N. et al., 2021 [40])

N o t e: *Equation 1*, where ΔP is pulse pressure, V is blood vessel volume, ΔV is the change in V, and ρ is blood density, V/ΔV can be expressed in terms of D and ΔD as follows: $V/\Delta V = (\pi L(D/2)^2)/[\pi L((D+\Delta D)/2)^2 - \pi L(D/2)^2] = D^2/[D2 + 2D\Delta D + \Delta D^2 + D^2] = D^2/(2D\Delta D + \Delta D^2)$. Since ΔD^2 is negligibly small compared with 2DΔD, it is ignored. The equation becomes: $V/\Delta V = D^2/2D\Delta D = D/2\Delta D$; *Equation 2*. Thus, V/ΔV in equation 1 can be replaced by D/2ΔD. Equation 1 becomes: $PWV^2 = \Delta P/\rho^* V/\Delta V = \Delta P/\rho^* D/2\Delta D$, and $D/\Delta D = 2\rho/\Delta P \cdot PWV^2$. *Equation 3*. Next, equation 3 is substituted into the equationof stiffness parameter β to obtain the new β (β'). $\beta' (= CAVI) = \ln(Ps/Pd) \times (D/\Delta D) = \ln(Ps/Pd) \times 2\rho/\Delta P \times PWV^2$

П р и м е ч а н и е: Формула Bramwell–Hill выражает взаимосвязь между объемным эластическим модулем и скоростью распространения пульсовой волны (СРПВ): $PWV^2 = \Delta P/\rho \cdot V/\Delta V$, (1) где PWV – СРПВ; ΔP – пульсовое давление; V – объем кровеносного сосуда; ΔV – изменения объема; ρ – плотность крови. Из формулы (1) следует: $V/\Delta V = D/\Delta D/2 = 2\rho/\Delta P \times PWV^2$, (2) где D – диаметр сосуда; ΔD – изменения диаметра. Учитывая, что $\beta = \ln(Ps/Pd) \times D/\Delta D$, тогда $\beta = \ln(Ps/Pd) \times 2\rho/\Delta P \times PWV^2 = CAVI$. Таким образом, CAVI отражает жесткость аорты, бедренной и большеберцовой артерии в целом и теоретически не зависит от влияния артериального давления. Для удобства сравнения с PWV формула преобразовывается: $CAVI = a\{(2\rho/\Delta P) \times \ln(Ps/Pd)\ PWV^2\} + b$

bial artery, and it is theoretically independent of blood pressure variations. CAVI is derived from the stiffness parameter β, expressed as $\beta = \ln(Ps/Pd) \times (D/\Delta D)$, however, unlike β, CAVI is calculated from the PWV over a specified length of the artery and the pressure change (ΔP), rather than the change in diameter (D/ΔD).

CAVI is proposed as a valuable indicator for estimating the risk of atherosclerosis due to its sensitivity to arterial stiffness. Research has shown that CAVI tends to increase linearly with age, and it is generally higher in men, which suggests greater arterial stiffness and an elevated risk of atherosclerosis (as demonstrated in Table 1) [42].

Furthermore, empirical research has identified elevated CAVI values in individuals presenting with risk factors such as diabetes mellitus and obesity, conditions frequently concomitant with atherosclerosis [40]. In a specific study, CAVI demonstrated a positive correlation with both carotid and coronary atherosclerosis. These findings propose that CAVI may serve as a preclinical marker for assessing the severity of atherosclerosis [41, 42].

CAVI reflects arterial resistance or compliance, indicating the degree of arterial sclero-

sis and providing insights into vascular function which is crucial for maintaining heart function and steady peripheral blood flow, the Windkessel effect (Figure 5). CAVI serves as a surrogate marker for arteriosclerosis and smooth muscle contraction. Additionally, it may play a role in protecting or improving left ventricular function and maintaining steady blood flow [43]. To substantiate these claims, further basic and clinical studies are necessary.

The Ankle-Brachial Index (ABI) is a straightforward and non-invasive test used to assess peripheral arterial disease (PAD) and to aid in the early diagnosis of atherosclerosis. The procedure involves placing blood pressure cuffs on both arms and at the ankles [39, 40, 42, 43]. A Doppler ultrasound probe is then used to measure the systolic blood pressure. ABI is calculated by dividing the systolic blood pressure at the ankle by the highest systolic blood pressure in the arms. Lower ABI values often suggest the presence of PAD, indicating a higher likelihood of systemic atherosclerosis. Conversely, an abnormally high ABI may indicate non-compressible vessels, which are commonly seen in older patients and those at risk for atherosclerosis. A study by Aboyans et al. emphasizes the significance of ABI as a reliable method for detecting the severity of systemic atherosclerosis and for predicting cardiovascular events. The ABI has been shown to be a strong predictor of myocardial infarction, stroke, and cardiovascular mortality. Furthermore, ABI is crucial in the early diagnosis of atherosclerosis, helping to identify individuals at risk for atherosclerosis-related complications. Patients with a lower ABI have an increased risk of atherosclerosis-related cardiovascular events. This is further supported by a study by Hussein et al. (2017), which demonstrated the role of low ABI as a potential predictor for subclinical atherosclerosis in asymptomatic individuals [43].

Normative indicators/ Нормативные показатели	
Normal level/ Нормальный уровень CAVI	CAVI < 8.0
Borderline values/ Пограничные значения	8.0 ≤ CAVI < 9.0
High values/ Высокие значения	CAVI ≥ 9.0

Note: CAVI – Cardio-Ankle Vascular Index

Примечание: CAVI – сердечно-лодыжечный сосудистый индекс

Table 1.
Cardio-Ankle Vascular Index normative indicators

Таблица 1.
Нормативные показатели сердечно-лодыжечного сосудистого индекса (CAVI)

In essence, sphygmography through indices such as CAVI and ABI offers non-invasive and practical method for the early detection of atherosclerosis. However, it is imperative to recognize that these measurements should be integrated with other established risk factors and diagnostic techniques to ensure an accurate identification and effective management of atherosclerotic disease.

Purpose of the study

To evaluate the relationship of cardiac-ankle vascular index (CAVI), ankle-brachial index (ABI) and brachiocephalic artery ultrasound findings and lipid profile in asymptomatic working-age patients with subclinical hypothyroidism.

Materials and methods

The design of the study involved a cross-sectional cohort analysis of data from 70 working-age patients with varying hormonal statuses of the thyroid gland but without clinical signs of chronic cerebral circulatory insufficiency. Patients were divided into two groups based on their thyroid gland hormonal status: Group 1: 46 patients with laboratory-confirmed hypothyroidism (TSH level > 4.0 mMU/l with normal

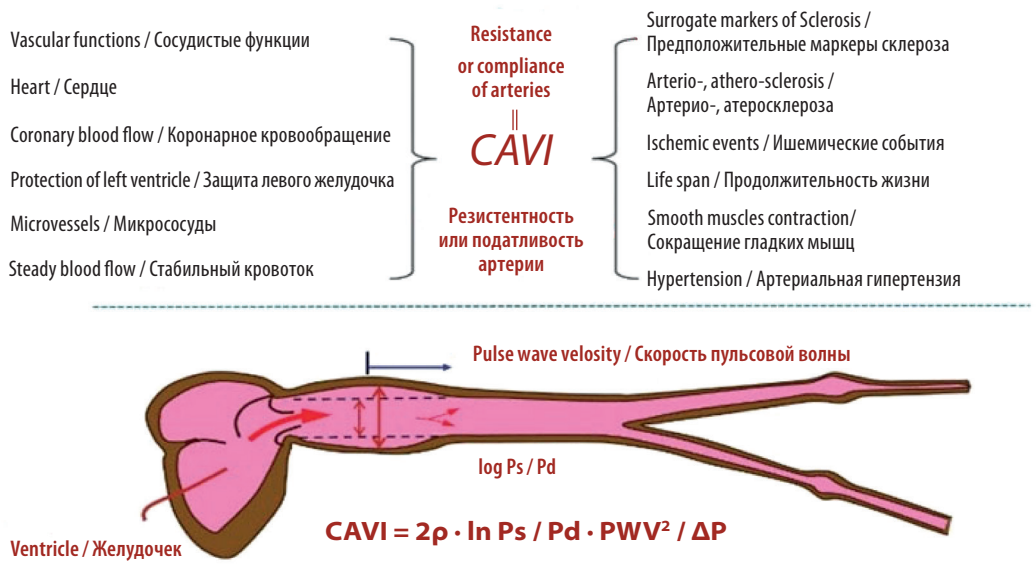

Figure 5.
Roles of the cardio-ankle vascular index (CAVI) in resistance or compliance of the artery as a surrogate marker of arteriosclerosis and also vascular function [39–42]

Рисунок 5.
Роль сердечно-лодыжечного сосудистого индекса (CAVI) в оценке сосудистой жесткости и податливости восходящей аорты, как одного из маркеров атеросклероза [39–42]

Table 2. Characteristics of the patients with different thyroid hormone statuses, which increase cardiovascular risk

Таблица 2. Характеристики пациентов с различным гормональным статусом щитовидной железы, увеличивающие сердечно-сосудистый риск

Characteristics*/ Признак*	Subclinical hypothyroidism/ Субклинический гипотиреоз (n = 46)	Normal thyroid function/ Нормальная функция щитовидной железы (n = 24)
Female, % (n)/ Женщины, % (n)	89.1 (41)	83.3 (20)
Male, % (n)/ Мужчины, % (n)	10.9 (5)	16.7 (4)
Age, years/ Возраст, лет	53.2 ± 4.01	51.8 ± 5.11
Smoking, % (n)/ Курение, % (n)	15.2 (7)	20.8 (5)
Obesity class I (BMI = 30–35 kg/m^2)/ Ожирение I тепени (ИМТ = 30–35 кг/м^2)	39.1 (18)	37.5 (9)
Arterial hypertension/ Артериальная гипертензия		
Stage 1, % (n)/ 1-й степени, % (n)	28.3 (13)	29.2 (7)
Stage 2, % (n)/ 2-й степени, % (n)	71.7 (33)	70.8 (17)
Stage 3, % (n)/ 3-й степени, % (n)	–	-

Note: *– no differences were found in the main characteristics of the established patient groups

Примечание: * – по основным характеристикам групп пациентов различий не выявлено

free thyroid hormone fractions) and Group 2: 24 patients without thyroid dysfunction. These groups were comparable in terms of age, gender composition, presence and severity of hypertension, family history of early cardiovascular events, and smoking habits (see Table 2). Prior to inclusion in the study, none of the patients had received levothyroxine therapy, iodine-containing or antithyroid drugs, or lipid-lowering therapy with statins.

All patients underwent an ultrasound examination of the carotid arteries (CA). The procedure was performed with the patient lying on their back after a short rest. The examination included an analysis of the structural and functional state of the following arteries:

- Common carotid arteries
- Internal carotid arteries
- External carotid arteries
- Subclavian arteries
- Vertebral arteries in segments V1 and V2

The assessment included the following parameters:

1. Patency and anatomical features of the arteries.

2. Speed and spectral Doppler parameters of the precerebral basin.

3. Thickness of the intima-media complex (IMC) of the common carotid arteries.

4. Presence of atherosclerotic lesions with detailed characteristics, including:

- Extent of atherosclerotic lesions
- Percentage of stenosis
- Surface condition
- Echogenicity
- Heterogeneity
- Signs of calcification of the atherosclerotic plaque (ASP)

The severity of stenosis of the precerebral arteries was determined using the European Carotid Surgery Trial (ECST) criteria. This involved calculating the ratio of the initial interadventitial diameter of the artery at the site of stenosis to the lumen diameter of the analyzed artery at the site of stenosis, expressed as a percentage.

Unstable ASP was identified based on ultrasound criteria obtained through visual assessment on a gray scale, which included:

- Hypo- and anechoic plaque structure
- Heterogeneous plaque structure
- Signs of an uneven surface of the ASP

To assess regional (segmental) vascular stiffness and prognosis of atherosclerosis, we used the method of volumetric sphygmography on the VaSera-1500 device (Fukuda Denshi). The CAVI index was calculated from ECG, phonocardiogram (PCG), wave registration of the brachial and tibial arteries, using a special algorithm for calculations (Figure 3 and 4). According to the recommendations of the creators of the VaSera device, CAVI values of 9.0 and higher are considered pathological. The ABI measurement is conducted simultaneously with the CAVI stiffness index measurement (5–10 min). To measure ABI, it is enough to replace the ankle cuffs with finger cuffs, without changing the patient's position, and press "Start" (+ 3–5 min). Interpretation of data for asymptomatic patients was conducted according to the 2016 the American Heart Association (AHA) and the American College of Cardiology (ACC) (AHA/ACC) Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease: Executive Summary [45]: the norm corresponds to the result in which both legs have values of $1.00 \leq ABI < 1.4$.

Determination of biochemical parameters of the lipid spectrum was carried out using an automatic biochemical analyzer Architect c4000 (Abbott, USA). Material for the study was collected from the cubital vein in the morning, strictly on an empty stomach. Lipidemia was diagnosed taking into account the characteristics of the lipidogram and included determination of the level of TC, TG, LDL-C, HDL-C, low- and high-density apolipoproteins.

Statistical analysis of the obtained data was performed using Excel and Statistica software (version 10.0, StatSoft, Inc., USA). The following statistical methods were applied:

1. Reliability of Data. Data were considered reliable, and differences between indicators were deemed significant if the error-free prediction value was equal to or greater than 95% ($p < 0.05$).

2. Assessment of Differences. The χ^2 goodness-of-fit test or Fisher's exact test (F) was used

to assess differences between independent samples on a qualitative basis.

3. Correlation Analysis. To determine the mutual influence of two characteristics, correlation analysis was conducted depending on the type of data presented. For normally distributed data, the Pearson method was used. For data that deviated from a normal distribution, the Spearman method was employed. The significance, direction of association, and strength of correlation interactions were interpreted based on the correlation coefficient (r) as follows: $r < 0.3$ – weak correlation, $0.3 < r < 0.69$ – moderate correlation, $r > 0.7$ or more – strong correlation.

This comprehensive approach to data analysis ensured the reliability and significance of the findings.

Results and discussion

The study of lipid metabolism parameters demonstrated statistically significantly higher group average values of TC (5.9±0.12 mmol/l versus 4.8±0.15 mmol/l ($p < 0.05$)), LDL-C (3.9±0.14 mmol/l versus 2.8±0.16 mmol/l ($p < 0.01$)), ApoB (1.2±0.03 versus 0.8±0.04 ($p < 0.01$)) and values of the ApoB/ApoA1 ratio (0.8±0.05 versus 0.5±0.02 ($p < 0.05$)), atherogenic coefficient (AC) (4.6±0.2 versus 2.8±0.22 ($p < 0.001$)) and lower levels of proatherogenic HDL cholesterol (1.0±0.09 mmol/l versus 1.3±0.06 mmol/l ($p < 0.05$)) in the group of patients with subclinical hypothyroidism relative to the result of the group without thyroid dysfunction (Table 3). In patients with subclinical hypothyroidism, compared with patients without thyroid dysfunction, there was a higher proportion of people with increased total cholesterol (95.7% (n = 44) versus 75.0% (n = 18) ($\chi^2 = 6.65$; $p < 0.05$)) and LDL-C (93.5% (n = 43) vs. 70.8% (n = 17) ($\chi^2 = 6.60$; $p < 0.05$)).

According to the WHO classification (D. Fredrickson, 1965) [7], in patients with subclinical hypothyroidism the proportion of people with the atherogenic type of hyperlipidemia was higher than in patients without thyroid dysfunction (93.5% (n = 43) versus 70.8% (n = 17) ($\chi^2 = 6.60$; $p < 0.05$)). We established type IIa hyperlipidemia in 84.8% (n = 39) of patients in the group with subclinical hypothyroidism versus 62.5% (n = 15) among patients without thyroid dysfunction ($\chi^2 = 4.44$; $p < 0.05$). We identified type IIb hyperlipidemia in 8.7% (n = 4) of patients with subclinical hypothyroidism and 8.3% (n = 2) of patients with normal thyroid function.

The study revealed that there were no ultrasound indications of hemodynamically significant stenosing atherosclerotic lesions in the carotid arteries among the examined working-age patients with varying thyroid hormonal statuses. This includes patients without signs of chronic cerebral circulatory insufficiency. The findings are summarized in Table 4.

We diagnosed ultrasound signs of atherosclerosis of the carotid arteries in 71.7% (n = 33) of patients with subclinical hypothyroidism versus 45.5% (n = 11) in people with normal thyroid function ($\chi^2 = 4.53$; $p < 0.05$). In the group of patients with thyroid hypofunction the proportion of people with multivessel atherosclerotic lesions was higher (32.6% (n = 15) versus 8.3% (n = 2) ($\chi^2 = 5.05$; $p < 0.05$), one or a combination of several signs of ASP instability (69.6% (n = 32) versus 33.3% (n = 8) ($\chi^2 = 8.45$; $p < 0.01$) Thickening of the intima-media complex of the CCA more than 0.9 mm was observed in 76.1% (n = 35) of patients with subclinical hypothyroidism versus 54.2% (n = 13) of patients without thyroid dysfunction ($\chi^2 = 6.41$; $p < 0.05$).

We have established a direct, moderately strong correlation between increased TSH levels and the atherogenic type of hyperlipidemia ($r = 0.60$; $p < 0.01$), atherosclerotic ($r = 0.58$; $p < 0.01$), multivessel ($r = 0.54$; $p < 0.05$) damage to the carotid arteries, the presence of signs of instability of the ASP ($r = 0.64$; $p < 0.01$).

The group average values of CAVI in the group of patients with subclinical hypothyroidism did not differ significantly from the result obtained in patients without thyroid dysfunction: R-CAVI was 7.7 (6.5-8.3) and 8.0 (6. 47-9.2), L-CAVI – 7.3 (6.2-8.3) and 7.6 (6.7-8.9). We did not find

Table 3.
Characteristics of the lipid spectrum of the patients included in the study with subclinical hypothyroidism and normal thyroid function

Таблица 3.
Характеристики липидограммы включенных в исследование пациентов с субклиническим гипотиреозом и нормальной функцией щитовидной железы

Characteristics/ Показатель	Subclinical hypothyroidism/ Субклинический гипотиреоз (n = 46)	Normal thyroid function/ Нормальная функция щитовидной железы (n = 24)
TC, mmol/L/ ОХ, ммоль/л	5.9±0.12*	4.8±0.15
LDL-C, mol/L/ ХС–ЛПНП, моль/л	3.9±0.14**	2.8±0.16
HDL-C, mmol/L/ ХС–ЛПВП, ммоль/л	1.0±0.09*	1.3±0.06
AC = (TC–HDL)/HDL/ КА (ОХ – ЛПВП)/ЛПВП	4.6±0.2***	2.8±0.22
TG, mmol/L/ ТГ, ммоль/л	1.7±0.13	1.8±0.15
ApoA1, g/L/ АпоА1, г/л	1.4±0.05	1.5±0.04
apoB, g/L/ АпоВ, г/л	1.2±0.03**	0.8±0.04
apoB/apoA1/ АпоВ/АпоА1	0.8±0.05*	0.5±0.02

Note: * – reliability of the difference of the characteristics when comparing with the group of patients with normal thyroid hormone status at $p < 0.05$; ** – at $p < 0.01$; *** – at $p < 0.001$; TC – total cholesterol; TG – triglycerides; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; AC – atherogenic coefficient; apoB – apolipoprotein B; apoA1 – apolipoprotein A1

Примечание: * – достоверность различия показателей при сравнении с группой пациентов с нормальным гормональным статусом щитовидной железы при $p < 0,05$; ** – при $p < 0,01$; *** – при $p < 0,001$; ОХ – общий холестерин, ТГ – триглицериды, ХС-ЛПНП – холестерин липопротеинов низкой плотности, ХС-ЛПВП – холестерин липопротеинов высокой плотности, КА – коэффициент атерогенности, рассчитанный по формуле КА = (ОХ – ЛПВП)/ЛПВП, АпоВ и АпоА1 – аполипопротеины низкой и высокой плотности

Table 4.
Signs of atherosclerotic lesions of brachiocephalic arteries in patients with subclinical hypothyroidism and in those with normal thyroid function

Таблица 4.
Признаки атеросклеротического поражения каротидных артерий у пациентов с субклиническим гипотиреозом и нормальной функцией щитовидной железы

Signs/ Показатель	Subclinical hypothyroidism/ Субклинический гипотиреоз (n = 46)	Normal thyroid function/ Нормальная функция щитовидной железы (n = 24)
Atheroma, % (n)/ Наличие АСБ, % (n)	71.7 (33)*	45.5 (11)
Atheroma (0–50%), % (n)/ АСБ (0-50%), % (n)	56.5 (26)	41.7 (10)
Atheroma (50–70%), % (n)/ АСБ (50–70%), % (n)	15.2 (7)	4.2 (1)
Atheroma (> 70%), % (n)/ АСБ (более 70%), % (n)	0	0
Univascular lesion, % (n)/ Односсудистое поражение, % (n)	39.1 (18)	37.5 (9)
Multivessel lesion (> 2 vessels), % (n)/ Многососудистое поражение (более 2-х сосудов), % (n)	32.6 (15)*	8.3 (2)
Signs of atheroma instability, % (n)/ Признаки нестабильной АСБ, % (n)	69.6 (32)**	33.3 (8)
Heterogeneous structure of atheroma, % (n)/ Гетерогенная структура АСБ, % (n)	65.2 (30)*	33.3 (8)
Atheroma rough surface, % (n)/ Неровность поверхности АСБ, % (n)	6.5 (3)	0
CCA IMC, mm/ КИМ ОСА, мм	1.1±0.19*	0.75±0.15
CCA IMC > 0.9 mm, % (n)/ КИМОСА > 0,9 мм, % (n)	76.1 (35)	54.2 (13)

Note: * – reliability of the difference of characteristics when comparing with the group of patients with normal thyroid hormone status at $p < 0.05$; **at $p < 0.01$; IMC – intima-media complex, CCA – common carotid artery

Примечание: * – достоверность различия показателей при сравнении с группой пациентов с нормальным гормональным статусом щитовидной железы при $p < 0,05$, ** – при $p < 0,01$, АСБ – атеросклеротическая бляшка, КИМ - комплекс интима-медиа, ОСА - общая сонная артерия

a relationship between CAVI and the presence of atherosclerotic lesions of the carotid arteries, ultrasound signs of plaque instability in the carotid arteries ($p = 0.073$ and $p = 0.163$).

The group average ABI values in the group of patients with normal thyroid function were higher than in the group of patients with subclinical hypothyroidism and were: R-ABI 1.14 (1.04-1.26) versus 1.04 (0.84-1.13) and L-ABI 1.19 (1.13-1.22) versus 1.05 (0.86-1.09) ($p < 0.01$ and $p < 0.001$, respectively). We divided patients within the groups into subgroups: with normal ABI values (both legs had values of $1.00 \leq ABI < 1.4$); "low" when at least one leg had a value < 1.00, and "high" when at least one leg was ≥ 1.40 or incompressible and the other leg was high/incompressible or normal.

We found in the group of patients with subclinical hypothyroidism the proportion with a low ABI index was statistically significantly higher: 34.7% (n = 16) versus 12.5% (n = 3) ($F = 0.057$; $p < 0.05$). There were no patients with an ABI index ≥ 1.40 in both groups. We established a direct association between a reduced ABI value in one of the legs and the presence of ultrasound signs of multivessel atherosclerotic lesions of the carotid system ($r = 0.337$, $p < 0.001$). We established a negative associationbetween a decrease in ABI index < 1.00 and atherogenic type IIa hyperlipidemia ($r = 0.43$; $p < 0.05$).

Recent epidemiological studies have demonstrated an inverse relationship between TSH levels –primarily in individuals with overt hypo- and hyperthyroidism – and the values of TC and LDL [7, 14, 22–25]. However, the issues of secondary hyperlipidemia in subclinical hypothyroidism, as well as the influence of TSH and free fractions of thyroid hormones on the values of HDL-C, TG, and apolipoproteins, remain poorly understood. Our data support the formation of secondary hyperlipidemia in patients with subclinical hypothyroidism, combined with a deficiency in HDL and confirm a more aggressive course of atherogenesis. This is illustrated through ultrasound visualization of atherosclerotic changes in the carotid arteries, in comparison with individuals without thyroid dysfunction. Evidence of early vascular remodeling processes and an independent risk factor for the development of transient ischemic attacks and stroke is a thickening of the intima-media complex of the common carotid artery of more than 0.9 ± 0.1 mm [46].

In the group of patients with subclinical hypothyroidism the obtained average group value of BMI (1.1±0.19 versus 0.75±0.15; $p < 0.05$) and higher proportion of persons with IMT CCA > 0.9 mm (76.1% (n = 35) versus 54.2% (n = 13) ($\chi^2 = 6.41$; $p < 0.05$)) in comparison with data from patients without thyroid dysfunction indicate the need for a more in-depth study of cause-and-effect relationships and development preventive algorithms for cardiovascular accidents in this category of people.

Disability at an early age and high mortality in working-age patients due to cardiovascular

pathology coupled with the high costs of outpatient and inpatient treatment place a significant financial burden on the budgets of both developed and developing countries. This includes expenses for rehabilitation, preferential provision, and complex interventional/surgical treatments. These challenges underscore the urgent need to introduce new scientifically based principles for the stratification of cardiovascular risk groups. More effective prevention strategies, including antiatherogenic approaches, are essential, particularly for comorbid patients.

A number of large studies over the past decade have demonstrated that arterial stiffness is an independent predictor of cardiovascular disease and mortality in the population. Its prognostic value is notably high at the preclinical stages of disease development. Most literature sources use an isolated estimate of CAVI values > 0.9. In our study, a third of the patients exhibited a significant decrease in the CAVI value. Interestingly, these same patients also had multivessel carotid artery disease as determined by ultrasound. This discrepancy can be attributed to significant atherosclerotic lesions, including those in peripheral arteries. Specifically, patients with subclinical hypothyroidism had a higher proportion with a reduced ABI value (34.7% versus 12.5%). ABI reflects peripheral circulation in smaller diameter arteries, which are less susceptible to calcification.

In addition, we established a direct association between a reduced ABI value in at least one leg and the presence of an atherogenic type of hyperlipidemia ($r = 0.43$; $p < 0.05$), as well as ultrasound signs of multivessel atherosclerotic lesions in the carotid system ($r = 0.337$, $p < 0.001$). This observation suggests that comorbid patients with subclinical hypothyroidism are predisposed to a more aggressive course of atherogenesis and the initiation of "rapid vascular aging".

Our results underscore the necessity for timely correction of cardiovascular risk factors and emphasize the importance of diagnosing atherosclerotic processes not only at the stage of fully formed atherosclerotic plaques (via ultrasound examination of the vascular bed and radiation diagnostic methods) but also at the microlevel. There is a need for the active implementation of a combined analysis of vascular stiffness in practical healthcare utilizing the characteristics of the main blood flow (CAVI alongside with ABI results). This approach enables an objective assessment providing valuable information about the true state of blood circulation in this patient category.

Conclusion

In clinically healthy working-age patients with subclinical hypothyroidism the proportion of individuals with ultrasound signs of multivessel atherosclerotic lesions of the carotid arteries is higher. Additionally, precerebral atherosclerosis occurs against the background of atherogenic type IIa secondary hyperlipidemia combined with insufficiency of antiatherogenic HDL-C, in comparison to individuals without thyroid dysfunction. The etiopathogenetic mechanisms of "early vascular aging", the criteria for stratification of risk groups for atherosclerosis-associated cardiovascular diseases, the selection of diagnostic algorithms for visualizing preclinical stages of atherogenesis, and timely antiatherogenic strategies in asymptomatic patients with comorbid thyroid pathology require further exploration.

Active implementation in practical healthcare of the assessment of regional (segmental) vascular stiffness using volumetric sphygmography based on the characteristics of the main (CAVI) and peripheral (ABI) blood flow can be proposed for diagnosing preclinical stages of atherogenesis in comorbid patients with endocrinopathies. Verification of a stenosing hemodynamically significant or non-hemodynamically significant atherosclerotic lesion of the coronary arteries, irrespective of the clinical component, is a factor of high cardiovascular risk necessitating immediate correction of hyperlipidemia.

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