We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,800
Open access books available

142,000
International authors and editors

180M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Graves' Disease and Cardiac Complications

Abdulla Arslan and Hakan Altay

Abstract

Graves' Disease is an autoimmune thyroid disease and a common cause of hyperthyroidism. Thyroid hormones have multiple adverse effect on cardiovascular system through many direct and indirect mechanisms. They increases heart rate, cardiac contractility, systolic and mean pulmonary artery pressure, cardiac output, diastolic relaxation, and myocardial oxygen consumption, whereas decrease systemic vascular resistance and diastolic pressure. All these hemodynamic changes in cardiovascular system can eventually lead to heart failure, tachyarrhythmias, systemic and pulmonary hypertension, if left untreated. Cardiovascular complications of Graves' Disease are frequent and important cause of increased morbidity and mortality. This chapter reviews the cardiovascular complications of Graves' hyperthyroidism with underlying mechanisms and treatment.

Keywords: Graves' Disease, cardiac complications, heart failure, thyrotoxicosis, pulmonary hypertension

1. Introduction

Robert Graves identified the association of goiter, palpitations, and exophthalmos in 1835 [1]. Although the cause of Graves' hyperthyroidism was initially thought to be thyrotropin, it was later understood that Graves' hyperthyroidism was clearly caused by thyroid stimulating antibodies-IgG- which bind to and activate to thyrotropin receptors on thyroid cells [2]. Although the incidence is not known exactly, manifest hyperthyroidism is common and affects 2–5% of the population [3]. Approximately 60–80% of hyperthyroidism cases have Graves' Disease due to regional factors, particularly iodine intake. Over a period of 20 years, the incidence in women is around 0.5 per 1000 annually and the most frequent onset age gap is 40–60; hence, Graves' Disease is most common autoimmune disorder in the United States [4]. Graves' Disease rate in men is between 1/5 and 1/10 and equal to women; however, the disease is unusual in children. The prevalence is lower in African-Americans in reference to Asians and Whites [5]. Graves' Disease has similarities with autoimmune hypothyroidism, including high serum concentrations of antibodies against thyroglobulin, thyroid peroxidase, and possibly the sodium-iodide cotransporter in thyroid tissue. These antibodies' concentrations vary among patients, and the antibodies themselves may modify the stimulatory effects of thyroid-stimulating antibodies. In some patients, the simultaneous production of antibodies that block the thyrotropin receptor reduces the stimulatory action of thyroid-stimulating antibodies. For these reasons there is no direct correlation between serum concentrations of thyroid-stimulating antibodies and serum thyroid hormone concentrations in patients with Graves' hyperthyroidism [6].

Thyroid hormones have major effects on the heart and cardiovascular system through many mechanisms. They increase heart rate, cardiac contractility, systolic and mean pulmonary artery pressure, cardiac output, diastolic relaxation, and myocardial oxygen consumption, and reduce systemic vascular resistance and diastolic pressure [7]. Cardiovascular symptoms have been showing some signs of patients clinical presentation for the physicians: palpitations, exercise intolerance, dyspnoea, angina-like chest pain, peripheral edema and congestive heart failure are common symptoms of hyperthyroidism [8, 9]. In hyperthyroid patients mortality is increased by 20% and the major causes of death are cardiac problems [10].

2. Graves' hyperthyroidism

The clinical manifestation and the laboratory findings aid to establish the diagnosis of Graves' Disease in hyperthyroidism patients. Especially, serum thyrotropin levels is very beneficial marker in hyperthyroidism because secretion is thyrotropin is substantially reduced by small amount of elevation in thyroid secretion. Nevertheless, the diagnosis should be confirmed via the serum free thyroxine measurements [11]. However, in the early periods, only triiodothyronine increase may occur; considering this condition serum free triiodothyronine levels should be examined in the presence of normal serum free thyroxine and low serum thyrotropin concentrations. On the other hand, serum total thyroxine and triiodothyronine measurements are not as reliable as aforementioned markers because the certain drug use may cause elevated values in thyroid hormone–binding proteins. Establishing the diagnosis in a patient with hyperthyroidism is shown here:

3. Algorhythm for the diagnosis of suspected Hyperthyroidism

In the first step: Measure serum thyrotropin and free thyroxine

1. Low serum thyrotropin and normal free thyroxine- → Measure serum free triiodothyronine:

   A. Normal serum free triiodothyronine; Subclinical Hyperthyroidism

   B. High serum free triiodothyronine- → Triiodothyronine Hyperthyroidism

2. Low serum thyrotropin and high free thyroxine- → Hyperthyroidism

Diagnosis of Graves' hyperthyroidism was established for patients with biochemical evidence of overt hyperthyroidism, i.e. **high levels** of serum free T4, free T3, TSH < 0.1 mIU/l accompanied by at least two of following parameters: diffuse goiter, Graves' ophthalmopathy, **increased level** of anti-TSH receptor antibodies (TRAb), antithyroid peroxidase antibodies (TPOAb).

4. Pathogenesis

4.1 Cardiac effects, molecular and cellular mechanisms

Cellular and molecular mechanisms by which thyroid exerts its action on almost every cell and organ in the body have been well studied [12]. Thyroid gland

maintains T4 and T3 excretion according to TSH levels. The thyroid gland primarily secretes T4 ($\approx$85%), which is converted to T3 by 5′-monodeiodination in the liver, kidney, and skeletal muscle. The heart function is mainly based on T3, because of the absence of myocyte intracellular deiodinase activity and T3 migrates into the myocyte instead T4 [13]. Then, the activity of T3 is administered after binding to thyroid hormone nuclear receptors (THRs). Then, these receptor proteins binds to thyroid hormone response elements (TREs) in the promoter regions of positively regulated genes thus regulates the transcription [12, 14]. T3 acts on THRs in the nucleus, and creating dimers of 9-cis-retinoic acid receptor (RXR) [15]: the formed complexes recognize some specific DNA consensus sequences, TREs, located in the enhanced region of the genes to initiate the transcription [16]. Although, TRs considered as a steroid hormone receptors, unlikely, bind to TREs regardless of whether ligand is present or not. TRs connect to TREs with 1 of 3 isoforms of retinoid X receptor (RXRα, RXRβ, or RXRᵞ) as homodimers or heterodimers [17]. While bound to T3, TRs induce transcription, and in the absence of T3 they repress transcription. Thyroid hormone upregulates α, but downregulates β-chain in myocytes [18]. Negatively regulated cardiac genes such as β-myosin heavy chain and phospholamban are induced in the absence of T3 and repressed in the presence of T3 [19, 20].

Thyroid hormone has a direct impact on cardiac activity through myocytes by achieving structural and regulatory gene expressions. The 2 isoforms of a contractile protein pertain to thick filament of cardiac myocyte is codified by myosin heavy chain gene.

The sarcoplasmic reticulum Ca^{2+}-ATPase and its inhibitor, phospholamban, regulate intracellular calcium cycling. Together they are largely responsible for enhanced contractile function and diastolic relaxation in the heart [21]. T3 levels are also intimately associated with the β –adrenergic receptors and sodium potassium ATPase.

Thyroid hormone cause extranuclear genome-free effects on both the cardiac myocyte and systemic vasculature. These effects of T3 can occur rapidly and do not involve

TRE-mediated transcriptional events [22]. These T3-mediated effects include changes in various membrane ion channels for sodium, potassium, and calcium, effects on actin polymerization, adenine nucleotide translocator-1 in the mitochondrial membrane, and a variety of intracellular signaling pathways in the heart and vascular smooth muscle cells (VSM)**A27**. The collaboration of the both genomic and nongenomic features of the T3 activity regulate the cardiovascular system.

Thyroid hormone express its activity in myocytes via various TREs, such as alpha myosin heavy chain fusion (MHC-α), sarcoplasmic reticulum calcium-activated ATPase (SERCA): which maintains calcium uptake during diastole, by calcium activated ATPase and phospholamban -the inhibitory cofactor- [23, 24] the cellular membrane Na-K pump (Na-K ATPase), β1 adrenergic receptor, cardiac troponin I, and atrial natriuretic peptide (ANP), and some genes are also suppressed, such as β-myosin heavy chain fusion (MHC-β), adenylyl cyclase (IV and V) and the Na-Ca antiporter [25–27]. The final effect of thyroid hormones in animal studies-and also similar effects have also been observed in preliminary human studies-is increased rate of V1 isoform of MHC (MHCα/α) synthesis that is characteristically faster in myocardial fiber shortening [28–30]. Thyroid hormones enhance myocardial relaxation by upregulating expression of SERCA, and downregulating expression of phospholamban. Cytoplasmic calcium concentration substantially decrease at the end of the diastole. This cause a higher magnitude of systolic transient of calcium; therefore heightens capacity for actin-myosin subunits activation. As a supportive evidence, a phospholamban deficient mice demonstrated no tachycardia in response to thyroid hormone treatment [31] on the

plasma membranes, T3 has extragenic actions on various ion channels such as Na/K ATPase, Na/Ca++ exchanger, and voltage gated K channels (Kv 1.5, Kv 4.2, Kv 4.3) affecting cardiovascular hemodynamics [32].

For instance, Na channel activation period augments in myocardium; this cause prolonged intracellular Na uptake and increased secondary Na-Ca antiporter functions. Thus underlying mechanism under the inotropic effect may be comparatively revealed [33]. T3 effects on L-type calcium channels directly by abbreviating the action potential period [34, 35]. The augmentation of β-adrenergic receptors the may be the main reason for the intense inotropic response to the thyroid hormones [36]. Although, G protein and β-receptors increased; circulating cathecolamine measurements remained similar [37]. The sensitivity of the cardiovascular system to adrenergic stimulation is not changed by thyroid hormones. The changes in the heart rate result from both an increase in sympathetic tone and decrease in parasympathetic tone [38, 39]. Rapid response for the Cardiac and vascular structures of the thyroid hormone response was not sufficiently clarified by genomic effects [40–42].

Hyperthyroidism elicits rapid hemodynamic response as well as non-genomic changes in plasma membranes. Authors, indicate that thyroid hormone stimulates acute phosphorylation of phospholamban. This pathway may be slightly responsible the collaboration between thyroid hormone and the adrenergic effects on the heart [43].

The use of β-adrenergic receptor antagonists in hyperthyroidism reduced heart rate, but systolic or diastolic contractile performance remained similar, supporting the direct cardiac muscle effect of thyroid hormone [44]. Meanwhile, thyroid hormone impacted on the sinoatrial node and caused oxidative stress in experimental studies. The heart rate is parallel to the sinoatrial activity, lower threshold for atrial activity, and shortened atrial repolarization [45]. Hemodynamic changes such as volume preload increase following the renin-angiotensin system activation or augmented contractility due to improved metabolic demand or the reduction in the direct effect of the thyroid hormone on heart muscle, decreased systemic vascular resistance caused by triiodothyronine-induced peripheral vasodilatation, lead to a dramatic impairment in cardiac output [7, 46, 47].

Preload is increased in a state of hyperthyroidism, and the reduced peripheral vascular resistance and elevated heart rate lead to increased cardiac output. The reduction in systemic vascular resistance lead to impaired renal perfusion pressure thus activates renin-angiotensin-aldosterone system (RAAS), hence sodium reabsorption and blood volume increase. In turn, this leads to increased preload, decreased afterload, and **ultimately** a significant increase in stroke volume [48]. Furthermore, it is suggested that T3 enhances renin substrate synthesis in liver and stimulates the cardiac expression of renin mRNA, leading to elevated cardiac renin levels and angiotensin II independent from the circulating renin and angiotensin. The expression of angiotensin II receptors in the myocardium increases in the hyperthyroid state [49]. These hemodynamic responses trigger atrial stretch trigger and stimulate atrial natriuretic peptide (ANP) secretion, resulting in more vasodilation. Such changes figure out a critical role of the myocardial RAAS in thyroxine-induced cardiac hypertrophy as well as potential therapeutic implications of agents that block this system.

Adrenomedullin, a polypeptide of 52 amino acids, is a potent vasodilator and thyroid gland is responsible for regulation transcription of adrenomedullin. Serum levels therefore proportionally increase in thyrotoxicosis [50]. Interestingly, however, Diekman and colleagues demonstrated that although systemic vascular resistance (SVR) is decreased and adrenomedullin is increased in thyrotoxicosis, restoration of euthyroidism normalized SVR but was not correlated with plasma adrenomedullin levels [51]. In the present study, only T3 was an independent determinant of SVR.

5. Clinical manifestations and Hemodynamic Effects of Thyroid Hormones

The clinical manifestations and the severity of the disease are strongly correlated to the duration of Graves' Disease and the patient age. More than half of the patients are symptomatic in time of diagnosis. The most frequent findings may be counted as nervousness, fatigue, a rapid heartbeat or palpitations, heat intolerance, and weight loss respectively. By age, weight loss and decreased appetite are frequently observed, whereas irritability and heat intolerance are less frequent. Atrial fibrillation is occasional below age 50. A firm, diffuse goiter of variable size presents in the 90% and 75% patients, respectively; when 50 years of age was hold as threshold [52].

Thyroid hormone has cardiovascular effects that include decreased SVR and increased resting heart rate, left ventricular contractility, and blood volume. Thyroid hormone reduce the peripheral arteriolar resistance and decrease mean arterial pressure, through the renin-angiotensin-aldosterone system. Also, T3 increases erythropoietin synthesis, which leads to an increase in red cell mass. Harmony of these effects contribute to increase in blood volume and preload. In hyperthyroidism, these combined mechanisms maximize cardiac output up to 300% higher when compared to control group. In hypothyroidism, the cardio-vascular effects are diametrically opposite and cardiac output may decrease by 30–50% [53].

Thyroid hormone shows its affects rapidly and non-genomic pathway through heart and blood vessels. Beyond what is reported above, In the peripheral vascular system, the elevated oxygen consumption, metabolic remnants and relaxation of arterial smooth muscle fibers by thyroid hormone eventuate in peripheral vasodilatation [32]. This dramatical decrease in peripheral vascular resistance (PVR) has a great role in hemodynamic changes caused by thyroid hormones [54]. Decreased PVR results in bradycardia, a selective increased blood flow towards visceral organs eventually, cause a decrease in diastolic pressure thus widen pulse pressure. Vasodilatation without elevated renal blood flow results in a reduction in renal perfusion thus activates the renin-angiotensin cascade. Hence, sodium retention and increased blood volume occurs [46]. Moreover, thyroid hormones effects on erythropoietin secretion; hence cause to increase in red cell mass and the blood volume [55]. Increased diastolic relaxation and blood volume improves left ventricular end-diastolic volume (LVEDV). Reduced PVR and increased LVEDV in together, augment preload and impair afterload; thus the stroke volume increases. Improved stroke volume and heart rate increase cardiac output, which cannot be only a consequence of an increased metabolic rate [56]. The correlation between systemic vascular resistance and systemic blood flow in hyperthyroidism is investigated previously, focusing on arterial vasoconstrictors in particular. On the contrary to the normal subjects, atropine and phenylephrine succeeded to decrease peripheral blood flow and cardiac output by 34% in hyperthyroidism group [57].

Studies including large cohorts determined that blood pressure levels widened throughout the entire spectrum of thyroid function [58]. In this study, Asvold et al. reported a linear correlation between TSH and both systolic and diastolic blood pressure, however other studies did not find a correlation [59]. Basal metabolism is triggered by thyroid hormones and a complete response develops in almost every tissue and organ system in the body, as a consequence of increased metabolic demands, hemodynamic changes in cardiac output, SVR, and blood pressure occur. On several counts, such changes are similar to the physiological response to exercise [60]. Pulse pressure tends to be widened in case of hyperthyroidism. Some current reports have determined that despite the low SVR in hyperthyroidism, arterial stiffness is increased [61]. Thus excess thyroid hormone typically enforce systolic

blood pressure to rise, the increase can therefore be quite dramatic in older patients with atherosclerosis led to impaired arterial compliance. Hyperthyroidism has been identified as the second most common reason for isolated systolic hypertension [62]. Efficient hyperthyroidism treatment and the administration of β-blockade to achieve normocardia reverses these changes. In hypothyroidism, endothelial dysfunction and impaired VSM relaxation eventuate in lower SVR [63]. These effects lead to diastolic hypertension in ≈30% of patients, and thyroid hormone replacement therapy restores endothelial-derived vasorelaxation and blood pressure to normal in most [64].

Sinus tachycardia is the most frequent ECG disorder. Intraventricular conduction delay in the form a right bundle branch block is observed in approximate of 15% patients.

Alternative, unknown reasons may also be present for the occurrence of atrioventricular block Increased dispersion of QT interval corrected by the heart rate (QTcD) and pulmonary hypertension may also be present, however underlying mechanisms are yet unclear; the similar cardiac and hemodynamic changes accompanying with the autoimmune disorders in Graves' patients probably contribute to conduction problems [65]. Hyperthyroidism leads to shortened action potential and altered expression of L-type calcium channel 1D, enhances Na and K permeability, and affects Na pump density [66]. The forced preload increase and altered total blood volume impose burden on cardiac workload, hence frequently myocardial hypertrophy develops.

6. Graves' Disease and atrial fibrillation

Patients with hyperthyroidism manifest more premature supraventricular depolarization and premature atrial complex (PAC; also referred to a premature atrial beat, premature supraventricular complex, or premature supraventricular beat), more nonsustained supraventricular tachycardias, and reduced heart rate variability [67]. The reduced variability is probably occurs as a consequence of decreased parasympathetic tone. These electrical stimulates may lead to paroxysmal atrial tachycardia, atrial fibrillation, and atrial flutter. The most frequent rhythm disorder is sinus tachycardia in hyperthyroidism [43]. Its clinical impact is overshadowed by atrial fibrillation. The rate of atrial fibrillation (AF) and other rare forms of supraventricular tachycardia in this disease varies between 2% and 20% The prevalence of atrial fibrillation in hyperthyroidism was determined as 13.8%, however peaked at up to 15% in patients over the age of 70 years. These results is significantly higher when compared to the rate of 2.3% in control group [66–69]. Atrial fibrillation often coexists with a rapid ventricular response. The occurrence of AF is more frequent in men and significantly increases with age, over 40 years in particular [69]. A current study revealed that the AF rate was below 2% in a cohort includes more than 13 k cases with hyperthyroidism. Early stage of disease or recognition may contribute to these result [70]. A stepwise increase in the prevalence was observed in the analysis based on age, especially peaked at ≈15% in patients >70 years old. This findings support data from the cohort of 40.628 hyperthyroid patients in the Danish National Registry. This database revealed that although 8.3% of the patients demonstrated an atrial fibrillation; male gender, the presence of ischemic or valvular heart disease or congestive heart failure were associated with the highest risk rates. Apparently, subclinical (mild) hyperthyroidism involves similar relative risk for atrial fibrillation as does overt disease [68]. This dilemma may be interpreted in favor of other accompanying diseases that occur in the older population. In unselected patients with atrial fibrillation, less than 1% were the

consequence of over-hyperthyroidism [71]. Consequently, although the abnormal thyroid function levels seems less reliable and indicative in the new-onset atrial fibrillation, establishing an euthyroid state and achieving sinus rhythm, justifies the value of TSH examining [7].

The left atrial size is enlarged in most of the patients with hyperthyroidism and AF rather than hyperthyroid people with sinus rhythm. Hyperthyroidism should not be accepted as the only reason for developing the new onset AF and possible underlying organic heart diseases should be investigated to avoid as serious cardiovascular events such as angina or heart failure. In an experimental study, connexin-40, a gap junction protein of myocardium which is essential for the transport of electrical activity upregulated by thyroid hormone in rats. This pathway may contribute to atrial fibrillation development in hyperthyroidism [72].

Atrial fibrillation generally reverts to sinus rhythm when an euthyroid state established. On the other hand, in young and early diagnosed patients β-Adrenergic blockade may be sufficient to regulate the ventricular rate. Higher dose may be required in case of elevated plasma clearance of β-blockers. Propranolol has an additional advantage by blocking T4 - T3 conversion in peripheral tissues. Nevertheless, cardio-selective β-blockers have a longer half-life and have similar cardiac effects. Intravascular administration of calcium blockers should be avoided considering the possible risk of a further fall in PVR: channel blockers, may cause potential adverse cardiovascular events such as blood pressure reduction via developing relaxation through smooth muscle cells of the resistance arterioles. Such treatment has been linked to acute hypotension and cardiovascular collapse [73]. Treatment of atrial fibrillation in the setting of hyperthyroidism includes β-adrenergic blockade. This can be accomplished with β 1-selective or nonselective agents, even in peroral usage, whereas treatments such as antithyroid therapy or radioiodine, which lead to a restoration of a chemical euthyroid state [7]. Although digitalis was an option in the treatment of hyperthyroidism and coexisting atrial fibrillation, due to the increased digitalis clearance and decreased sensitivity of the hyperthyroid heart to digitalis necessitated higher doses for optimal treatment beside leading to less predictable responses [74, 75]. How much risk does the systemic embolization include in the setting of thyrotoxicosis is yet unclear. It is still controversial whether to administer an anticoagulant therapy in patients with AF is efficient to prevent systemic embolization. Accordingly, each patient should be evaluated individually considering the risk of bleeding over embolization [76]. Hyperthyroidism in younger patients without any cardiac disease except for AF, the risk of anticoagulant therapy **may exceed its benefits**. However, it would be wise to administer anticoagulant drugs to older patients with previously diagnosed or suspected heart diseases or AF with longer duration. Oral anticoagulants doses should be trimmed considering that hyperthyroid patients will require less medication than euthyroid ones, **due to faster elimination of vitamin-K** dependent clotting factors [77]. Early diagnosis and full treatment radioiodine or thioureas demonstrated a reversion to sinus rhythm most patients within 2 to 3 months [70]. Older patients (>60 years old) with atrial fibrillation with longer duration are more resistant to spontaneous reversion to sinus rhythm. For this reason, electrical or pharmacological cardioversion are advised to attempt if the AF continues after an euthyroid state achieved chemically. Following an adequate treatment most of the patients turn into sinus rhythm permanently. Disopyramide (300 mg/d) administration after successful cardioversion, contribute to remain in sinus rhythm when compared to those not treated [76].

Reversion and maintenance from AF to sinus rhythm is unusual before the euthyroid state is achieved; therefore electrical cardioversion should be avoided before euthyroid condition. In another experimental study, the authors remarked

the downregulator effects T3 via connexin-43 phosphorylation in diabetic rats. Thus, cardiac adaption to hyperglycemia reduced and the heart become **prones** to ventricular arrhythmias [78].

7. Graves' Disease and heart failure

Early manifestations regarding heart failure may be present in patients with hyperthyroidism [7, 14, 79]. Majority of the patients with hyperthyroidism suffer from exercise intolerance and exertional dyspnea, due to the loss of skeletal and respiratory muscle strength. Hyperthyroid patients can demonstrate congestive heart failure symptoms regardless of prior cardiac injury. This phenomenon has inaccurately identified "high-output heart failure," in the presence of paradoxical features involving enhanced cardiac contractility and output characterized by thyroid hormone excess [7]. Decreased cardiac contractility, reduced diastolic compliance, and pulmonary congestion are true manifestations of the heart failure however these can be consequences of severe and chronic hyperthyroidism, tachycardia, and **atrial fibrillation also** [80–82]. The use of "high output heart failure" has not abandoned in late decades, considering the potential of the heart to enhance the output at both rest and exercise. However, In the setting of low vascular resistance and decreased preload, cardiac functional reserve is compromised thus lose the capacity of accommodating the demands of maximal or even submaximal exercise [83]. High-output heart failure may demonstrate dyspnea on exertion, fatigue, and fluid retention with peripheral edema, pleural effusion, hepatic congestion, and PAH [82]. Heart failure develops approximately in the 6% of thyrotoxic patients. Beyond that, dilated cardiomyopathy with reduced left ventricular systolic dysfunction occurs less than 1%, due to a tachycardia-mediated mechanism causing an elevated cytosolic calcium levels during diastole with impaired contractility of the ventricle and diastolic dysfunction, often with tricuspid regurgitation [84]. A research conducted by Yue *et al*., diastolic dysfunction was found to be more prominent in thyrotoxic patients older than 40 years of age, whereas in younger ones a demonstrated a reduction in peripheral vascular resistance and improved cardiac output were outstanding [85]. However, severe and chronic hyperthyroidism may exaggerate sinus tachycardia or atrial fibrillation; hence, produce rate-related left ventricular dysfunction and heart failure [86]. This clarifies the reason why several patients manifesting the combination of hyperthyroidism, low cardiac output, and impaired left ventricular function had AF at the time of diagnosis [7]. However, pre-existent ischemic or hypertensive heart disease may also contribute the to the development of heart failure in hyperthyroid patients [14, 86].

Mitral valve prolapse is more frequently reported in patients with Graves' Diseases. The latter may be a predisposing factor for the elonged the left atrial diameter and atrial fibrillation [87]. The risk for AF which may lead to congestive heart increases in the presence of low TSH levels, especially among patients over 60 years old [88, 89]. The high prevalence of pulmonary artery hypertension that comprises several signs of heart failure, such as neck vein distension and peripheral edema, may be caused by right heart strain [90, 91]. Similarly, reduced pulmonary compliance and skeletal muscle dysfunction may lead to the exercise intolerance and exertional dyspnea in such patients [14]. Distinctively, thyrotoxic cardiomyopathy represents a myocardial damage that caused by toxic effects as a result of excessive thyroid hormone activation. This condition leads to dynamic and structural changes such as myocyte energy production, intracellular metabolism, and myofibril contractile function. Left ventricular hypertrophy, heart rhythm disturbances, primary atrial fibrillation, dilation of the heart chambers, heart failure, PAH, and diastolic dysfunction constitutes the main manifestations [48].

Although, β-adrenergic blockage was contraindicated in previous decades in the treatment of thyrotoxic cardiac events, nowadays the use of such drugs considered as first-line therapy [92]. Digitalis and diuretics are not recommended in the heart failure accompanying pulmonary congestion [60].

The definitive treatment option for the hyperthyroidism is 131I-radioiodine [93]. Optimal hyperthyroidism treatment goals to establish an euthyroid state commonly represents a recovery from atrial fibrillation to sinus rhythm and a dissolution of the cardiac manifestations [76, 79]. Studies pointing out how crucial is an adequate and sufficient treatment concluded that the cardiovascular complications arising from thyrotoxicosis are the primary cause of death [94].

8. Graves' Disease and arterial hypertension

Thyroid hormone causes decreased resistance in peripheral arterioles through a direct effect on VSM cells and decreased mean arterial pressure, which, when sensed in the kidneys, activates the renin-angiotensin-aldosterone system and increases renal sodium absorption. T3 also induces erythropoietin synthesis, which leads to an increase in red cell mass. These changes combine to promote an increase in blood volume and preload. Hyperthyroidism has been identified as the second most common reason for isolated systolic hypertension [62]. Because of the reversible effects of hyperthyroidism hypertension, efficient hyperthyroidism treatment and the administration of β-blockade to achieve normocardia reverses hypertension, heart rate variability and arrhythmias. Iryna Tsymbaliuk et al. [95] reported that there are 95% arterial hypertension between Graves' hyperthyroidism patients, especially demonstrating high systolic blood pressure, as result of low vascular resistance, elevated resting heart rate and blood volume due to excess of thyroid hormones [95, 96]. Moreover, they showed that arterial hypertension was developed secondary to Graves' hyperthyroidism and associated with diminished quality of life. Restoring of euthyroid state resulted in elimination of arterial hypertension or stabilization of blood pressure levels in patients with a history of arterial hypertension, which is consistent with other studies.

The role of euthyroidism restoration is supported by findings from other studies showing the direct effect of hyperthyroid state on the cardiovascular system; in animal studies, the excess of thyroid hormones had a major impact on the cardiomyocytes, whereas beta-adrenergic or angiotensin receptor stimulations played a minor role [79, 97]. And in the study, as a result, improvement of cardiovascular parameters in relatively short follow up time was achieved after restoring of euthyroid state by antithyroid therapy accompanied by administration of beta-blockers and ACE inhibitors.

9. Graves' Disease and pulmonary hypertension

About 1/5 of pulmonary hypertension cases are shown to be concomitantly occurring with thyroid disease [98]. Pulmonary artery hypertension (PAH) is identified as mean pulmonary arterial pressure levels higher than 25 mm Hg at rest [81]. Increased pressure in the left atrium is transmitted backwardly to pulmonary veins. This activates baroreceptors ending up with a reflex contraction in the arterioles. Elevated pulmonary artery pressure aggravates the right ventricular workload. This overload forces the right ventricle to contract laboriously to maintain blood flow towards pulmonary vasculature. However, this process eventually leads to increased pulmonary resistance and PAH [48]. Although, current knowledge regarding hemodynamics of

PAH in hyperthyroidism has not well explained yet, decrease in PAH after establishing an euthyroid state may be considered as a supportive evidence for a causal relationship [99]. A current study asserts a direct relation between TSH receptor antibodies and PAH, thus a possible autoimmune-mediated pulmonary vascular remodeling may be conducted [101]. Hyperthyroidism should be excluded in patients with PAH; moreover, in case of coexisting hyperthyroidism and dyspnea, every patient should be examined for PAH either [98, 100].

PAH has been associated with thyroid dysfunction, mainly hyperthyroidism. It has been suggested that SVR lowering effect of thyroid hormone may not occur in the pulmonary vasculature [60]. PAH and atrioventricular valve regurgitation have been both documented with a high prevalence [90]. Various articles have revealed that hyperthyroidism may manifest as right heart failure and tricuspid regurgitation [91]. A research including of 23 cases with hyperthyroidism originating from Graves' Disease documented that 65% of those patients had PAH. Following an adequate treatment for the Graves' Disease, pulmonary artery pressure levels returned to normal values in almost all patients [100, 101].

Right heart failure and peripheral edema accompanying hyperthyroidism may be reasoned by this reversible increase in pulmonary artery pressure [60, 91]. Primary pulmonary hypertension is defined as the levels of pulmonary artery pressure above 25 mm Hg at rest and 30 mm Hg during exercise and frequently seen in young women. It has a progressive nature and mostly leads to right heart failure. A link between pulmonary hypertension and thyroid disease (i.e., hypothyroidism and hyperthyroidism) has been elucidated in recent [102]. Hypothyroidism rate was determined as 22% in a study including 40 patients with primary pulmonary hypertension [103]. There are several evidences indicating the importance of the autoimmune disease's role in both hypothyroid and hyperthyroid linked cases of primary pulmonary hypertension [91, 101, 103]. Thyroid dysfunction therefore should always be examined in the presence of primary pulmonary hypertension.

10. Thyroid hormone effects on lipid metabolism

Increased serum lipid levels in hypothyroidism is well-known. Hypothyroidism causes hypercholesterolemia especially augments low-density lipoproteins (LDL) and apolipoprotein B. Although, estimated prevalence of overt hypothyroidism in patients with hypercholesterolemia is between 1.3% to 2.8%, hypercholesterolemia is observed in 90% of the patients with hypothyroidism [104]. Altered lipid profile levels manifest even in subclinical hypothyroidism. Some authors revealed reversible increased LDL levels in subclinical hypothyroidism after thyroid hormone replacement. On the contrary, some other studies have determined no changes in LDL levels despite increased total cholesterol levels in subclinical hypothyroidism [105]. The underlying mechanisms of the hypercholesterolemia in hypothyroidism involves impaired fractional clearance of LDL by decreased LDL receptors and receptor activity in the liver [106]. Cholesterol catabolism is regulated by cholesterol 7α-hydroxylase [107]. This liver-origin enzyme has a negative correlation with T3 and may reduce catabolism and cause elevated serum cholesterol levels associated with hypothyroidism [103]. The increased serum lipid levels in subclinical hypothyroidism are strongly associated with increased cardiovascular risk [108]. This high risk may be reversed by thyroid hormone replacement therapy to establish euthyroid condition [106]. If left untreated, the dyslipidemia accompanying with the diastolic hypertension associated with hypothyroidism lead the patient prone to atherosclerosis [53, 86].

11. Subclinical hyperthyroidism and heart

The impact of thyroid hormones especially the subclinical hyperthyroidism on cardiovascular system faces an ever-increasing interest in last decades. Subclinical hyperthyroidism represents low serum TSH levels accompanying with normal serum free T4 and T3 concentration and its prevalence varies from 0.6–16% [109]. Persistent abnormal TSH measurements have to be re-examined within 2–3 months from initial values [109, 110]. There are two main categories regarding subclinical hyperthyroidism: Grade 1 defines a mildly low serum TSH (0.1–0.45 mIU/L) levels whereas Grade 2 represent lower levels of serum TSH (< 0.1 mIU/L). Subclinical hyperthyroidism may have exogenous or endogenous etiology. Exogenous origin mainly occurs as a result of a TSH suppressive therapy (or excessive use of levothyroxine) for thyroid carcinoma. Endogenous reasons resembles overt hyperthyroid state causes including mild Graves' Disease, multinodular goiter, and autonomous functioning thyroid nodule. Various authors have evaluated the effects of subclinical hyperthyroidism on cardiovascular and skeletal systems, particularly in older populations. Nanchen et al. analyzed conducted a study with a large cohort composed of patients with subclinical hyperthyroidism and observed a significantly higher hospitalizations rate due to heart failure in older patients, especially in those with grade 2 subclinical hyperthyroidism [111]. A distinct inverse proportion between TSH level and the risk of AF have been concluded in previous studies [112]. Furthermore, current retrospective studies with large cohorts have obviously determined a link between subclinical hyperthyroidism and cardiovascular events especially heart failure. More importantly, all-cause mortality observed higher in this group [113]. The European Thyroid Association recommends full treatment in patients older than 65 years with grade 2 subclinical hyperthyroidism. Beyond that, same guideline suggests to treat milder grade if any additional heart disease or other significant comorbidities or risk factors present [110].

12. Treatment

Recent treatment options for Graves' hyperthyroidism include antithyroid drugs, radioactive iodine, and surgery. In addition β-adrenergic blockade is targeted to blockade cathecolamine discharge. The cardiovascular symptoms stimulated by hyperthyroidism resolve after an adequate treatment regardless of utilizing radioactive iodine or antithyroid drug. Hyperthyroidism may exaggerate preexisting cardiovascular diseases by increasing demand for myocardial oxygen, contractility and heart rate. In such circumstances, silent coronary artery disease, angina or compensated heart failure and even endothelial dysfunction develop [114]. Tachycardia control by using β-blockers should be added into treatment in the management of heart failure. Nevertheless, possible contraindications have to be considered in each individuals. Furosemide may aid to reduce volume overload. However, requirement of more Na-K-ATPase in the myocardium due to İncreased blood volume (distribution) in euthyroid heart failure patients result in relative resistance to digoxin [77]. Beta blockers, especially propranolol and atenolol aid to control palpitations by decelerating the heart rate in case of sinus tachycardia [115]. Although, all types of calcium channel blockers are utilized in the management of newly emerged atrial fibrillation, in the presence of thyrotoxicosis, intravenous administration increase adverse effects. The vasodilator and negative inotrope effects of these drugs may cause hypotension and even cardiovascular collapse [116]. Further precautions are required in case of atrial fibrillation, marked palpitations, or severe tachycardia [7, 92].

In case of heart failure resisting despite the heart rate decelerated, or if the patient is in advanced age, or has diagnosed or suspected preexisting heart disease, or has hypertension standard treatment protocols should be applied. In occasional conditions such as hyperthyroidism or thyroid storm requires close cardiovascular monitoring and management of other comorbidities (infection, trauma, acute psychiatric illness) [92, 117]. The efficacy of anticoagulant drugs has been less investigated into correctable causes of AF such as hyperthyroidism. Our clinical routine tends to initiate antithrombotic agents as in general population. After euthyroid state established, and in the documented absence of AF during at least three months, terminating the anticoagulant therapy should be concluded. However, the patients should be kept in close follow-up with routine intervals in terms of heart rate. Although, some clinics demand further documentation, 24 hours of continuous monitoring without AF and the absence of any sign and symptoms regarding AF is sufficient to terminate anticoagulant therapy in our protocol. However, two clinicians decide whether to discontinue anticoagulant treatment according to CHA_2DS_2-VASc score, regardless of rhythm.

13. Conclusion

It's important to bear in mind that significant cardiac complications of Graves' Disease (dilated cardiomyopathy, atrial fibrillation, systemic hypertension and pulmonary hypertension) may occur in previously fit young patients without cardiac disease. All these cardiac complications increase mortality and morbidity in patients with Graves' Disease. Most of the time cardiac function recovers if Graves' Disease is specifically treated and cardiac interventions are done in a timely fashion. Therefore early diagnosis and definitive treatment of hyperthyroidism is crucial for prevention of the development of thyrotoxic cardiomyopathy.

Author details

Abdulla Arslan* and Hakan Altay
Department of Cardiology, Faculty of Medicine, Baskent University,
Istanbul, Turkey

*Address all correspondence to: apaslan@msn.com

IntechOpen

References

[1] Anthony P. Weetman , MD, D.SC GRAVES' DISEASE Review Article, The New England Journal of Medicine

[2] Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM. The thyrotropin (TSH) receptor: interaction with TSH and autoantibodies. Endocr Rev 1998;19:673-716. [Erratum, Endocr Rev 1999;20:100.]

[3] Bulow PI, Laurberg P, Knudsen N, et al. Increase in incidence of hyprthyroidism predominantly occurs in young people after iodine fortification of salt in Denmark. J Clin Endocrinol Metab 2006; 91: 3830-3834

[4] Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol 1997;84:223-243.

[5] Vanderpump MPJ, Tunbridge WMG. The epidemiology of autoimmune thyroid disease. In: Volpe R, ed. Autoimmune endocrinopathies. Vol. 15 of Contemporary endocrinology. Totowa, N.J.: Humana Press,1999:141-62.

[6] Takata I, Suzuki Y, Saida K, Sato T. Human thyroid stimulating activity and clinical state in antithyroid treatment of juvenile Graves' disease. Acta Endocrinol (Copenh) 1980;94:46-52.

[7] Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med 2001; 344:501.

[8] Ghandour A, Reust C. Hyperthyroidism: a stepwise approach to treatment. J Fam Pract 2011; 60: 388-395

[9] Palitzsch KD. Prevention and multimodal therapy of hyperthyroidism. Internist (Berl) 2008; 49: 1428-1436

[10] Brandt F, Green A, Hegedüs L, Brix TH. A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. Eur J Endocrinol 2011; 165:491-497.

[11] Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995;273:808-812.

[12] Brent G. The molecular basis of thyroid hormone action. N Engl J Med. 1994;331:847-853

[13] Everts ME, Verhoeven FA, Bezstarosti K, Moerings EP, Hennemann G, Visser TJ, Lamers JM. Uptake of thyroid hormones in neonatal ratcardiac myocytes. Endocrinology. 1996;137:4235-4242

[14] Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. Endocrine Rev. 2005;26:704-728.

[15] Leng X, Bianco J, Tsai SY, Ozato K, O'Malley BW, Tsai MJ. Mechanisms for synergic activation of thyroid hormone receptor and retinoid X receptor on different response elements. J Biol Chem 1994; 269: 31436-31442

[16] Ribeiro RC, Apriletti JW, West BL, et al. The molecular biology of thyroid hormone action. Annual N Y Acad Sci 1995; 758: 266-289

[17] Lazar MA, Chin WW. Nuclear thyroid hormone receptors. J Clin Invest.1990;86:1777-1782

[18] Ojamaa K, Klemperer JD, MacGlivray SS. Thyroid hormone and hemodynamic regulation of beta-myosin heavy chain promoter in the heart. Endocrinology 1996; 137: 802-808

[19] Wu Y, Koenig RJ. Gene regulation by thyroid hormone. Trends EndocrinolMetab. 2000;11:207-211.

[20] Hu X, Lazar MA. Transcriptional repression by nuclear hormone receptors. Trends Endocrinol Metab. 2000;11:6-10

[21] Mintz G, Pizzarello R, Klein I. Enhanced left ventricular diastolic function in hyperthyroidism: noninvasive assessment and response to treatment. J Clin Endocrinol Metab. 1991;73:146-150

[22] Hiroi Y, Kim H-H, Ying H, Furuya F, Huang Z, Simoncini T, Noma K, Ueki K, Nguyen N-H, Scanlan TS, Moskowitz MA, Cheng S-Y, Liao JK. Rapid nongenomic actions of thyroid hormone. Proc Natl Acad Sci U S A. 2006;103:14104-14109

[23] Dillman WH. Biochemical basis of thyroid hormone action in the heart. Am J Med 1990; 88: 626-630

[24] Kiss E, Jakab G, Kranias EG, et al. Thyroid hormoneinduced alteration in phospholamban protein expression: regulatory effects on sarcoplasmic reticulum Ca2+ transport and myocardial relaxation. Circ Res 1994; 75:245-251

[25] Tsika RW, Bahl JJ, Leinwand LA, Morkin E. Thyroid hormone regulates expression of a transfected human alphamyosin heavy chain fusion gene in fetal rat heart cells. Proc Natl Acad Sci USA 1990; 87: 379-383.

[26] Averyheart-Fullard V, Fraker LD, Murphy AM, Solaro RJ. Differential regulation of slow skeletal and cardiac troponon I mRNA during development and by thyroid hormone in rat heart. J Mol Cell Cardiol 1994; 26: 609-616

[27] Morkin E. Regulation of myosin heavy chain genes in the heart. Circulation 1993; 87: 1451-1460.

[28] Izumo S, Nadal-Ginard B, Mahdavi V. All members of the MHC multigene family respond to thyroid hormone in a highly tissue-specific manner. Science 1986; 231:597-600

[29] Ladenson PW, Sherman SI, Boughman RL. Reversible alterations in myocardial gene expression in a young man with dilated cardiomyopathy and hypothyroidism. Proc Natl Acad Sci USA 1992; 89: 5251-5255

[30] Magner J, Clarck W, Allenby P. Congestive heart failure and sudden death in a young woman with thyrotoxicosis. West J Med 1988; 110: 759-760

[31] Kiss E, Brittsan AG, Elds I, et al. Thyroid hormone-induced alterations in phospholamban deficient mouse hearts. Circ Res 1998; 83: 608-13

[32] Panagoulis C, Halapas A, Chariatis E, Driva P, Matsakas E. Hyperthyroidism and heart. Hellenic J Cardiol 2008; 49:169-175

[33] Kasturi S, Ismail-Beigi F. Effect of thyroid hormone on the distribution and activity of Na, K ATPase in ventricular myocardium. Arch Biochem Biophys 2008; 475: 121-127

[34] Ojamaa K, Sabet A, Kenessey A, et al. Regulation of rat cardiac Kv 1.5 gene expression by thyroid hormone is rapid and chamber specific. Endocrinology 1999; 140: 3170-3176.

[35] Chen WJ, Yeh YH, Lin KH, Chang GJ, Kuo CT. Molecular characterisation of thyroid hormone-inhibited atrial Ltype calcium channel expression: implication for atrial fibrillation in hyperthyroidism. Basic res Cardiol 2011; 106:163-174

[36] Hammond HK, White FC, Buxton IL, Salzstein P, Brunton LL, Longhurst JC. Increased myocardial beta-recepors and adrenergic responses in hyperthyroid pigs. Am J Physiol 1987; 252: H283–H290

[37] Levey GS, Klein I. Cathecholamine thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. Am J Med 1990; 88: 642-646

[38] Ojamaa K, Klein I, Sabet A, Steinberg SF. Chnages in adenylyl cyclase isoforms as a mechanism for thyroid hormone modulation of cardiac beta adrenergic receptor responsiveness. Metabolism 2000; 49: 275-279

[39] Klein I, Ojamaa K. Thyrotoxicosis and the heart. Endocrinol Metab Clin North Am 1998; 27: 51-62

[40] Davis PJ, Davis FB. Acute cellular actions of thyroid hormone and myocardial function. Ann Thorac Surg 1993; 56 (Suppl.): S16-23

[41] Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary artery by-pass surgery. N Eng J Med 1995; 333: 1522-1527

[42] Walker JD, Crawford FA, Kato S, et al. The novel effects of 3,5,3′-triiodo-L-thyronine on myocyte contractile function and beta adrenergic responsiveness in dilated cardiomyopathy. J Thorac Cardiovasc Surg 1994; 108: 672

[43] Cacciatori V, Bellavere F, Pessarosa A, et al. Power spectral analysis of heart rate in hyperthyroidism. J Clin End Metab 1996; 81: 2828

[44] Ojamaa K, Kenessey A, Klein I. Thyroid hormone regulation of phospholamban phosphorylation in the rat heart. Endocrinology 2000; 141: 2139-2144

[45] Messarah M, Saoudi M, Boulakaud MS, Feki AE. Oxidative stress induced by thyroid dysfunction in rat erythrocytes and heart. Environ Toxicol Pharmacol 2011; 31: 33-41

[46] Resnick LM, Laragh JH. Plasma rennin activity in syndromes of hyroid hormone excess and deficiency. Life Sci 1982; 30: 585-586

[47] Ojamaa K, Klemperer JD, Klein I. Acute effects of thyroid hormone on vascular smooth muscle. Thyroid 1996; 6:505

[48] Vargas-Uricoechea H, Bonelo-Perdomo A, Sierra-Torres CH. Effects of thyroid hormones on the heart. Clin Investig Arterioscler. 2014 Nov-Dec;26(6):296-309

[49] Nabbout LA, Robbins RJ. The cardiovascular effects of hyperthyroidism.Methodist DeBakey Cardiovasc J. 2010 Apr-Jun;6(2):3-8

[50] Imai T, Hirata Y, Iwashina M, Marumo F. Hormonal regulation of rat adrenomedullin gene in vasculature. Endocrinology. 1995;136:1544-1548

[51] Diekman MJ, Harms MP, Endert E, Wieling W, Wiersinga WM. Endocrine factors related to changes in total peripheral vascular resistance after treatment of thyrotoxic and hypothyroid patients. Eur J Endocrinol. 2001;144:339-346

[52] Nordyke RA, Gilbert FI Jr, Harada ASM. Graves' disease: influence of age on clinical findings. Arch Intern Med 1988;148:626-631

[53] Danzi S, Klein I. Thyroid hormone and the cardiovascular system. Minerva Endocrinologica. 2004;29:139-150

[54] Park KW, Dai HB, Ojamaa K, Lowenstein E, Klein I, Sellke FW. The direct vasomotor effect of thyroid hormones on rat skeleteal muscle resistance arteries. Anesth Analog 1997; 85: 734-738

[55] Klein I, Levey GS. Unusual manifestations of hypo thy roidism. Arch Intern Med 1984; 144: 123-128

[56] Fadel BM, Ellahham S, Ringel MD, Lindsay J, Wartofsky L, Burman KD. Hyperthyroid heart disease. Clin Cardiol 2000; 23: 402-408

[57] Theilen EO, Wilson WR. Hemodynamic effects of peri pheral vasoconstriction in normal and thyrotoxic subjects.J Appl Physiol 1967; 22: 207-210

[58] Asvold BO, Bjoro T, Nilsen T, Vatten LJ. Association between blood pressure and serum TSH concentration within the reference range: a population-based study. J Clin Endocrinol Metab. 2007;9:841-845

[59] Volzke H, Alte D, Dorr M, Wallaschofski H, John U, Felix SB, Rettig R. The association between subclinical hyperthyroidism and blood pressure in a population-based study. J Hypertens. 2006;24:1947-1953

[60] Danzi S, Klein I. Thyroid hormone and blood pressure regulation. Cur Hypertens Rep. 2003;5:513-520

[61] Palmieri EA, Fazio S, Palmieri V, Lombardi G, Biondi B. Myocardial contractility and total arterial stiffness in patients with overt hyperthyroidism: acute effects of beta1-adrenergic blockade. Eur J Endocrinol.2004;150:757-762

[62] Prisant LM, Gujral JS, Mulloy AL. Hyperthyroidism: a secondary cause of isolated systolic hypertension. J Clin Hypertens. 2006;8:596-599

[63] Napoli R, Biondi B, Guardasole V, Matarazzo M, Pardo F, Angelini V, Fazio S, Sacca L. Impact of hyperthyroidism and its correction on vascular reactivity in humans. Circulation. 2001;104:3076-3080

[64] Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Chiadoni L, Salvetti A, Ferrannini E, Monzani F. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. J Clin Endocrinol Metab. 2003;88:3731-3737

[65] Guntekin U, Gunes Y, Tuncer M, et al. QTc dispersion in hyperthyroidism and its association with pulmonary hypertension. Pacing Clin Electrophysiol 2009; 32: 494-499

[66] Bielecka-Dabrowa A, Mikhailidis DP, Rysz J, Banach M. The mechanisms of atrial fibrillation in hyperthyroidism. Thyroid Res 2009; 2: 4

[67] Wustmann K, Kucera JP, Zanchi A, et al. Activation of electrical triggers of atrial fibrillation in hyperthyroidism. J Clin Endocrinol Metab 2008; 93:2104

[68] Auer J, Scheibner P, Mische T, et al. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. Am Heart J 2001; 142: 838

[69] Vardas PE, Mavrakis HE. Atrial fibrillation: a symptom treated as a disease? Hellenic J Cardiol 2006; 47: 191-193

[70] Nakazawa H, Lythall DA, Noh J, Ishikawa N, Sugino K, Ito K, Hardman SM. Is there a place for the late cardioversion of atrial fibrillation? A long-term follow-up study of patients with post-thyrotoxic atrial fibrillation. Eur Heart J. 2000;21:327-333

[71] Krahn AD, Klein GJ, Kerr CR, Boone J, Sheldon R, Green M, Talajic M, Wang X, Connolly S. How useful is thyroid function testing in patients with recent-onset atrial fibrillation? The Canadian Registry of Atrial Fibrillation Investigators. Arch Intern Med. 1996;156:2221-2224

[72] Almeida NA, Corderio A, Machado DS, et al. Connexin 40 messenger ribonucleic activity is posotovely regulated by thyroid hormone (TH)acting in cardiac atria via

the THreceptor. Endocrinology 2009; 150: 546-554

[73] Nakazawa HK, Sakurai K, Hamada N, Momotani N, Ito K. Management of atrial fibrillation in the post-thyrotoxic state. Am J Med 1982; 72: 903-906

[74] Kim D, Smith TW. Effects of thyroid hormone on sodium pump sites, sodium content, and contractile responses to cardiac glycosides in cultured chick ventricular cells. *J Clin Invest*. 1984;74:1481-1488. 87

[75] Roti E, Montermini M, Roti S, Gardini E, Robuschi G, Minelli R, Salvi M, Bentivoglio M, Guiducci U, Braverman LE. The effect of diltiazem, a calcium channel-blocking drug, on cardiac rate and rhythm in hyperthyroid patients. Arch Intern Med. 1988;148:1919-1192

[76] Shimizu T, Koide S, Noh JY, Sugino K, Ito K, Nakazawa H. Hyperthyroidism and the management of atrial fibrillation. Thyroid. 2002;12:489-493.

[77] Chaudhury S, Ismail-Beigi F, Gick GG, Levenson E, Edel man IS. Effect of thyroid hormone on the abundance of Na,K,ATPase alpha subunit messenger ribonucleic acid.Mol Endocrinol 1987; 1: 83-89

[78] Lin H, Mitasikova M, Dlugosova K, et al. Thyroid hormones suppress epsilon PKC-signalling, downregulate connexin- 43 and increase lethal arrhythmia susceptibility in nondiabetic and diabetic rats. J Phsiol Pharm 2008; 59: 271-285

[79] Osman F, Franklyn JA, Holder RL, Sheppard MC, Gammage MD. Cardiovascular symptoms and cardiac rate and rhythm abnormalities improve with treatment in patients with hyperthyroidism. J Am Coll Cardiol. 2007;49:71-81

[80] Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am. 2014 Jun;43(2):517-528

[81] Klein I, Danzi S. Thyroid disease and the heart. Curr Probl Cardiol. 2016 Feb;41(2):65-92

[82] Biondi B. Mechanisms in endocrinology: Heart failure and thyroid dysfunction. Eur J Endocrinol. 2012 Nov;167(5):609-618

[83] Kahaly GJ, Kampmann C, Mohr-Kahaly S. Cardiovascular hemodynamics and exercise tolerance in thyroid disease.Thyroid 2002; 12: 473

[84] Dahl P, Danzi S, Klein I. Thyrotoxic cardiac disease. Curr Heart Fail Re 2008; 5: 170-176.

[85] Yue WS, Chong BH, Zhang XH, et al. Hyperthyroidisminduced left ventricular diastolic dysfunction: implication in hyperthyroidism-related heart failure. Clin Endocrinol (Oxf) 2011; 74: 636-643

[86] Klein I. Endocrine disorders and cardiovascular disease. In: Zipes DP,Libby P, Bonow R, Braunwald E, eds. *Braunwald's Heart Disease: ATextbook of Cardiovascular Medicine*. 7th ed. Philadelphia, Pa. W.B.Saunders; 2005:2051-2065.

[87] Evangelopoulou ME, Alevizaki M, Toumanidis S, Piperingos G, Mavrikakis M, Sotou D, Evangelopoulou K, Koutras DA. Mitral valve prolapse in autoimmune thyroid disease: an index of systemic autoimmunity? Thyroid. 1999;9:973-977

[88] Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med. 2004; 164:1675-1678

[89] Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PW, Benjamin EJ, D'Agostino RB. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994;331:1249-1252

[90] Merce J, Ferras S, Oltra C, Sanz E, Vendrell J, Simon I, Camprubi M, Bardaji A, Ridao C. Cardiovascular abnormalities in hyperthyroidism: a prospective Doppler echocardiographic study. Am J Med. 2005;118:126-133

[91] Paran Y, Nimrod A, Goldin Y, Justo D. Pulmonary hypertension and predominant right heart failure in thyrotoxicosis. Resuscitation. 2006; 69:339-341.

[92] Ventrella S, Klein I. Beta-adrenergic receptor blocking drugs in the management of hyperthyroidism. The Endocrinologist. 1994;4:391-399

[93] Delit C, Silver S, Yohalem SB, Segal RL. Thyrocardiac disease and its management with radioactive iodine I-131. JAMA. 1961;29:262-267

[94] Franklyn JA, Sheppard MC, Maisonneuve P. Thyroid function and mortality in patients treated for hyperthyroidism. JAMA. 2005;294:71-80

[95] Tsymbaliuk I, Unukovych D, Shvets N, Dinets A (2015) Cardiovascular Complications Secondary to Graves' Disease: A Prospective Study from Ukraine. PLoS ONE 10(3): e0122388. doi:10.1371/ journal.pone.0122388

[96] Scerrino G, Morfino G, Paladino NC, Di Paola V, Amodio E, Gulotta G, et al. Does thyroid surgery for Graves' disease improve health-related quality of life? Surgery today. 2013; 43(12):1398-405. Epub 2012/12/12. doi: 10.1007/s00595-012-0442-z PMID: 23229839

[97] Jiang SY, Xu M, Ma XW, Xiao H, Zhang YY. A distinct AMP-activated protein kinase phosphorylation site characterizes cardiac hypertrophy induced by L-thyroxine and angiotensin II. Clin Exp Pharmacol Physiol. 2010; 37(9):919-25. doi: 10.1111/j.1440-1681.2010.05404.x PMID: 20497424

[98] Vallabhajosula S, Radhi S, Cevik C, Alalawi R, Raj R, Nugent K. Hyperthyroidism and pulmonary hypertension: an important association. Am J Med Sci. 2011 Dec;342(6):507-512

[99] Siu CW, Zhang XH, Yung C, Kung AW, Lau CP, Tse HF. Hemodynamic changes in hyperthyroidism-related pulmonary hypertension: a prospective echocardiographic study. J Clin Endocrinol Metab. 2007 May;92(5):1736-1742

[100] Sugiura T, Yamanaka S, Takeuchi H, Morimoto N, Kamioka M, Matsumura Y. Autoimmunity and pulmonary hypertension in patients with Graves' disease. Heart Vessels. 2015 Sep;30(5):642-646

[101] Marvisi M, Zambrelli P, Brianti M, Civardi G, Lampugnani R, Delsignore R. Pulmonary hypertension is frequent in hyperthyroidism and normalizes after therapy. Eur J Intern Med. 2006;17:267-271

[102] Ma RC, Cheng AY, So WY, Hui DS. Thyrotoxicosis and pulmonary hypertension. Am J Med. 2005;118:927-928

[103] Curnock AL, Dweik RA, Higgins BH, Saadi HF, Arroliga AC. High prevalence of hypothyroidism in patients with primary pulmonary hypertension. Am J Med Sci. 1999;318:289-292

[104] Duntas LH. Thyroid disease and lipids. Thyroid. 2002;12:287-293

[105] Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU. The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function and quality of life in subclinical hypothyroidism: randomised, crossover trial. J Clin Endocrinol Metab. 2007;92:1715-1723

[106] Rush J, Danzi S, Klein I. Role of thyroid disease in the development of statin-induced myopathy. The Endocrinologist. 2006;16:279-285

[107] Drover VAB, Agellon LB. Regulation of the human cholesterol 7α-hydroxylase gene (*CYP7A1*) by thyroid hormone in transgenic mice. Endocrinology. 2004;145:574-581

[108] Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med. 2000;132:270-278

[109] Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. Ann Intern Med. 2002 Dec 3;137(11):904-914.

[110] Biondi B, Bartalena L, Cooper DS, Hegedus L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J. 2015 Sep;4(3):149-163

[111] Nanchen D, Gussekloo J, Westendorp RG, et al. Subclinical thyroid dysfunction and the risk of heart failure in older persons at high cardiovascular risk. J Clin Endocrinol Metab. 2012 Mar;97(3):852-861

[112] Selmer C, Olesen JB, Hansen ML, et al. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. BMJ. 2012 Nov 27;345: e7895

[113] Selmer C, Olesen JB, Hansen ML, et al. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. J Clin Endocrinol Metab. 2014 Jul;99(7):2372-2382

[114] Gu LQ, Zhao L, Zhu W, et al. Relationships between serum levels of thyroid hormones and serum concentrations of symmetric dimethylarginine (ADMA) and N-terminal-pro B-type natriuretic peptide (NT-proBNP) in patients with Graves' disease. Endocrine 2011; 39: 266-271

[115] Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016; 26:1343}}

[116] Subahi A, Ibrahim W, Abugroun A. Diltiazem-Associated Cardiogenic Shock in Thyrotoxic Crisis. Am J Ther 2018; 25:e666.

[117] Klein I, Biondi B. Endocrine disorders and cardiovascular disease. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, Bonow RO, Mann DL, Tomaselli GF, Bhatt D (Eds), Saunders Elsevier, Philadelphia 2019. p.1807.