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Hypothyroidism and subclinical hypothyroidism and their influence on autonomic cardiovascular regulation and metabolism

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The aim of this review is to expose different opinions in the literature on the influence of TH and TSH on the autonomic vegetative regulation of cardiovascular function and metabolism in marked and subclinical hypothyroidism (sHT). Hypothyroidism causes changes in hemodynamics and in lipid metabolism, which are predisposing risk factors for cardiovascular diseases. Subclinical hypothyroidism proceeds asymptomatically but there are changes in the cardiovascular system and its regulation, as well as a possible need for hormonal treatment. Although according to literature sources the social and age groups studied are heterogeneous and different tests have been used to investigate the autonomic vegetative regulation, no single model for investigation and therapeutic behavior, especially in sHT, has yet been established. Heart rate variability (HRV) is determined by the balance of afferent sympathetic and parasympathetic influences on cardiac structures and can be used for risk stratification of cardiovascular complications in patients with hypothyroidism. Early detection of autonomic dysfunction and its treatment may improve the overall prognosis as well as the quality of life of patients with hypothyroidism and sHT and limit the rates of cardiovascular morbidity and mortality in these patients.
Key words: hypothyroidism; subclinical hypothyroidism; autonomic cardiovascular regulation; heart rate variability.

Iodine deficiency is still one of the main problems related to public health in many countries despite successfully implemented strategies for its elimination [1, 2]. Iodine deficiency causes a series of mental and physiological disorders called iodine deficiency disorders. Iodine is a trace element that is involved in the structure of thyroid hormones [3, 4]. The absorption of iodine can be suppressed by some environmental factors, such as smoking (due to the presence of thiocyanates), nitrates, etc. [5]. The risk of iodine deficiency is particularly high in risk groups of the population such as children, pregnant women, and postpartum women [6, 7]. Hypothyroidism and sHT are widely spread endocrinological diseases, [8] dependent on the factors added iodine, age, sex and race. Hormonal changes in hypothyroidism are characterized by low levels of iodine-containing thyroid hormone (TH) of the thyroid gland, resulting in elevated thyroid-stimulating hormone (TSH) levels [9]. In sHT the TSH levels are elevated above the upper reference limit most often with normal TH levels. Thyroid hormones play an important role in the regulation of cardiovascular and metabolic physiology. Although sHT progresses asymptomatically, there are changes in the cardiovascular system and its regulation, as well as a possible need for hormonal treatment. Hypothyroidism causes changes in hemodynamics (Fig. 1): increase in the systemic vascular resistance, diastolic arterial pressure, peripheral arterial resistance, mean arterial pressure and afterload, while the cardiac minute volume, the blood volume, the myocardial contractility and the activity of the renin-angiotensin-aldosterone system (RAAS) decrease [9]. Some authors associate

autonomic dysfunction in sHT with the presence of prehypertension, and in addition to a family history of hypertension predict the development of hypertension [10], whereas Walsh et al. report that sHT is not associated with hypertension [11]. Heart rate variability (HRV) is determined by the balance of efferent sympathetic and parasympathetic influences on cardiac structures and can be used for risk stratification of cardiovascular complications in patients with hypothyroidism [12]. In subclinical and marked hypothyroidism, there are also changes in the lipid metabolism (Fig. 2) with elevated serum lipid and C-reactive protein levels, endothelial dysfunction, decreased NO production, and vitamin D3 deficiency, which are risk factors for cardiovascular diseases [13]. According to literature sources, there are studies of the correlation between sympathovagal balance, overweight [14] and metabolism [15, 16]. Our review article uses 47 literature sources from the Pub Med database, 11 of which were from the last 5 years.

The average number of patients with hypothyroidism studied in most literature sources ranges between 30 and 60, and the age group studied is heterogeneous. There are also significantly larger studies of 647 patients with adjustments for socio-demographic and clinical status. The assessment of the autonomic nervous system (ANS) function has been compared with various tests according to Ewing's and Clarke's criterion: parasympathetic (deep breathing test, 30:15 ratio and Valsalva-VR ratio) and sympathetic tests (handgrip dynamometer test and postural hypotension test) [17]. HRV is determined by the balance of the efferent innervation of the sympathetic and parasympathetic nerves on the cardiac structures and is examined as an LF/HF ratio (LF-low frequency power; HF-high frequency power) by spectral-frequency analysis with fast Fourier transform [18]. The ratio indicates the ANS activity and reflects the ability of the cardiovascular system (CVS) to respond rapidly, dynamically and efficiently to stress [19]. HRV recording time in different studies varies from 10-15 min to 24 h [20]. When measuring HRV, the body mass index (BMI) is also examined because of the existing correlation between these two parameters [14-16]. According to literature sources, there are studies of the correlation between sympathovagal balance, overweight [14] and metabolic rate [15, 16]. Millis et al. studied the effect of a high carbohydrate and lipid diet on HRV and found an increase

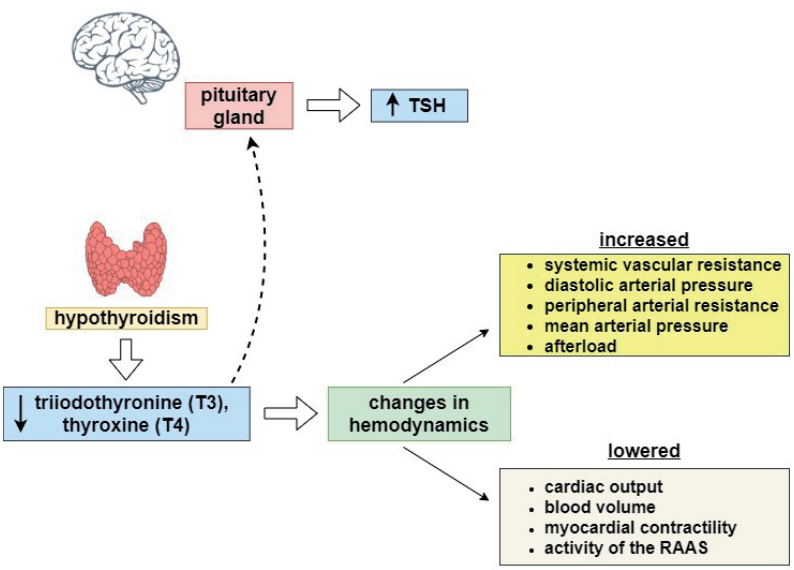

Fig. 1 Changes in the hemodynamics in case of hypothyroidism [9]

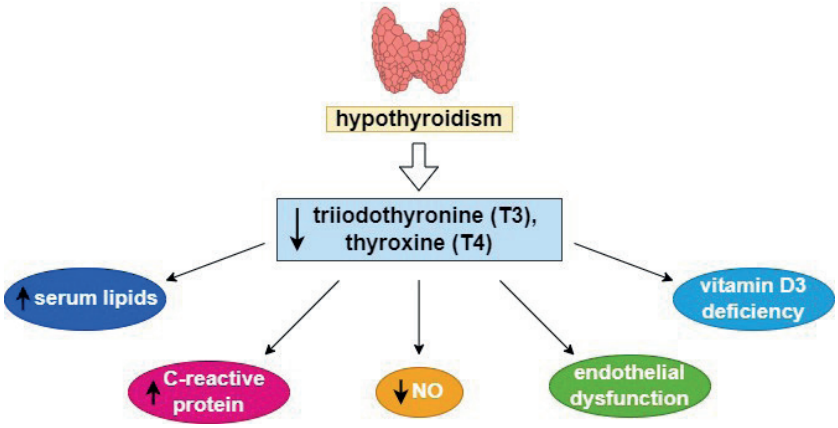

Fig. 2 Changes in lipid metabolism in hypothyroidism [13]

in sympathetic activity [16]. They suggested that the sympathetic modulation caused by carbohydrate metabolism is associated with high resting energy expenditure. HRV testing is a method which can also be used for risk stratification of cardiovascular complications in patients with hypothyroidism [12]. Cacciatori et al. [21] suggest that power spectral analysis is more sensitive than other standard tests for investigating the ANS function. For the hemodynamic study, the systolic BP and the diastolic BP were measured. The assessment of HRV and the simultaneous presence of QT dispersion in electrocardiography (ECG) in hypothyroid patients also represent a useful method to monitor cardiovascular risk [10, 22-24]. The biochemical analysis of blood in these studies includes plasma FT4, TSH and FT3 levels; lipid profile and antibodies. There is evidence of correlation between the presence of antiperoxidase antibodies and modulation of autonomic regulation and changes in TSH in patients with sHT [25, 26].

When considering the question of the influence of hypothyroidism on autonomic cardiac regulation, two groups of authors' opinions are formed. The first group establishes a relationship between TH and changes in autonomic cardiac regulation, with three different directions of changes - predominance of sympathetic activity, predominance of parasympathetic activity, and changes in both sympathetic and parasympathetic activity. The second group of authors found no association between TH and changes in cardiac regulation by ANS.

Relationship between TH level and changes in the autonomic cardiac regulation in hypothyroidism and subclinical hypothyroidism

Changes in the autonomic cardiac regulation with predominance of sympathetic activity. According to most authors, TH influence autonomic regulation [26]. The mechanisms leading to these disturbances are explained by the high plasma adrenaline level with the reduced receptor or post-receptor sensitivity of myocardium [27-29], reduced chronotropic response to β adrenergic stimulation, increased TSH release which directly affects the sympathetic tone [30]. Manhem [28] found increased plasma noradrenaline levels in patients with hypothyroidism, a sign of increased general sympathetic activity. Belezikian et al. [29] performed detailed studies on the influence of TH on alpha- and beta-adrenergic receptors and adrenergic response in a wide range of experimental animals and tissues and showed that TH deficiency is associated with increased sympathetic influence on the cardiovascular autonomic regulation, which is confirmed in patients with hypothyroidism [21, 31].

Autonomic dysfunction is described in both subclinical and marked hypothyroidism [12, 26]. Benly et al. analyzed HRV in 647 participants with subclinical thyroid dysfunction (mean age about 53 years) with adjustment for sociodemographic and clinical characteristics. They concluded that sHT had a lower HRV [26]. Moldabek [12] found an imbalance of the autonomic nervous regulation with a predominance of sympathetic activity against a background of attenuation of parasympathetic activity in 85.7 ± 5.4% of patients with hypothyroidism. Galetta et al. [10] suggested that, despite the clinical picture in patients with sHT, thyroid hormone deficiency is associated with increased sympathetic influence on the cardiovascular system, and a correlation of TSH with the balance between sympathetic and parasympathetic activity was observed. An increase in sympathetic and a decrease in parasympathetic activity is also reported in the studies of Kartik [32]. Some authors even report that decreased parasympathetic activity normalizes after recovery of hypothyroidism to the euthyroid stage [33]. Cacciatore et al. [21] explained the changes in the sympathetic function of ANS by the occurrence of secondary adaptation of the cardiovascular system.

Changes in the autonomic cardiac regulation with decreased sympathetic activity. Another group of authors found changes in autonomic cardiac regulation with a decrease in sympathetic activity. Heemestra et al. [13]found a decrease in the sympathy-thalamic balance characterized by decreased cardiovascular sympathetic activity and vagal modulation in patients with acute short-term hypothyroidism. They investigated the impact of thyroxine replacement therapy on ANS by measuring the urinary catecholamine excretion and examining HRV. Xing et al. [10] investigated HRV in patients with hypothyroidism and found more frequent autonomic dysfunctions with a higher level of vagal tone, meaning that these abnormalities could be partially improved by thyroxine therapy.

Changes in the autonomic cardiac regulation with changes in the sympathetic and parasympathetic activity. A third group of authors [17, 34] found changes in both the sympathetic and the parasympathetic activity. Aarti S. Mahajan et al. [34] observed a more frequent and pronounced sympathetic dysfunction, although they also observed a selective parasympathetic dysfunction, finding that TSH levels did not correlate with the type or degree of autonomic dysfunction. They describe the impaired sympathetic function at low TSH levels and demonstrate that hypothyroidism is associated with a reduction in the sympathovagal modulation of the heart rate and that autonomic abnormalities may begin early in the subclinical stage of hypothyroidism and are comparable in severity to those seen in patients with hypothyroidism. Rajesh Kumar Paul et al. [17] found that both sympathetic and parasympathetic autonomic functions are changed in patients with hypothyroidism. Reviewing many studies Heemestra et al. [13], postulated that heterogeneity in the studied population, the cause and duration of disease may account for the different changes in the autonomic nervous regulation observed.

Adaptation of the cardiovascular system in dynamic physiological tests. Dynamic physiological tests are also important for the adaptation of the autonomic regulation of the cardiovascular system. Rosagnela et al. [35] found that sHT had significantly higher sympathetic and lower parasympathetic modulation in orthostatic compared to the baseline at rest. Almas Saulo Peters et al. [36] also found slower cardiovascular adaptation in women with sHT on dynamic testing in the transition from rest to submaximal effort with the constant workload, compared with euthyroid women. Drbalová et al. [37] found no changes in HRV in patients with sHT in the upright position during an orthostatic test.

Lack of correlation between TH and TSH and the autonomic regulation of the cardiovascular system in hypothyroidism and subclinical hypothyroidism

Some authors [37, 38] found no correlations

between the TH level and the autonomic regulation of the cardiovascular system. Peixoto de Miranda ae al. examined HRV in 15 105 healthy participants and in 647 participants with sHT (mean age about 53 years), a much larger sample size than any other study with adjustments for the variables: age, sex, race, and the factors: hypertension, dyslipidemia, diabetes, smoking, body mass index, alcohol use and leisure-time physical activity [37]. In conclusion, their results showed that patients with sHT had lower overall heart rate variability and that there was no association of TH with the HRV variable. Some researchers also found that the autonomic imbalance was not related to the TSH levels [19, 26, 34].

Role of vitamin D3 for TH, TSH, metabolism and autonomic cardiac regulation in hypothyroidism and subclinical hypothyroidism

Vitamin D3 plays an important role in the regulation of bone metabolism and calcium-phosphorus homeostasis. For the first time, Barchetta et al. [39]. provide evidence that there is a relationship between vitamin D3 concentration and serum TSH. Most patients with hypothyroidism suffer from hypovitaminosis D3 and hypocalcemia [40]. The importance of vitamin D3 in autoimmune, metabolic and cardiovascular diseases has been studied [41]. There is also evidence of its influence on the cardiovascular system and metabolism through effects on endothelium, renin-angiotensin-aldosterone system, and nitric oxide. Ahi Salma found that non-autoimmune hypothyroidism as well as hypothyroidism are associated with vitamin D3 deficiency [42]. There is a correlation between vitamin D3 deficiency and autoimmune diseases or thyroid cancer and is a correlation between vitamin D3 concentration and antibody titers in autoimmune thyroid diseases [43]. The role of vitamin D3 deficiency in Hashimoto's thyroiditis is thought to be related to higher autoantibody (TGAb) levels. Experimental data indicate a direct effect of vitamin D3 on the expression of type 2 deiodinase, causing subsequent peripheral conversion of T4 to T3. It is believed that in patients with autoimmune hypothyroidism, vitamin D3 deficiency should be investigated at the time of diagnosis and monitored at regular intervals [44]. Some authors found correlations between vitamin D3 deficiency and HRV changes [45], while others found none [46]. Despite the multiple studies, the functional relationships between TH, vitamin D3 and the cardiovascular system have not yet been investigated [47]. Further studies determining the role of vitamin D3 deficiency in non-immune hypothyroidism are needed.

CONCLUSION

Despite the heterogeneous social and age groups which participated in the study and the use of different tests to investigate autonomic regulation, no single model for research and therapeutic behavior, especially in sHT, has yet been established. Early detection of autonomic dysfunction and its treatment may improve the overall prognosis as well as the quality of life of patients with hypothyroidism and sHT and limit cardiovascular morbidity and mortality rates in these patients.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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МАНІФЕСТНИЙ ТА СУБКЛІНІЧНИЙ ГІПОТИРЕОЗ ТА ЇХ ВПЛИВ НА АВТОНОМНУ СЕРЦЕВО-СУДИННУ РЕГУЛЯЦІЮ ТА МЕТАБОЛІЗМ

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Мета огляду – представити різні думки в літературі щодо впливу тиреоїдних гормонів та тиреотропних гормонів на вегетативну регуляцію серцево-судинної системи та обмін речовин при маніфестному та субклінічному гіпотиреозі

(сГТ). Гіпотиреоз викликає зміни гемодинаміки та ліпідного обміну, які є факторами ризику серцево-судинних захворювань. Субклінічний гіпотиреоз проходить безсимптомно, але є зміни з боку серцево-судинної системи та її регуляції, а також можлива потреба у гормональному лікуванні. Незважаючи на те, що соціальна та вікова приналежність досліджуваних груп за літературними даними неоднорідна і для вивчення вегетативної регуляції використовуються різні тести, досі не встановлено єдиної моделі дослідницької та терапевтичної поведінки, особливо при сГТ. Варіабельність серцевого ритму визначається балансом симпатичних та парасимпатичних еферентних впливів на структури серця та може бути використана для стратифікації ризику серцево-судинних ускладнень у хворих з гіпотиреозом. Раннє виявлення вегетативної дисфункції та її лікування можуть покращити загальний прогноз, а також якість життя пацієнтів з гіпотиреозом та сГТ та знизити серцево-судинну захворюваність та смертність у цих пацієнтів.

Ключові слова: гіпотиреоз; субклінічний гіпотиреоз; вегетативна регуляція серцево-судинної системи; варіабельність серцевого ритму.

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