ORIGINAL ARTICLE

Subclinical Hypothyroidism as a Risk Factor for Cardiovascular Disease

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ABSTRACT

Nowadays, more than 485 million people in the world suffer from cardiovascular diseases (CVD). According to large epidemiological studies, the group of CVD is the leading cause of death in the world. One of the neurohumoral mechanisms that appears to be a risk factor for CVD is thyroid dysfunction. In this regard, in recent years, more and more attention is paid to the study the influence of subclinical hypothyroidism on the occurrence and development of cardiovascular disorders.

MeSH words: cardiovascular diseases, subclinical hypothyroidism

INTRODUCTION

According to the World Health Organization, cardiovascular diseases (CVD) and their complications are the most important causes of morbidity and mortality worldwide, with enormous costs for the health care system [1]. Nowadays, more than 485 million people in the world suffer from CVD [2]. In the age group over 40, the likelihood of cardiac pathology development increases every 5-6 years with aging, amounting to 52.7% in the age group from 55 to 60 years. [3] According to large epidemiological studies, the group of CVD is the leading cause of death in the world. Moreover, 30% of the deceased are people of working age. [4]

Chronic heart failure, which is the end stage of most CVDs, also retains its position as one of the most common causes of hospitalization and death worldwide [5]. CHF has a particularly poor prognosis: more than half of patients with clinically expressed heart failure (CHF II-III functional classes) die within 5 years, and in severe and terminal heart failure (CHF III-IV functional classes), the same number die in within the first year from the date of confirmation of the diagnosis. Despite the fact that over the past 30 years there has been significant progress in the treatment of this disease, the mortality rate is still extremely high [6].

One of the neurohumoral mechanisms that appears to be a risk factor for CVD is thyroid dysfunction. It is known that thyroid hormone receptors are found in the myocardium of the heart and vascular endothelium, as a result of which even small fluctuations in their level in the blood can have significant consequences for the functional state of the cardiovascular system [7] In this regard, in recent years, more and more attention is paid to the study the influence of subclinical hypothyroidism on the occurrence and development of cardiovascular disorders.

Subclinical hypothyroidism (SCH) is usually characterized by an increase in thyroid-stimulating hormone (TSH) and a normal level of free thyroxine (FT4). The diagnosis of persistent SCH is considered to be confirmed when the level of TSH in the blood is more than 10 mU / L or at least twofold determination of the level of TSH in the range of 4-10 mU / L [8]. Depending on the population studied, the prevalence of SCH ranges from 3 to 15%, while a higher incidence of SCH is observed in women and the elderly [9]. The risk of progression of subclinical hypothyroidism into overt hypothyroidism is estimated at 2 to 6% per year, and the risk is significantly higher in women with TSH over 10 mU / L and positive antibodies to thyroperoxidase (anti-TPO) [10]

CHF and myocardial fibrosis: Several studies have shown that SCH increases the risk of cardiovascular events and overall mortality, which proves its role as an independent predictor of CVD [10, 11]. It is also recognized that SCH can be an indirect cause of CHF, as a result of which the recommendations of the American College of Heart and the American Heart Association for the diagnosis and treatment of heart failure in adults include an

examination of the functional status of the thyroid gland [12]. Despite the fact that SCH is directly associated with an increased risk of CHF, the relationship between it and clinical outcomes in patients with CHF remains uncertain. The results of the studies are rather contradictory: some of them describe an increase in the risk of overall mortality or hospitalization for patients with CHF and SCH, while others have not obtained similar data [13]. A recent meta-analysis of 14 studies found a significant association between SCH and the main outcomes of CHF, such as sudden cardiac death and / or hospitalization [14]. In the study of L. Kannan et al. with the participation of 1365 patients, it was found that SCH at a TSH level of ≥7 mU / L against a background of pre-existing CHF is associated with a poor prognosis [15]. In contrast, N. Samuel et al. note that an increase in TSH levels is a predictor of mortality in univariate analysis, but this relationship disappears after adjusting for age and natriuretic peptide level; thus, it was concluded that SCH is associated with worse survival in patients with CHF, but at the same time it is not an independent predictor of mortality [16]. Similar results were obtained by A. Perez et al. in the CORONA study [17]. Nevertheless, large-scale studies of the mutual influence of CHF and SCH have not been carried out, which dictates the need for a more detailed consideration of this comorbid pathology, in particular its pathogenetic aspects. In this regard, the efforts of researchers in recent years have been aimed at elucidating these mechanisms, as well as applying the results obtained to conduct further research using elaborated criteria for selecting patients.

Special attention should be paid to data on the development of cardiac fibrosis in patients with subclinical thyroid dysfunction, and the severity of these processes directly depends on the level of TSH. In a recent study by Yao Z. et al. determined whether there are diffuse changes in the myocardium in SCH using the modern technique of T1 mapping in cardiac MRI. In patients with SCH, a significant increase in T1 time was noted, especially at a TSH level of ≥10 µIU / ml. In addition, left ventricular diastolic function as measured peak filling rate (PFR) was significantly lower in patients with TSH levels ≥10 µIU / ml. Thus, the authors confirm the presence of a positive correlation between the TSH level and fibrotic changes in the myocardium [18]. Similar results were achieved in another study, where the assessment of the myocardial state was carried out using cardiovascular magnetic resonance - based T1 mapping in overt and subclinical hypothyroidism, as well as with euthyroidism as a control group. The values of the left ventricular myocardium T1, left ventricular longitudinal strain (LVLS), radial deformation of the left ventricular myocardium (LVRS), left ventricular circumferential strain (LVCS) were determined. LV myocardial T1 in patients with SCH was higher than in the group with euthyroidism; LVLS, LVCS, LVRS in the group with SCH were lower than in the control group, which also indicates a positive correlation between TSH and fibrotic changes in the left ventricular myocardium [19].

In the modern scientific literature there is a lot of evidence for the detection of latent and overt biochemical disorders in patients with SCH, the main of which are dyslipidemia and, in particular, increased low density lipoprotein (LDL), hyperhomocysteinemia, and blood hypercoagulation. The authors believe that due to such changes, the risk of adverse cardiovascular events increases significantly [20].

In addition, SCG can negatively affect such significant risk factors for atherothrombotic diseases as the level of C-reactive protein (CRP) and homocysteine in blood plasma. So, in the study of Vayá A. et al. it was noted that in the group with SCH, there was more increase in plasma viscosity (PV), fibrinogen, CRP, homocysteine and red blood cell distribution width (RDW) compared with the control group, in which euthyroidism was observed. Consequently, patients with SCH have a high cardiovascular risk, characterized primarily by an increase in PV, fibrinogen, homo-cysteine, and RDW [21].

It is known that systemic inflammation contributes to the formation and progression of cardiometabolic complications, and TSH, in turn, can stimulate the production of some biomarkers of this pathological process. Gupta G. et al. found that elevated TSH levels positively correlated with CRP, interleukin-6 (IL-6) and erythrocyte sedimentation rate. It is noteworthy that the levels of inflammatory markers subsequently increased as the disease progressed and in the absence of treatment. In addition, there were high levels of total cholesterol, triglycerides and LDL cholesterol in the group with SCH, and the level of HDL was significantly lower than in the group with euthyroidism. In this regard, such persons in the future may have a risk of further progression of CVD, including worsening of the course of CHF [22]. For another study, obese patients were selected and divided into groups with euthyroidism and SCH [23]. TSH and inflammatory markers were analyzed before and 12 months after bariatric surgery. Patients with SCH had significantly higher levels of interleukin-6, TNF-α and C-reactive protein than patients with euthyroidism. 12 months after surgery, the frequency of SCH decreased from 31.8 to 2.3% (p <0.001); TSH level was significantly reduced in both groups, but more pronounced in the group with SCH (p <0.001). Godinjak A. et al. came to the conclusion that SCH is associated with an increase in CRP, homocysteine, TNF-α, uric acid and increases the risk of CVD in postmenopausal women. Moreover, SCH is associated with a higher incidence of such diseases, regardless of age and duration of postmenopause (p = 0.0007) [24].

Diastolic dysfunction: Changes in thyroid status in SCH are associated with changes in a number of heart parameters, which are manifested, first of all, by diastolic dysfunction of the left ventricular (LVDD). In this regard, a study was carried out in which the relationship between the level of thyroid hormones and the cardio-ankle vascular index (CAVI) and left ventricular diastolic function was assessed. Compared to the control group, patients with SCH had significantly higher values of the N-terminal pro-brain natriuretic peptide (NT-proBNP), CRP and CAVI, as well as lower values of the early diastolic mitral annular velocity (e'). In the SCH group, CAVI was significantly associated with NT-proBNP, CRP, and e', which confirms the risk of developing cardiovascular pathology in the presence of SCH [25].

Recently, more and more studies have been devoted to a detailed examination using modern methods of instrumental diagnostics of the relationship between SCH

and functional disorders of the cardiovascular system, which includes the above-mentioned LVDD. Vitale et al. assessed the function of the left ventricular myocardium in SCG using standard Doppler and pulse-wave tissue Doppler echocardiography. Standard Doppler imaging has shown an increase in preejection period (PEP), an increase in the ratio of pre-ejection period to ejection time (PEP / ET), and isovolumic relaxation time (IVRT) in SCH. According to pulsed-wave tissue Doppler echocardiography, the corrected ratio of myocardial preejection time to myocardial ejection time (PCTm / CTm), as well as corrected myocardial relaxation time (RTm) at the level of the level of posterior septum were positively associated with TSH [26]. In another study, it was shown that SCG negatively affects the diastolic function of the heart in CHF patients with preserved ejection fraction (CHFpEF) to the control group, where the euthyroid state was recorded. Pathogenesis of these disorders Meng Y. et al. associated with elevated levels of B-type brain natriuretic peptide (BNP) and CRP detected in patients with SCH [27]. Also, interesting information on the comprehensive assessment of LVDD in individuals with SCH was obtained by Nakanishi K. et al. as a result of Speckle-tracking echocardiography. In the group with SCH, there was a significant impairment of left atrial (LA) function during the reservoir phase (accumulation period), as well as during the conduit phase (flow period) compared with patients with euthyroidism. In addition, the relationship between the presence of SCH and a decrease in LA function during the reservoir phase did not depend on age, traditional cardiovascular risk factors, and corresponding laboratory and echocardiographic parameters [28].

Arterial stiffness and endothelial dysfunction: A number of authors testify to the significant role of SCH as a risk factor for cardiovascular events associated not only with LVDD, but also with arterial stiffness. A small number of scientific works are devoted to vascular stiffness in SCH. The study of Lambrinoudaki I. et al. involved 106 healthy postmenopausal women with TSH levels within the laboratory reference range (0.4–4.5 µIU / ml). Vascular structure and function were assessed by determining the following parameters: intima-media thickness (IMT), pulse wave velocity (PWV), augmentation index (AI) and flow-mediated dilatation (FMD). Average PWV values linearly increased with an increase in TSH, and individuals with serum TSH above 2.5 µIU / ml had significantly higher PWV values compared to patients with TSH below 2.5 µIU / ml. Thus, women with TSH levels in the upper reference range have increased arterial stiffness compared to women with lower TSH levels [29]. This is confirmed by the results obtained by Owen et al., who found that arterial stiffness increasing against the background of SCH and decreases during 6 months of L-thyroxine therapy, while systolic and diastolic myocardial functions are similar to those in the control group and remain unchanged after treatment [30].

The impact of SCH on endothelial dysfunction (ED) is also devoted to a small number of studies, which emphasizes the need to accumulate knowledge on this issue. It has been proven that SCH affects the production of nitric oxide (NO) and promotes increased degradation of vasodepressor intermediates, which is a trigger factor for the occurrence of ED and impaired coronary blood flow through specific molecular pathways in endothelial cells. Based on this data, Lee S.W. et al. performed 385 coronary angiographies with ergonomic challenge test (EPT) in patients without concomitant cardiovascular risk factors; 165 had a positive EPT (EPT (+)) and 220 negative (EPT (-)). Further, the relationship between spasm of the coronary artery and SCH, as well as the presence of TPOAb in the blood serum, was assessed. The proportion of individuals with SCH among those with EPT (+) was significantly higher than among those with EPT (-). Moreover, the EPT (+) group had significantly more positive TPOAb than the EPT (-) patients. The authors found a positive correlation between EPT (+) and the incidence of high titer of TPOAb among patients with SCH. From this, it can be concluded that SCH and high titer TPOAb are significantly associated with coronary vasospasm in patients without CVD risk factors [31]. It is generally known that ED is diagnosed with a decrease in the bioavailability of nitric oxide (NO) and / or an increase in one of the vasoconstrictor factors, such as endothelin-1 (ET-1). In a study by Ahirwar A.K. et al. the relationship of elevated TSH levels with the above mediators of endothelial dysfunction was evaluated in patients with metabolic syndrome (MS) compared with healthy people from the control group. Among 50 patients with MS, 22 had subclinical hypothyroidism, and 3 had manifest hypothyroidism. The serum TSH level was significantly higher in cases of MS compared with healthy people. It was found that in the group of patients with MS there was a lower level of NO and a higher level of ET-1 in comparison with the control group. There was a positive correlation between TSH and ET-1 ($r = 0.341$, $p = 0.001$) and negative - with NO ($r = -0.331$, $p = 0.001$). Thus, an elevated TSH level in SCH causes ED, which in turn can lead to MS and concomitant diseases [32]. In another study, FMD and IMT were determined in patients with SCH and in healthy people from the control group to clarify the function of the endothelium. Patients received levothyroxine sodium (50 mcg / day) for 2 months, after which FMD and IMT were re-assessed. Patients with SCH and controls were relatively similar in IMT, but FMD was significantly lower with SCH than with euthyroidism. After therapy with levothyroxine sodium, a significant increase in FMD was observed. Thus, patients with SCH have endothelial dysfunction that responds to therapy with levothyroxine sodium, in other words, is reversible [33].

Despite the fact that a lot of ED biomarkers are currently described, the search for the most universal of them that could satisfy any requirements of test theory is still ongoing. According to A.E. Berezin, endothelial microparticles (EMPs) can be considered as such markers. In particular, the apoptotic phenotype of circulating EMPs, including CD144 + / CD31 + / annexin V + and CD31 + / annexin V +, mediates endothelial dysfunction, which contributes to the worsening of CHF and significantly increases the risk of CVD. It is also assumed that the imbalance between the two subpopulations of EMP reflects the severity of ED. In this regard, a violation of the ratio of circulating EMPs can be used as a predictor of adverse clinical events with a high prognostic potential [34]. In a prospective study, Berezin A.E. et al., the number of circulating EMPs with the CD31 + / annexin V + phenotype in patients with SCH was significantly higher than in

patients without SCH (p <0.001), which was reflected in an increase in the ratio of EMPs CD31 + / annexin V + to CD62E + in the group with SCH (p <0.001). TSH, SCH, NT-proBNP, NYHA CHF FC, CRP, dyslipidemia, and uric acid concentration were independent predictors of an increase in the ratio of EMP CD31 + / annexin V + to CD62E +. Thus, SCH in patients with CHF is associated with a violation of the ratio of subpopulations of endothelial microparticles, which is an early biological marker of endothelial dysfunction with a possible prognostic potential in the form of CVD progression and their unfavorable clinical outcomes [35].

Arterial hypertension: Recently, given the high medical and social significance of hypertension, the study of the pathophysiological mechanisms of increasing blood pressure (BP) is of particular interest. Researchers include among such factors a violation of the thyroid status, which actively affects the regulation of blood pressure [36]. Zhang J. et al. in their recent work evaluated the relationship between subclinical thyroid dysfunction and hypertension. It has been proven that hypertension is associated with subclinical hypothyroidism, and in women with SCH, hypertension was significantly more common than in men [38]. Cai P. et al. analyzed the characteristics of BP by measuring office blood pressure and daily ambulatory blood pressure monitoring in SCH and euthyroidism. The results showed that daytime systolic blood pressure (SBP), nocturnal SBP, nocturnal diastolic blood pressure (DBP), 24-hour SBP, and 24-hour DBP were significantly higher in patients with SCH than in patients with euthyroidism. In addition, the SCH group was independently associated with persistent hypertension and "masked" hypertension [36]. Ittermann T. et al. suggest that SCH be considered a risk factor for hypertension, since there is a statistically significant relationship between TSH levels and increased blood pressure [39]. In a study by Jian W.X. et al. in patients in the group with SCH (TSH> 4.8 µIU / ml) and in the group with high-normal TSH (2.5-4.8 µIU / ml), increased blood pressure was more often observed, compared with individuals who had low-normal TSH (0 , 3-2.5 µIU / ml) (p <0.05). This suggests that both SCH and high-normal TSH levels are independent risk factors for arterial hypertension [40].

CONCLUSIONS

Summing up the above, it can be noted that the significance of pathological processes in thyroid dysfunction observed in the CVS is very high. However, there is still no clear understanding of the biochemical and pathophysiological mechanisms of the development of these changes and their dependence on the specific level of thyroid hormones. It is necessary to clarify the clinical significance of their correction with hormone replacement therapy. The few available studies on the use of L-thyroxine for the treatment of CHF patients concern small groups of patients, therefore, they cannot be considered reliable and require full-scale studies. All this opens up new opportunities for further activities with the aim of resolving contradictions and finding answers to a number of issues regarding the relationship between SCH and CVD and which we currently face in therapeutic practice.

REFERENCES

1. World Health Organization. Global status report on noncommunicable diseases 2014. https://www.who.int/nmh/publications/ncd-status-report-2014/en/. Accessed July 10, 2020.
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789-858. doi:10.1016/S01406736(18)32279-7.
3. Mosquera PA, San Sebastian M, Waenerlund AK, Ivarsson A, Weinehall L, Gustafsson PE. Income-related inequalities in cardiovascular disease from mid-life to old age in a Northern Swedish cohort: A decomposition analysis. Soc Sci Med. 2016;149:135-44. doi: 10.1016/j.socscimed.2015.12.017.
4. Chazov I.E., Oshchepkova E.V. Experience in combating cardiovascular diseases in Russia. Analiticheskiy vestnik. 2015: 44 (597); 4-8. (In Russ.)
5. Tokmachev RE, Kravchenko AYa, Budnevsky AV, Ovsyannikov ES, Tokmachev EV, Chernik TA. Features of the Functional Status and Cytokine Profile of Patients with Chronic Heart Failure in Combination with Chronic Obstructive Pulmonary Disease. International Journal of Biomedicine. 2021;11(1):9-13. doi:10.21103/Article11(1)_OA1.
6. Lewis KS, Butler J, Bauersachs J, Sandner P. The three-decade long journey in heart failure drug development. Handb Exp Pharmacol. 2017;243:1–14. doi: 10.1186/s12872-019-1055-x.
7. Wiersinga WM. The role of thyroid hormone nuclear receptors in the heart: evidence from pharmacological approaches. Heart Fail Rev. 2010;15(2):121-4. doi: 10.1007/s10741-008-9131-9.
8. Russian Association of Endocrinologists. Clinical guidelines: Hypothyroidism. 2019. P.38. (In Russ.)
9. Gosi SKY, Garla VV. Subclinical Hypothyroidism. 2021 Jan 26. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 30725655.
10. Moon S, Kim MJ, Yu JM, Yoo HJ, Park YJ. Subclinical Hypothyroidism and the Risk of Cardiovascular Disease and All-Cause Mortality: A Meta-Analysis of Prospective Cohort Studies. Thyroid. 2018 Sep;28(9):1101-1110. doi: 10.1089/thy.2017.0414.
11. Vale, C., Neves, J.S., von Hafe, M. et al. The Role of Thyroid Hormones in Heart Failure. Cardiovasc Drugs Ther 33, 179–188 (2019). doi:10.1007/s10557-019-06870-4.
12. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation. 2009;119(14):1977-2016. doi: 10.1161/CIRCULATIONAHA.109.192064.
13. Tokmachev R.E., Drobysheva E.S., Kravchenko A.Ya., Tokmachev E.V., Pertsev V.A., Shapovalova M.M. Features of the course of chronic heart failure in elderly patients with thyroid dysfunction. Preventive medicine. 2020; 23 (5-2): P. 63. (In Russ)
14. Yang, G., Wang, Y., Ma, A. et al. Subclinical thyroid dysfunction is associated with adverse prognosis in heart failure patients with reduced ejection fraction. BMC Cardiovasc Disord. 2019; 19(83). doi:10.1186/s12872-019-1055-x.

15. Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, Cappola TP, Cappola AR. Thyroid Dysfunction in Heart Failure and Cardiovascular Outcomes. Circ Heart Fail. 2018;11(12):e005266. doi: 10.1161/CIRCHEARTFAILURE.118.005266.

16. Samuel N., Cuthbert JJ, Brown OI, Kazmi S, Cleland JGF, Rigby AS, Clark AL. Relation Between Thyroid Function and Mortality in Patients With Chronic Heart Failure. Am J Cardiol. 2021; 139:57-63. doi: 10.1016/j.amjcard.2020.10.034.

17. Perez A.C, Jhund P.S, Stott D.J. et al. Thyroid-stimulating hormone and clinical outcomes: the CORONA trial (controlled rosuvastatin multinational study in heart failure). JACC Heart Fail. 2014; 2: 35-40. doi: 10.1016/j.jchf.2013.07.008.

18. Zhi Yao, Gao X, Liu M, et al. Diffuse Myocardial Injuries are Present in Subclinical Hypothyroidism: A Clinical Study Using Myocardial T1-mapping Quantification. Sci Rep. 2018;8(1):4999. doi:10.1038/s41598-018-22970-x.

19. Liu M, Liu W, Zhang P, An J, Wang G. Left ventricular myocardial T1 mapping and strain analysis evaluate cardiac abnormality in hypothyroidism. Int J Cardiovasc Imaging. 2019;35(3):507-515. doi: 10.1007/s10554-018-1456-4.

20. Harada PHN, Buring JE, Cook NR, Cobble ME, Kulkarni KR, Mora S. Impact of subclinical hypothyroidism on cardiometabolic biomarkers in women. J Endocr Soc. 2017; 1:113–123. doi: 10.1210/js.2016-1085.

21. Vayá A, Giménez C, Sarnago A, Alba A, Rubio O, Hernández-Mijares A, Cámara R. Subclinical hypothyroidism and cardiovascular risk. Clin Hemorheol Microcirc. 2014;58(1):1-7. doi: 10.3233/CH-141871. PMID: 25339098.

22. Gupta G, Sharma P, Kumar P, Itagappa M. Study on subclinical hypothyroidism and its association with various inflammatory markers. J Clin Diagn Res. 2015; 9(11):BC04–B6. doi: 10.7860/JCDR/2015/14640.6806.

23. Zhu C, Gao J, Mei F, Lu L, Zhou D, Qu S. Reduction in Thyroid-Stimulating Hormone Correlated with Improved Inflammation Markers in Chinese Patients with Morbid Obesity Undergoing Laparoscopic Sleeve Gastrectomy. Obes Surg. 2019;29(12):3954-3965. doi: 10.1007/s11695-019-04063-4.

24. Godinjak A., Velija-Ašimi Z., Bureković A., Kulić M., Gicić S., Serdarević F. Subclinical inflammation: The link between increased cardiovascular risk and subclinical hypothyroidism in postmenopausal women. CMBEBIH 2017; 62: 235-240. doi:10.1007/978-981-10-4166-2_35.

25. Masaki M, Komamura K, Goda A et al. Elevated arterial stiffness and diastolic dysfunction in subclinical hypothyroidism. Circ J. 2014;78(6):1494–1500. doi: 10.1253/circj.cj-13-1556.

26. Vitale G, Maurizio G, Gelsy AL et al. Left ventricular myocardial impairment in subclinical hypothyroidism assessed by a new ultrasound tool: pulsed tissue Doppler. J Clin Endocrinol Metab. 2002;87(9):4350-5. doi: 10.1210/jc.2002-011764.

27. Meng Y, Zhao T, Zhang ZY, Zhang DK. Association between sub-clinical hypothyroidism and heart failure with preserved ejection fraction. Chin Med J (Engl). 2020;133(3):364-366. doi:10.1097/CM9.0000000000000631.

28. Nakanishi K, Daimon M, Yoshida Y, Sawada N, Hirose K, Iwama K, Yamamoto Y, Ishiwata J, Hirokawa M, Kaneko H, Nakao T, Mizuno Y, Morita H, Di Tullio MR, Homma S, Komuro I. Subclinical Hypothyroidism as an Independent Determinant of Left Atrial Dysfunction in the General Population. J Clin Endocrinol Metab. 2021;106(4):e1859-e1867. doi: 10.1210/clinem/dgaa730.

29. Lambrinoudaki I, Armeni E, Rizos D, Georgiopoulos G, Kazani M, Alexandrou A, Deligeoroglou E, Livada A, Psychas C, Creatsa M, Bouboulis G, Alevizaki M, Stamatelopoulos K. High normal thyroid-stimulating hormone is associated with arterial stiffness in healthy postmenopausal women. J Hypertens. 2012;30(3):592-9. doi: 10.1097/HJH.0b013e32834f5076.

30. Owen PJ, Rajiv C, Vinereanu D, Mathew T, Fraser AG, Lazarus JH. Subclinical hypothyroidism, arterial stiffness, and myocardial reserve. J Clin Endocrinol Metab. 2006;91(6):2126-32. doi: 10.1210/jc.2005-2108.

31. Lee SW, Cho KI, Kim HS, Heo JH, Cha TJ. The Impact of Subclinical Hypothyroidism or Thyroid Autoimmunity on Coronary Vasospasm in Patients without Associated Cardiovascular Risk Factors. Korean Circ J;45(2):125-130. doi:10.4070/kcj.2015.45.2.125.

32. Ahirwar AK, Singh A, Jain A, Patra SK, Goswami B, Bhatnagar MK, Bhattacharjee J. Raised TSH is associated with endothelial dysfunction in Metabolic Syndrome: A case control study. Rom J Intern Med. 2017;55(4):212-221. doi: 10.1515/rjim-2017-0023.

33. Niknam N, Khalili N, Khosravi E, Nourbakhsh M. Endothelial dysfunction in patients with subclinical hypothyroidism and the effects of treatment with levothyroxine. Adv Biomed Res. 2016;5:38. doi:10.4103/2277-9175.178783

34. Berezin AE, Kremzer AA, Martovitskaya YV, Samura TA, Berezina TA. The predictive role of circulating microparticles in patients with chronic heart failure. BBA Clin. 2014;3:18-24. doi:10.1016/j.bbacli.2014.11.006

35. Berezin AE, Kremzer AA, Martovitskaya YV, Samura TA, Berezina TA. The Association of Subclinical Hypothyroidism and Pattern of Circulating Endothelial-Derived Microparticles Among Chronic Heart Failure Patients. Res Cardiovasc Med. 2015; 4(4):e29094. doi:10.5812/cardiovascmed.29094

36. Feskova A.A., Kravchenko A.Ya. Features of the clinical course of hypertension against the background of subclinical hypofunction of the thyroid gland. Systems analysis and management in biomedical systems. 2015; 14 (3): 473-476. (In Russ.)

37. Zhang J, Huang C, Meng Z, Fan Y, Yang Q, Zhang W, Gao Y, Yang Z, Cai H, Bian B, Li Y, Yu X, Du X, Xu S, Nie J, Liu M, Sun J, Zhang Q, Gao Y, Song K, Wang X, Zhao L. Gender-Specific Differences on the Association of Hypertension with Subclinical Thyroid Dysfunction. Int J Endocrinol. 2019; 2019:6053068. doi: 10.1155/2019/6053068.

38. Cai P, Peng Y, Chen Y, Wang Y, Wang X. Blood pressure characteristics of subclinical hypothyroidism: an observation study combined with office blood pressure and 24-h ambulatory blood pressure. J Hypertens. 2021; 39(3):453-460. doi: 10.1097/HJH.0000000000002655.

39. Ittermann T, Thamm M, Wallaschofski H, Rettig R, Völzke H. Serum thyroid-stimulating hormone levels are associated with blood pressure in children and adolescents. J Clin Endocrinol Metab. 2012;97(3):828-34. doi: 10.1210/jc.2011-2768.

40. Jian WX, Jin J, Qin L, Fang WJ, Chen XR, Chen HB, Su Q, Xing HL. Relationship between thyroid-stimulating hormone and blood pressure in the middle-aged and elderly population. Singapore Med J. 2013;54(7):401-5. doi: 10.11622/smedj.2013142.