World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

Effects of Hyperthyroidism on the Heart

Irida Kecaj [1,*], Ergita Nelaj [1], Ilir Gjermeni[1], Kei Xhixhabesi [1], Jonilda Shukulli [1] and Ina Refatllari [2]

[1] *Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania.*
[2] *Department of Cardiology, University Hospital Center "Mother Teresa", Tirana, Albania.*

World Journal of Advanced Research and Reviews, 2024, 22(02), 2020–2027

Publication history: Received on 19 April 2024 revised on 28 May 2024; accepted on 30 May 2024

Article DOI: https://doi.org/10.30574/wjarr.2024.22.2.1659

Abstract

Thyroid hormones have a significant cellular and hemodynamic effect, playing an important role on cardiac function and structure. On the basis of the understanding of the cellular mechanisms of action of thyroid hormones on the heart and cardiovascular system, we can explain the changes in cardiac output, cardiac contractility, arterial pressure, vascular resistance and rhythm disorders, that results from thyroid dysfunction. It is important to know cardiovascular complications in hyperthyroidism, because of their high frequency in clinical presentation and increased mortality and morbidity risk.

The importance of the recognition of the effects of thyroid disorders on the heart, comes from various studies, where it is established that the restoration of normal thyroid function is accompanied by cardiovascular hemodynamic improvements. In the present review, we discuss how hyperthyroidism affects cardiovascular system.

Keywords: Hyperthyroidism; Heart Failure; Atrial Fibrillation; Subclinical Hyperthyroidism**.**

1. Introduction

1.1. Role of Thyroid Hormone Action in Homeostasis

The precise cellular and molecular mechanisms by which the thyroid exerts its effects on every tissue and organ of the body have been well studied. Thyroid hormones, tetraiodothyronine (T4) and triiodothyronine (T3), are synthesized by the thyroid gland in response to thyroid-stimulating hormone (TSH). The production and secretion of thyroid hormones (TH) is regulated by the hypothalamic thyroid-releasing hormone (TRH), which determines the equilibrium between serum thyroid stimulating hormone (TSH) and TH concentration. T3 is the biologically active thyroid hormone, which is mostly generated peripherally by 5′-monodeiodination of T4 (in the liver, kidney, and skeletal muscle) [1].The deiodination of T4, T3, and other iodothyronines is an integral component of TH homeostasis. All deiodinases are membrane-anchored proteins of 29–33kDa that share substantial sequence homology, catalytic properties and contain selenocysteine as the key residue within their catalytic centers. They catalyze and sequentially remove stereo-specific iodine atoms from T4, generating active and inactive isomers of both T3 and diiodothyronine (T2). The deiodinases play an important role in customizing TH signaling is the main way in which TH exert its metabolic effects.[2]. There are three types of deiodinases. Most of the circulating T3 is derived from Type 1. Type 1 (D1), is localized to the plasma membrane and expressed in thyroid, liver and kidney, and catalyzes removal of inner or outer ring iodine atoms in equimolar proportions to generate T3, reverse T3 (rT3), or T2, depending on the substrat [3]. There is no significant intracellular deiodinase activity in cardiac cells. Therefore, the heart relies mainly on the action of T3 since that is the hormone transported into the myocyte [4]. Both T4 and T3 circulate in the blood (> 95%) bound to thyroxine-binding globulin and a family of other hormone-binding proteins. The remaining unbound T3 is transported through a variety of membrane transport proteins to the cell nucleus to regulate expression of selected genes [5]

* Corresponding author: Irida KECAJ

1.2. Molecular Mechanisms of Thyroid Hormone Action on Cardiac Myocytes

The cellular actions of TH are mediated by the binding of T3 to nuclear receptors. It is T3 and not T4 that is transported into the cardiac myocyte. Thyroid hormones exert their intracellular cardiac effects through two mechanisms: genomic and nongenomic.T3 has both genomic and nongenomic effects on the cardiac myocyte, but most of the effects are exerted through genomic actions, which consist of T3 linking to nuclear receptors that bind to thyroid-responsive elements (TREs) in the promoter of target genes. These receptor proteins exist in 2 isoforms, α and β (TRα and TRβ), and bind to TH response elements in the promoter regions of TH-responsive genes. TRα and TRβ activate expression of positively regulated genes in the presence of T3 and repress expression in its absence [6]. There are several key myocyte-specific genes regulated by this mechanism (Table 1). Thyroid hormone-regulated genes are also involved in structural and regulatory proteins, and long-term exposure to high T3 levels can increase the synthesis of cardiac proteins, leading to cardiac hypertrophy and dysfunction [7].

Table 1 T3-Regulated Cardiac Genes [modified from the reference 4]

Positively Regulated Genes	Negatively Regulated Genes
α-MHC	β-myosin heavy chain
Sarcoplasmic reticulum Ca2+ ATPase	Phospholamban
Voltage-gated potassium channels	Thyroid hormone receptor α1
Na+/K+ ATPase	Adenylyl cyclase catalytic subunits
β1-adrenergic receptor	Na+/Ca2+ exchanged

Nongenomic mechanisms are identified by their rapid rate of action and include direct modulation of membrane ion channel[4].TH have two major non-genomic effects, on cardiomyocytes of several membrane ion channels, such as Na+, K+, and Ca2+ channels[8]. Nongenomic effects are usually receptor-independent and largely occur at the plasma membrane, regulating ion transporter activity, provoking rapid changes in the cardiac myocyte plasma membrane and cytoplasmic organelles, which includes changes in sodium, potassium, and calcium ion channels, changes in actin cytoskeleton polymerization, and changes to the intracellular signaling pathways in the heart and smooth muscle cells [9]. Both the non-genomic and genomic effects of T3 act in concert to regulate cardiac function and cardiovascular hemodynamics. For example, TH upregulate expression of the sarcoplasmic reticulum calcium-activated ATP-ase and down regulate phospholamban expression, thereby enhancing myocardial relaxation. Moreover, the improved calcium reuptake during diastole may have a favorable effect on myocardial contractility. They also increase expression of the more rapid contractile isoforms of the myosin heavy chain (α isoforms), which contributes to enhanced systolic function. TH lower systemic vascular resistance, increase blood volume, and have inotropic and chronotropic effects on cardiac function. These changes on both the circulation and the heart itself result in increased cardiac output, which has been described in hyperthyroidism [10].

1.3. Hemodynamic Repercussions of Hyperthyroidism

1.3.1. Effect on the Renin-Angiotensin-Aldosterone (RAA) axis

In hyperthyroidism preload is increased, peripheral vascular resistance is reduced and heart rate is elevated, which leads to increased cardiac output. The reduced systemic vascular resistance results in decreased renal perfusion pressure and activation of the renin-angiotensin-aldosterone system (RAAS), thereby increasing sodium reabsorption and blood volume, leading this to increased preload, decreased afterload, and a significant increase in stroke volume[10].Thyroid hormones are known to increase the response of tissues to the action of the sympathetic system, or can also activate the RAS without involving the sympathetic nervous system. Numerous studies have reported that thyroid hormones might modulate the RAS and have evidenced a relationship between the thyroid state and RAS components at both plasma and tissue levels [11]. Thyroid hormones play a major role in the growth and development of various tissues, including the kidney and lung, which are major sites of renin and ACE synthesis, and enhances the cardiac expression of renin mRNA, leading to increased cardiac levels of renin and angiotensin II that are independent of the circulating renin and angiotensin [12]. In hyperthyroid state the expression of angiotensin II receptors increases in the myocardium. These hemodynamic changes cause stretching of the atrial fibers that trigger the secretion of atrial natriuretic peptide (ANP), which causes more vasodilation. All these changes suggest a central role of the myocardial RAAS in thyroxine-induced cardiac hypertrophy as well as potential therapeutic implications of medications that block this system [7].

1.3.2. Action on Catecholamine Sensitivity

The increased heart rate, widened pulse pressure, and increased cardiac output of patients with hyperthyroidism resemble a state of increased adrenergic activity and a direct effect of thyroid hormone[13].The results of several investigations have suggested that thyroid hormone itself has direct inotropic and chronotropic effects on the heart. It is observed that plasma catecholamine levels and turnover rates are not increased in hyperthyroidism, and G protein the β-adrenergic receptor density is altered in a time- and tissue-dependent manner, resulting in increased tissue sensitivity to catecholamines [14]. The changes in the heart rate result from both an increase in sympathetic tone and decrease in parasympathetic tone [15].The sensitivity of the cardiovascular system to adrenergic stimulation is not changed by thyroid hormones [13, 14].This is supported by the fact that administration of a β-adrenergic receptor antagonist to patients with hyperthyroidism slows the heart rate, but does not alter systolic or diastolic contractile performance [16], confirming that thyroid hormone acts directly on cardiac muscle[13]. There is an increase in heart rate at rest, blood volume, systolic volume, myocardial contractility and diastolic function, resulting in a hyperdynamic cardiovascular state characteristic of hyperthyroidism. (Fig. 1)

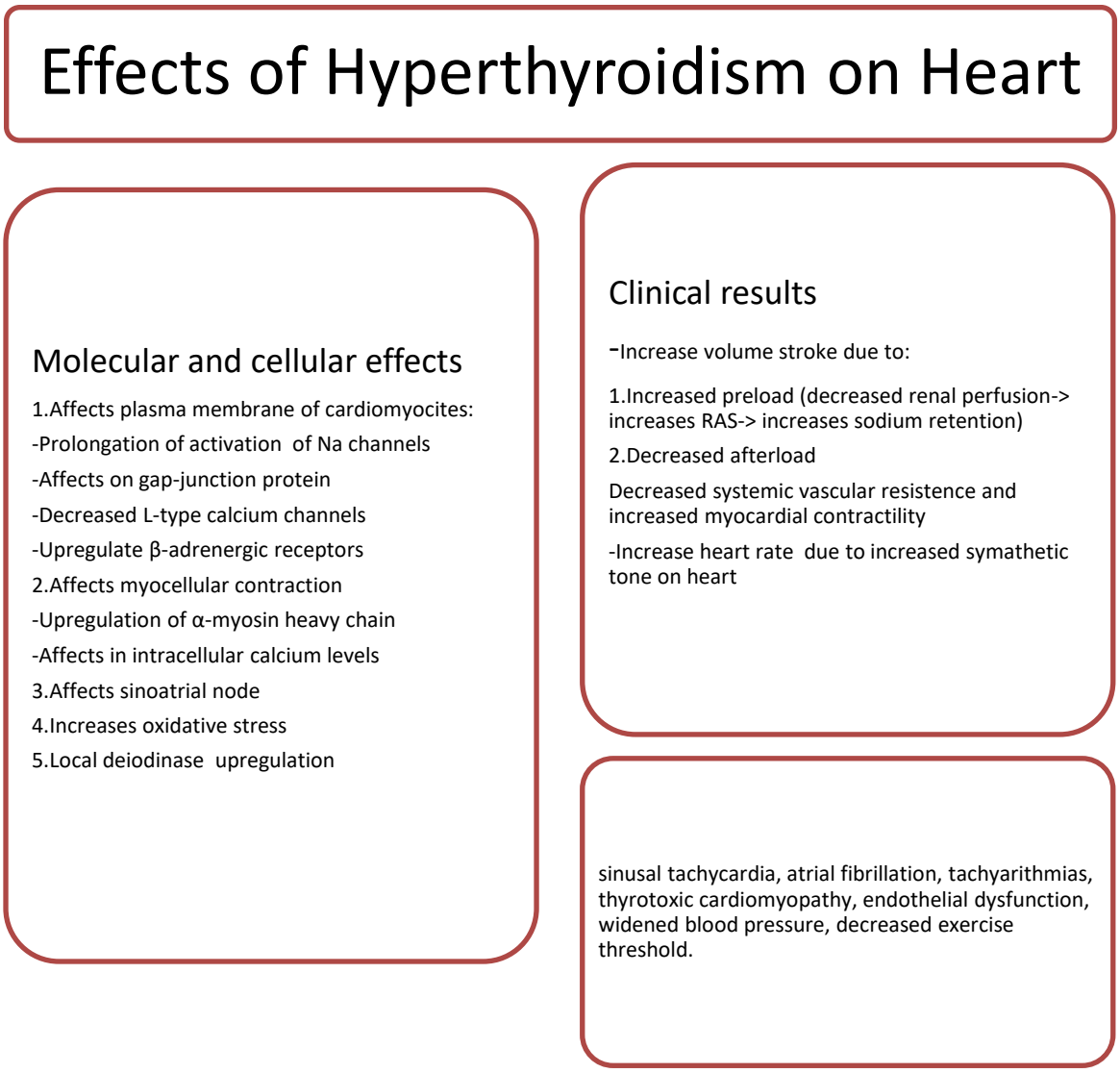

Figure 1 Summary of molecular and clinical effects of hyperthyroidism on cardiovascular system.

1.4. Hyperthyroidism and the Heart Failure

Cardiovascular function has a close relationship with thyroid status due to the direct action of T3 on cardiomyocytes, the autonomic system, vascular smooth muscle and the endothelium. Therefore, thyroid dysfunction can be accompanied by multiple structural and/or functional alterations of the heart that ultimately lead to heart failure. The

main changes are: Increases in heart rate, cardiac contractility, systolic and mean pulmonary artery pressure, cardiac output, diastolic relaxation, and myocardial oxygen consumption; Reductions in systemic vascular resistance and diastolic pressure[17]. Hemodynamic changes caused by hyperthyroidism predispose the patient to heart failure. Patients with hyperthyroidism may have signs and symptoms indicative of heart failure in absence of prior cardiac injury [18]. This state has been called "high-output failure," with paradoxical features such as enhanced cardiac output and contractility that are characterized by overproduction thyroid hormone [5]. The true heart failure manifests as a decreased cardiac contractility, pulmonary congestion and abnormal diastolic compliance, which results in severe or chronic hyperthyroidism, as a consequence of exaggerated sinus tachycardia or atrial fibrillation [18]. Preexistent ischemic or hypertensive heart disease may also predispose the hyperthyroid patient to development heart failure[19]. Both Graves' and Hashimoto's diseases are associated with an increased prevalence of mitral valve prolapse, and later in turn may predispose to enlargement of the left atrium and atrial fibrillation[20]. Thyrotoxic cardiomyopathy is known myocardial damage caused by toxic effects of overproduction thyroid hormone, resulting in altered myocyte energy production, intracellular metabolism, and myofibril contractile function, with main manifestations are left ventricular hypertrophy, heart rhythm disturbances, primary atrial fibrillation, dilation of the heart chambers, heart failure, PAH, and diastolic dysfunction[18]. On the basis of the high prevalence of pulmonary artery hypertension that many of the signs of heart failure, such as neck vein distension and peripheral edema, may be caused by right heart strain [21,22].

Therapy with β-adrenergic blockade medication to reduce heart rates should be first-line therapy [23]. The use of digitals with diuretics is appropriate in patients with overt heart failure and pulmonary congestion [24]. The treatment of choice for the hyperthyroidism is with 131I-radioiodine [23], which is both safe and effective especially when used in conjunction with β-adrenergic blockade. Cure of the hyperthyroidism and a restoration of the euthyroid state, frequently results in a reversion of the atrial fibrillation to sinus rhythm and a resolution of the cardiac manifestations [25].

1.5. Hyperthyroidism and the Atrial Fibrillation

Sinus tachycardia is the most common arrhythmia in hyperthyroidism and is almost present in all patients [26]. Characteristic of this disease is an increased in resting heart rate. The prevalence of atrial fibrillation in this disease ranges between 2% and 20%, which increases with age. When analyzed by age, a stepwise increase in prevalence was present, which peaked at ≈15% in patients >70 years old. Lars Frost et al identified that among 40,628 patients with hyperthyroidism from Danish National Registry over a 20 year period, 8.3% had atrial fibrillation or flutter within 30 days from the date of diagnosis, with risk factors for atrial fibrillation in patients with hyperthyroidism similar to those in general population like age, male sex, ischemic heart disease, congestive heart failure and valvular heart disease [27].Other factors associated with the presence of AF in hyperthyroidism are: obesity, chronic kidney disease, proteinuria, female gender, serum-free T4 concentration, and transaminase concentrations [28]. Atrial fibrillation usually is persistent rather than paroxysmal. Early screening for TSH, free T4, and total T3. is especially important for detecting thyroid dysfunction in this patient demographic [29].The several mechanisms that contribute in the development of atrial fibrillation in hyperthyroid patients include :elevated left atrial pressure that leads to increased left ventricular mass and impaired ventricular relaxation [30]; ischemia resulting from raised resting heart rate [31]; and increased atrial ectopic activity[32]. Hyperthyroidism is associated with coagulation abnormalities such as shortened activated partial thromboplastin time, increased fibrinogen levels, and increased factor VII and factor X activity [10], all of which contribute to the risk of cardiac blood clot formation in these patients.

Rapid diagnosis of hyperthyroidism and successful treatment with either radioiodine or thioureas is associated with a reversion to sinus rhythm in a majority of patients within 2 to 3 months [33]. Cardiac arrhythmias, of which atrial fibrillation is most frequent contribute to excess mortality from cardiovascular and cerebrovascular events by inducing heart failure and predisposing to embolic events. In younger patients with hyperthyroidism and atrial fibrillation, in the absence of organic heart disease, hypertension, or other independent risk factors for embolization, the benefits of anticoagulation may be outweighed by the risk, meanwhile aspirin provides a reduction of risk for embolic events and appears to offer a safe alternative [34].

1.6. Hyperthyroidism and Pulmonary Hypertension

Pulmonary hypertension is an increase in mean pulmonary artery pressure > 25 mm Hg at rest, or > 30 mm Hg during exercise, which is classified into five groups based on etiologies and pathophysiologic mechanisms: Group 1-pulmonary arterial hypertension; Group 2-PAH due to left heart disease; Group 3-PAH due to lung disease or hypoxia; Group 4-chronic thromboembolic PAH); and Group 5-PAH due to unclear multifactorial mechanisms [35]. Both pulmonary hypertension and atrioventricular valve regurgitation have been documented to occur with a high prevalence in thyroid disease patients. Approximately 20% of patients with pulmonary hypertension have thyroid disease, which is more frequent than the general population [36]. Several studies reported the effects of hyperthyroidism on the occurrence of

increased vascular pulmonary arterial pressure. Although the mechanism of PAH in hyperthyroidism is uncertain, its reversal once the euthyroid state is restored supports a causal relationship. The proposed mechanisms are the direct effects of thyroid hormones on pulmonary vascular proliferation, the chronotropic effects of hormones on the cardiovascular system, and autoimmune-mediated endothelial dysfunction [37]. Thyroid disease should be considered in the differential diagnosis of primary pulmonary hypertension.

1.7. Amiodarone-Induced Hyperthyroidism

Amiodarone has multiple effects on myocardial depolarization and repolarization that make it an extremely effective antiarrhythmic drug, but because of its high iodine content, can cause changes in thyroid function tests that result in either hypothyroidism (5% to 25% of treated patients) or hyperthyroidism (2% to 10% of treated patients)[38]. Amiodarone inhibits the conversion of T4 to T3 as a result of the inhibition of 5′-deiodinase activity, and the iodine released from amiodarone metabolism can directly inhibit thyroid gland function [39]. Amiodaron-induced hyperthyroidism range from 2% to 10% and vary directly with duration of treatment. There exists 2 forms of amiodarone-induced hyperthyroidism (AIT). Type 1 AIT occurs in patients with preexistent thyroid disease and goiter and more often is present in regions where iodine intake is low. In contrast, Type 2 AIT is caused by an inflammatory process that causes increased release of thyroid hormones in patients without underlying thyroid disease [40].It is usually not possible to distinguish between these two types. Mixed forms of AIT also occur, posing a diagnostic and therapeutic challenge. Type 1 AIT is treated with thionamides, and type 2 AIT is treated with oral glucocorticoids, while mixed forms may require a combination of thionamides and steroids. Although most treatment protocols suggest cessation of the amiodarone and use of thioureas in relatively high doses, neither of these interventions have been shown to lead to predictable benefits [34]. In rare cases, surgical thyroidectomy has proven to be effective, making it a valid option in cases resistant to medical therapy. The decision to interrupt the therapy with amiodarone or not requires interaction between the cardiologist and endocrinologist [40].

1.8. Subclinical Hyperthyroidism and the Heart

Subclinical hyperthyroidism is defined as a low or undetectable serum TSH concentration in the presence of normal levels of serum T4 and T3, and is a common medical finding, particularly in elderly people [41].The prevalence of subclinical hyperthyroidism ranges from 0.6 to 1.8% in adults, depending on age, sex and iodine status. Depending on serum TSH value, subclinical hyperthyroidism is classified into two categories: Grade 1, with mildly low but detectable serum TSH (0.1-0.45 mIU/L), and Grade 2, with lower levels of serum TSH(< 0.1 mIU/L).

In the last years has gained attention due to its health-related conditions, especially at the cardiovascular level. Although patients with subclinical hyperthyroidism often do not experience symptoms of hyperthyroidism, they have an increased risk for cardiovascular disease, dementia, and osteoporosis [26]. A 10-year cohort study of older patients, showed that subclinical hyperthyroidism was associated with increased risk for cardiovascular mortality and atrial fibrillation [42]. Subclinical hyperthyroidism is associated with a higher incidence of major adverse of cardiovascular events, because of increased factor X activity, which results in hypercoagulable state [43]. An increased carotid intima-media thickness has also been reported in subclinical hyperthyroidism [44]. Altogether, subclinical hyperthyroidism not only results in an increased risk of death from cardiovascular disease (HR 1.29; 95% CI: 1.02–1.62), but as well as leads to other effects, such as an increased left ventricular mass, sinus tachycardia, and diastolic dysfunction[42]. The European Thyroid Association recommends treating grade 2 subclinical hyperthyroidism in patients older than 65 years and to consider treating milder grades in the presence of heart disease or other significant comorbidities or risk [45].

2. Conclusions

Hyperthyroidism is a common thyroid disorder with many effects on almost all systems in the body, including the gastrointestinal system, bone metabolism, dermatological effects, and the cardiovascular system. Cardiovascular effects are the most common and dangerous effects. Hyperthyroidism causes high cardiac output and left ventricular hypertrophy in the early stage, and biventricular dilatation and congestive heart failure in the late stage. Atrial fibrillation and pulmonary hypertension as a result of untreated hyperthyroidism are associated with an increased risk of morbidity.

The recognition and detection of these manifestations in patients with thyroid disease, as well as the reinforcement of the need for thyroid function tests in patients with cardiovascular disease, are very important.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest regarding the publication of this paper.

References

[1] Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. Type 2 iodothyroninedeiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest. 2005; 115: 2524–2533.

[2] A. Orozco, R.C. Valverde, A. Olvera, G. García. Iodothyroninedeiodinases: a functional and evolutionary perspective. J Endocrinol, 215 (2012), pp. 207-219 http://dx.doi.org/10.1530/JOE-12-0258 | Medline.

[3] M. Dentice, A. Marsili, A.M. Zavacki, P. Reed Larsen, D. Salvatore. The deiodinases and the control of intracellular thyroid hormone signaling during cellular differentiation. BiochimBiophysActa, 1830 (2013), pp. 3937-3945 http://dx.doi.org/10.1016/j.bbagen.2012.05.007 | Medline

[4] Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007 Oct 9;116(15):1725-35.

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

[6] J.Z. Lin, D.H. Sieglaff, C. Yuan, J. Su, A.S. Arumanayagam, S. Firouzbakht, et al. Gene specific actions of thyroid hormone receptor subtypes. Plos one, 8 (2013), pp. e52407.http://dx.doi.org/10.1371/journal.pone.0052407 | Medline.

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

[8] Giammanco M., Di Liegro C. M., Schiera G., Di Liegro I. (2020). Genomic and Non-Genomic Mechanisms of Action of Thyroid Hormones and Their Catabolite 3,5-Diiodo-L-Thyronine in Mammals. Int. J. Mol. Sci. 21:ijms21114140. 10.3390/ijms21114140.PubMed.

[9] P.J. Davis, F. Goglia, J.L. Leonard. Nongenomic actions of thyroid hormone.Nat Rev Endocrinol, 12 (2016), pp. 111-121.

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

[11] Barreto-Chaves MLM, Carrillo-Sepu´lveda MA, Carneiro-Ramos MS, Gomes DA &Diniz GP 2010 The crosstalk between thyroid hormones and the renin–angiotensin system. Vascular Pharmacology 52 166–170. (doi:10.1016/j.vph.2009.10.009)

[12] Gomes DA &Diniz GP 2010 The crosstalk between thyroid hormones andthe renin–angiotensin system. Vascular Pharmacology 52 166–170. (https://doi.org/10.1016/j.vph.2009.10.009).

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

[14] Hoit BD, Khoury SF, Shao Y, Gabel M, Liggett SB, Walsh RA. Effects of thyroid hormone on cardiac beta-adrenergic responsiveness in conscious baboons. Circulation. 1997 Jul 15;96(2):592-8. doi: 10.1161/01.cir.96.2.592. PMID: 9244231.

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

[16] Biondi B, Fazio S, Carella C, et al. Control of adrenergic overactivity by beta-blockade improves the quality of life in patients receiving long-term suppressive therapy with levothyroxine. J Clin Metab. 1994;78:1028–33. PubMed

[17] Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. N Engl J Med. 2001 Feb 15;344(7):501-9. http/ doi: 10.1056/NEJM200102153440707. PMID: 11172193.

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

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

[20] 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.

[21] 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.

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

[23] Klein I, Becker DV, Levey GS. Treatment of hyperthyroid disease. Ann Intern Med. 1994; 121: 281–288.

[24] Danzi S, Klein I. Thyroid hormone and blood pressure regulation. Curr Hypertens Rep. 2003; 5: 513–520

[25] 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.

[26] Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Sacca L, Filetti S, Lombardi G, Perticone F. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J ClinEndocrinolMetab.2000; 85: 4701–4705.

[27] 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.

[28] Ta˘nase DM, Ionescu SD, Ouatu A, Amba˘ rus¸ V, Arsenescu-Georgescu C. Risk assessment in the development of atrial fibrillation at patients with associate thyroid dysfunctions. Rev Med ChirSoc Med Nat Iasi. 2013 Jul-Sep;117(3):623-9.

[29] Bielecka-Dabrowa A, Mikhailidis DP, Rysz J, Banach M. The mechanisms of atrial fibrillation in hyperthyroidism. Thyroid Res. 2009 Apr 2;2(1):4.

[30] Staffurth JS, Gibberd MC, Fui SN. Arterial embolism in thyrotoxicosis with atrial fibrillation. Br Med J. 1977 Sep 10;2(6088):688-90.

[31] Frost L, Vestergaard P, Mosekilde L. Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study. Arch Intern Med. 2004 Aug 9-23;164(15):1675-8.

[32] Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med. 1994 Nov 10;331(19):1249-52.

[33] 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.

[34] Klein I, Danzi S. Thyroid disease and the heart. Circulation. 2007 Oct 9;116(15):1725-35. doi: 10.1161/CIRCULATIONAHA.106.678326. Erratum in: Circulation. 2008 Jan 22;117(3):e18. PMID: 17923583.

[35] ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Humbert M, Kovacs G, Hoeper MM, et al. Eur Heart J. 2022;43:3618–3731. PubMed.

[36] 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):507-12.

[37] Scicchitano P, Dentamaro I, Tunzi F, Ricci G, Carbonara S, Devito F, Zito A, Ciampolillo A, Ciccone MM. Pulmonary hypertension in thyroid diseases. Endocrine. 2016 Dec;54(3):578-587. doi: 10.1007/s12020-016-0923-8. Epub 2016 Mar 19. PMID: 26994930.

[38] Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. Endocr Rev. 2001; 22: 240–254.

[39] Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. Ann Intern Med. 2006; 126: 63–73.

[40] Bogazzi F, Bartalena L, Tomisti L, Rossi G, Tanda ML, Dell'Unto E, Aghini-Lombardi F, Martino E. Glucocorticoid response in amiodarone-induced thyrotoxicosis resulting from destructive thyroiditis is predicted by thyroid volume and serum free thyroid hormone concentrations. J ClinEndocrinolMetab.2007; 92: 556–562.

[41] Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid.2003; 13: 3–126.

[42] Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Asvold BO, Sgarbi JA &Volzke H et al.Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Archives of Internal Medicine 2012 172 799–809. (https://doi.org/10.1001/archinternmed.2012.402).

[43] Erem C Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. Clinical Endocrinology 2006 64 323–329. (https://doi.org/10.1111/j.1365-2265.2006.02464.x). PubMed.

[44] Volzke H, Robinson DM, Schminke U, Ludemann J, Rettig R, Felix SB, Kessler C, John U &Meng W Thyroid function and carotid wall thickness. Journal of Clinical Endocrinology and Metabolism 2004 89 2145–2149. (https://doi.org/10.1210/jc.2003-031028). PubMed.

[45] Biondi B, Bartalena L, Cooper DS, Hegedus L, Laurberg P, KahalyGJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J. 2015 Sep;4(3):149-63.