Chapter 8

Impact of Thyroid Disease on Heart Failure

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Abstract

The modern vision concerning the physiological actions and pathological relevance of endocrine cardiac system is a very complex one. Decreased or increased action of thyroid hormone (hypo- or hyperthyroidism) on different cellular and molecular pathways in the heart plays an important role in the development and progression of myocardial remodelling and heart failure. Cardiovascular signs and symptoms that accompany both hyperthyroidism and hypothyroidism are presented, highlighting that correction of thyroid dysfunction most often reverses the abnormal cardiovascular hemodynamics.

Keywords: hyperthyroidism, hypothyroidism, heart failure, thyroid hormones, natriuretic peptides

1. Introduction

The modern vision concerning the physiological actions and pathological relevance of endocrine cardiac system is a very complex one. It is well-known that thyroid hormones and endocrine cardiac systems are strictly correlated in both physiological [1] and pathological conditions, especially in patients with cardiac diseases [2, 3]. Thyroid disease is the second most common endocrine disorder after diabetes mellitus, being present in 5–10% of the population. Current estimates suggest that the incidence of thyroid disease in adult female population is higher than in adult males, but with advancing age, especially beyond the eighth decade of life, the incidence in males rises to be equal to that of females [4]. Thyroid hormone has a homeostatic role on the cardiovascular system, especially in the presence of heart failure (HF). HF is a major public health issue, being currently diagnosed in approximately 23 million patients worldwide [5].

Many studies have recently confirmed that persistent subclinical thyroid dysfunction is associated with the development of HF by changes in cardiac structure and function [6, 7]. The term subclinical thyroid disease is used to define the state having an abnormal serum thyroid-stimulating hormone (TSH) concentration (below or above the statistically defined lower or upper limit of the reference range: 0.45–4.50 mIU/L) in the presence of normal serum thyroid hormones concentrations (free thyroxine and triiodothyronine within their reference ranges). Subclinical thyroid disease may progress to overt thyroid disease. Overt thyroid dysfunction is defined by an abnormality of both the TSH and thyroid hormones. Untreated overt hyperthyroidism and hypothyroidism have been reported to be common causes of HF [8].

Unfortunately, the impact of thyroid disease on HF and, implicitly, the full potential of the therapeutic use of thyroid hormones in treating and/or preventing HF, has not been adequately studied. This chapter addresses the effects of thyroid hormones on cardiac function and the clinical consequences of thyroid dysfunction.

2. Cellular and molecular mechanisms underlying the effects of thyroid hormones on the cardiovascular system

The hypothalamic-pituitary-thyroid axis is responsible for the regulation of thyroid metabolism involving the following steps: (step 1) hypothalamus produces thyrotropin-releasing hormone (TRH), needed to monitor the thyroid hormone concentrations; (step 2) TRH stimulates the pituitary to produce TSH; (step 3) under the action of TSH, thyroid gland secretes 85–90% thyroxine (T4) and 10–15% triiodothyronine (T3), the primary circulating thyroid hormones; (step 4) T4 is converted to T3 by the deiodinase system (D1–D3) in the liver, kidney, and skeletal muscle; (step 5) thyroxine binding globulin (TBG) is responsible for carrying T4 and T3 to the tissues.

Maintenance of thyroid hormone homeostasis is required for proper cardiovascular function [9]. Actually, an altered thyroid hormone metabolism leads to cardiac parameters changes by acting on some molecular pathways involved in cardiac hypertrophy and HF progression. Thyroid hormone may act directly on transcription on specific and nonspecific cardiac genes that include α and β myosin heavy chain (MHC-α and MHC-β, respectively), sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA), atrial natriuretic peptide, sodium-potassium adenosine triphosphatase (Na-K-ATPase), β-adrenergic receptor and cardiac troponin I (genomic effect) [10–12], or on plasma membrane, sarcoplasmic reticulum (a specialized type of smooth endoplasmic reticulum that regulates the calcium ion concentration in the cytoplasm of striated muscle cells) and mitochondria (nongenomic effect) [13].

Many invasive and noninvasive measurements have shown that T3 plays an important role in modulating cardiac function [14]. T3 is the active form of thyroid hormone in the heart, because no significant myocyte intracellular deiodinase activity takes place at heart level. In fact, there is no experimental study to prove the conversion of T4 to T3 in cardiomyocytes. Due to their lipophilic nature, T3 and T4 can easily diffuse through the cytoplasmic membrane of cardiomyocytes. Lipophilic T3 enters the nucleus and binds to inactive nuclear thyroid hormone

receptors, which are encoded by the c-erbA proto-oncogene families. Further, the complex recognizes one of the several DNA consensus sequences and the thyroid response elements, located in the enhancer region of target genes [15]. The subsequent binding of the T3-receptor complexes to DNA regulates the expression of genes, encoding for structural and functional cardiac proteins (regulating calcium cycling in the cardiac myocyte) [16]. Thus, T3 modulates heart rate, cardiac contractility and arterial peripheral resistance, being essential to preserve both cardiac morphology and performance in adult life. In these circumstances, it is easy to understand why an altered thyroid status in patients with cardiovascular disorders could modify cardiac gene expression and contribute to impaired cardiac function.

A decrease in serum T3 needs to be analysed very carefully, because there are two possible causes: (i) low levels of T3 associated with low levels of T4 and high levels of TSH suggest a dysfunction of the thyroid gland itself (hypothyroidism), most often caused by an autoimmune disease (Hashimoto's thyroiditis) and/or iodine deficiency; (ii) low levels of T3 or free T3 (FT3) with normal T4 and low or normal TSH suggest a dysfunction which is unrelated to thyroid gland. This particular pattern has three names as follows: euthyroid sick syndrome, non-thyroidal illness syndrome, or low T3 syndrome.

The exact cause of low T3 syndrome is not known, but it is assumed that it occurs as a result of modified expression of the deiodinases (reduced enzyme activity of 5-monodeiodinase responsible for converting T4 into T3 in peripheral tissues) [17], modified entry of thyroid hormone into tissue (damage membrane) [18], or altered signalling due to changes in thyroid hormone receptors. Clinical and experimental evidence have shown that low T3 syndrome has been found in about 30% of HF patients, being associated with HF New York Heart Association (NYHA) functional class III–IV [19]. Furthermore, low T3 syndrome is considered a strong prognostic predictor of death in patients with HF, contributing to the progressive deterioration of cardiac function and myocardial remodelling in HF [17]. This might be explained by the fact that HF develops as the result of the added stress of health conditions, and a single risk factor may be sufficient to cause this syndrome.

Risk factors	Inflammatory markers	Cellular events	Cardiac events
Thyroid dysfunction	IL-1 β, IL-6, IL-8,	Fibroblast proliferation	Cardiac failure
Diabetes	TNF-α, CRP	Collagen synthesis	
Viral infections		Matrix metalloproteinases activation	
High blood pressure		Mechanical stress	
Coronary artery disease		Cardiomyocyte hypertrophy	
Heart attack		Cardiomyocyte apoptosis/necrosis	
Congenital heart defects			
Heart arrhythmias			
Valvular heart disease			

Table 1. Risk factors and mechanisms that are involved in the development of heart failure.

Actually, pathophysiological phenomena behind HF involve a compensatory activation of hormonal, neurohumoral, immunological, and proinflammatory systems as can be seen from **Table 1**.

Thyroid dysfunction triggers an inflammatory cascade. The balance between T-helper type 1 (Th1) and type 2 (Th2) lymphocytes may determine the outcome of autoimmune thyroid diseases. According to cytokine profiles, both Th1 and Th2 response have been supposed to be involved in the pathogenesis of Hashimoto's thyroiditis (the most common cause of hypothyroidism) and Graves' disease (the most common cause of hyperthyroidism), but with deviation toward Th1 pattern in Hashimoto's thyroiditis and toward Th2 pattern in Graves' disease. Autoimmune thyroid diseases have serum antibodies reacting with thyroglobulin, thyroid peroxidase, or TSH receptor and these antibodies might be cytotoxic. High antibodies concentrations correlate with proinflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), responsible for oxidative stress, thyroid damage, and the loss of thyroid function [20]. Furthermore, many studies have shown that proinflammatory cytokines (IL-6, IL-1β, and TNF-α) are cardiodepressant and play a pathogenic role in HF, contributing to cardiac remodelling, which is a progressive process (**Table 1**). Also, it is known that IL-6 is a hallmark of the acute phase of low T3 syndrome [21]. Inflammatory biomarker C-reactive protein (CRP) is mainly produced in response to IL-6 and plays many pathophysiological roles in the inflammatory process in HF, in direct relation to deterioration of NYHA functional class and cardiac performance. In patients with Hashimoto's thyroiditis, there was a positive correlation between TgAb and hs-CRP ($r = 0.55$, $P = 0.01$) [22], CRP being inversely correlated with T3 and T3 levels, inversely correlated to the presence and severity of HF [23].

Plasma concentration of natriuretic peptides, including B-type natriuretic peptide (BNP), particularly its amino-terminal fragment (NT-proBNP) and A-type natriuretic peptide (ANP), and especially its amino-terminal fragment (NT-proANP) or mid-regional fragment (MR-proANP), can be used as an initial diagnostic test of HF, especially in the non-acute setting when echocardiography is not immediately available [24]. NT-proBNP, NT-proANP, and MR-proANP have longer half-lives, are more stable and, consequently, are more reliable analytes of prolonged cardiac overload than are the biologically active peptides [25]. NT-proBNP is considered a prognostic determinant of HF progression, it levels paralleling the degree of left ventricular dysfunction [26]. High NT-proBNP concentrations predict cardiac-related mortality in HF patients.

Recent attention has been drawn to the relation of thyroid hormone, inflammatory biomarkers, such as IL-6 and CRP, and natriuretic peptides. Many authors studied natriuretic peptides levels in different thyroid function states and found that their serum levels were strongly affected by thyroid function. Generally, natriuretic peptides are elevated in overt and subclinical hyperthyroidism and reduced in overt and subclinical hypothyroidism. Thus, Christ-Crain et al. [27] have found statistically significant higher serum NT-proBNP and proANP concentration in hyperthyroid patients compared to hypothyroid and euthyroid subjects. Kato et al. [28] measured ANP and BNP levels in 130 patients with thyrotoxicosis and correlated them with HF severity and thyroid function. The levels of BNP and ANP were elevated in thyrotoxic patients. After therapy, when euthyroidism was established, a normalization of their levels has

been noted. The authors concluded that the measurement of serum BNP levels in thyrotoxic patients is useful for monitoring cardiovascular conditions of HF. Pakula et al. [29] assessed echocardiographically diameters of cardiac cavities, left ventricular mass, left ventricular ejection fraction, and NT-proBNP in 101 patients with thyroid dysfunction, free from any cardiovascular disease. They have shown that hyperthyroidism, in both its clinical and subclinical forms, results in a significant increase in NT-proBNP serum levels, their results being in line to those obtained by Christ-Crain et al. [27]. Moreover, they noted that despite normalization of plasma levels of TSH, the treatment with levothyroxine (L-T4) did not restore a hyperthyroidism-induced increase in plasma NT-proBNP levels. These findings are in accordance with Stanciu et al. [30], who investigated the effects of short-term overt hypothyroidism and exogenous subclinical hyperthyroidism on NT-proBNP and NT-proANP, in patients with differentiated thyroid cancer treated with radioactive iodine (^{131}I—RAI). As illustrated in **Figures 1** and **2**, serum levels of NT-proBNP and NT-proANP were significantly higher in subclinical hyperthyroidism (t2) than in overt hypothyroidism (t1) (6185 ng/L, IQR: 1689–8778 ng/L vs. 21.6 ng/L, IQR: 13.9–203 ng/L and 674 ng/L, IQR: 529–858 ng/L vs. 309 ng/L, IQR: 23.7–580 ng/L, respectively, $P < 0.001$). The authors have found that FT3 positively regulates NT-proANP production from cardiac myocytes, NT-proANP more accurately reflecting direct thyroid hormone effects, than NT-proBNP. Stanciu et al. concluded that short-term acute hypothyroidism, due to L-T4 withdrawal, and subclinical hyperthyroidism, due to suppressive doses of L-T4, induce deleterious effects on natriuretic peptides profiles during RAI therapy.

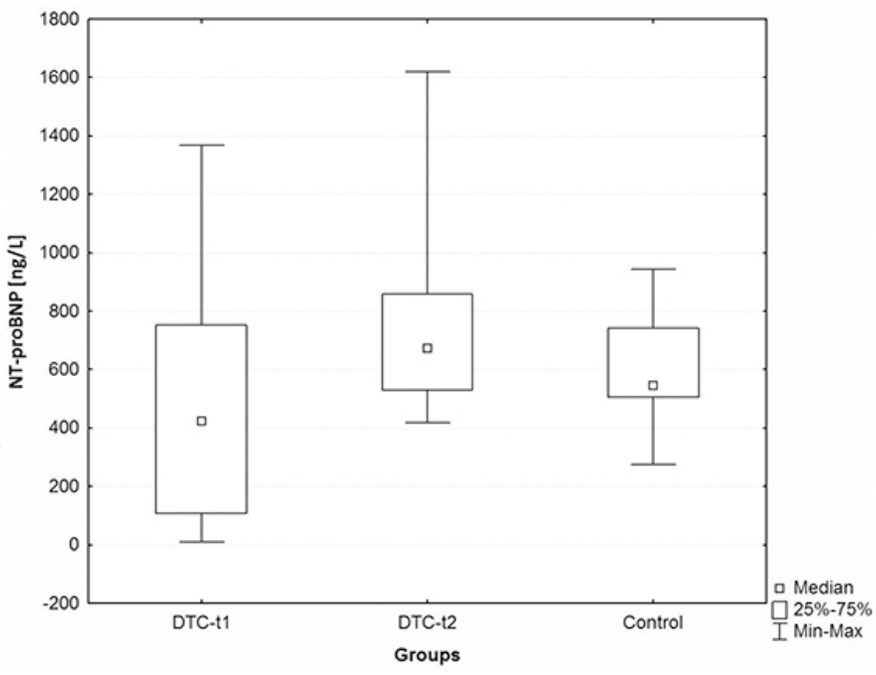

Figure 1. Median NT-proBNP levels in patients with differentiated thyroid cancer (DTC) compared with healthy euthyroid controls. DTC-t1: short-term overt hypothyroidism after levothyroxine withdrawal; DTC-t2: subclinical hyperthyroidism during suppressive levothyroxine therapy ($P < 0.001$ vs. DTC and healthy controls; $P < 0.001$ vs. DTC-t1 and DTC-t2).

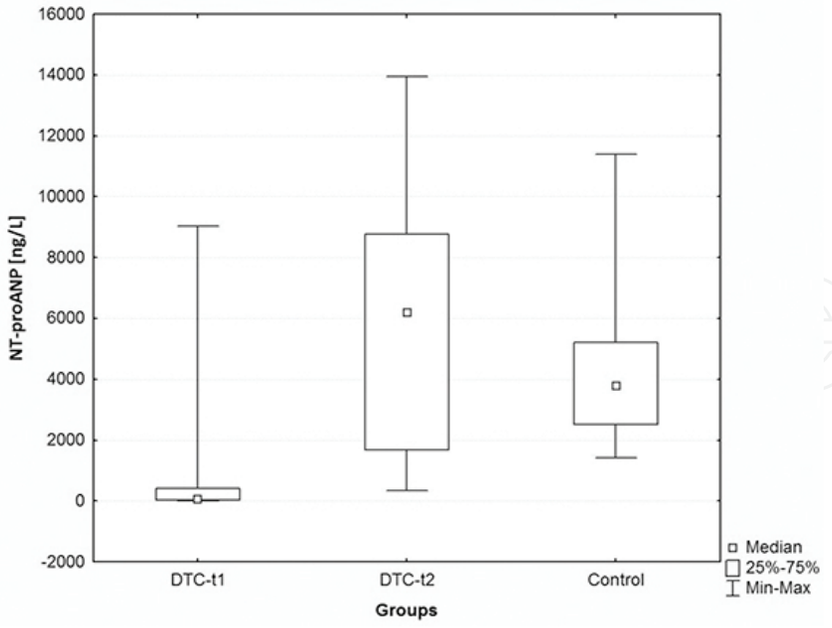

Figure 2. Median NT-proANP levels in patients with differentiated thyroid cancer (DTC) compared with healthy euthyroid controls. DTC-t1: short-term overt hypothyroidism after levothyroxine withdrawal; DTC-t2: subclinical hyperthyroidism during suppressive levothyroxine therapy ($P < 0.001$ vs. DTC and healthy controls; $P < 0.001$ vs. DTC-t1 and DTC-t2).

Brozaitiene et al. [31] studied the relationship and prognostic impact of thyroid hormones, inflammatory biomarkers, and NT-proBNP on long-term outcomes in coronary artery disease (CAD) patients with HF. Multivariate linear regression models, adjusted for age, gender, and body mass index, revealed that (ln) NT-proBNP was associated with hs-CRP ($\beta = 0.59$, $P < 0.001$), (ln) IL-6 ($\beta = 0.254$, $P < 0.001$), free thyroxine (FT4) ($\beta = 0.100$, $P = 0.011$), and T4 ($\beta = 0.112$, $P = 0.019$). Their results showed that thyroid hormones (i.e. FT4 level and FT3/FT4 ratio) together with NT-proBNP level may be valuable and simple predictors of long-term outcomes of CAD patients after experiencing acute coronary syndrome.

The question is: is this due to a compensatory mechanism, secondary to the thyroid hormone changes, or is it due to a direct action of thyroid hormone on the secretion of natriuretic peptides? The presented data have shown that natriuretic peptides are directly stimulated and regulated by thyroid hormones and immunological factors. Thyroid dysfunction triggers proinflammatory cytokines, known as stimulators of NT-proANP and NT-proBNP release. All of these leads to the idea that the thyrometabolic state must be taken into account when NT-proBNP or NT-proANP are assessed as markers of HF.

3. Impact of hyperthyroidism on heart failure

Endogenous hyperthyroidism (overproduction of thyroid hormone) and exogenous hyperthyroidism (ingestion of excessive amounts of thyroid hormone, i.e. suppressive doses of L-T4 to treat thyroid cancer) are associated with palpitations, tachycardia, exercise intolerance,

dyspnea on exertion and increased heart rate. Patients with overt and subclinical hyperthyroidism are at increased risk of atrial arrhythmias and HF, because long-term exposure to thyroid hormone excess exerts unfavourable effects on cardiac morphology and function by increasing left ventricular mass, arterial stiffness, and left atrial size [32]. More than that, autoimmune hyperthyroidism (Graves' disease) has been frequently linked to autoimmune cardiovascular involvement (pulmonary arterial hypertension, myxomatous cardiac valve disease, and autoimmune cardiomyopathy). The effects of thyroid hormones on the heart and peripheral vasculature include decreased systemic vascular resistance (SVR) and diastolic blood pressure and increased resting heart rate, left ventricular contractility and pulmonary arterial pressure, as can be seen from **Table 2**. In overt hyperthyroidism, these combined effects increase cardiac output by 50–300% more than in normal subjects [33], resulting in right ventricular failure, as a consequence of immune-mediated endothelial damage [34]. Also, in patients with overt hyperthyroidism, a high prevalence of left ventricular hypertrophy and an increase in the contractility of the left ventricle and ejection fraction have been reported [34].

Variables	Hyperthyroidism	Hypothyroidism
Thyroid hormones	↑	↓
Oxidative metabolism	↑	↓
Natriuretic peptides	↑	↓
Lipids and lipoproteins	↓	↑
Heart rate	↑	↓
Systemic vascular resistance	↓	↑
Cardiac output	↑	↓
Cardiac contractility	↑	↓

Note: ↑, increased; ↓, decreased.

Table 2. Cardiovascular effects of thyroid dysfunction.

Subclinical hyperthyroidism can contribute to HF by increasing of heart rate and left ventricular mass, by worsening diastolic function and by predisposing to atrial fibrillation (AF) [35]. AF occurs in 10–25% of patients with hyperthyroidism (subclinical hyperthyroidism: RR = 1.31; 95% CI: 1.19–1.44 and overt hyperthyroidism RR = 1.42; 95% CI: 1.22–1.63) [36]. Actually, hyperthyroidism alters cardiac ion channel expression and function, increases heart rate and shortens atrial effective refractory period (ERP). The main cellular mechanisms of atrial contractile dysfunction are downregulation of the Ca^{2+} inward current and impaired release of Ca^{2+}. In fact, downregulation of the L-type Ca^{2+} inward current and upregulation of inward rectifier K^{+} currents lead to shortening of action potential duration and atrial EPR, providing a substrate for AF. High levels of thyroid hormones can increase automaticity and enhance

triggered activity in cardiomyocytes from pulmonary veins, resulting in atrial tachyarrhythmias.

In the last few years, many authors have attempted to show that exogenous subclinical hyperthyroidism, due to suppressive doses of L-T4, exerts many significant effects on the cardiovascular system, resulting in cardiovascular dysfunction [34–39]. A population-based prospective study was conducted in Denmark [38]. A total of 609 subjects from general practice, aged 50 years or above, with normal left ventricular function, were examined during a median of 5 years of follow-up. The incidence of stroke was increased among subjects with subclinical hyperthyroidism, HR = 3.39 (95% CI: 1.15–10.00, $P = 0.027$) after adjusting for sex, age, and AF. The authors concluded that subclinical hyperthyroidism seems to be a risk factor of developing major cardiovascular events, especially stroke in older adults from the general population with normal left ventricular function.

Collet et al. [39] performed another large analysis of prospective cohort studies. Individual data on 52,674 participants were pooled from 10 cohorts. Coronary heart disease events were analysed in 22,437 participants from 6 cohorts with available data, and the incidence of AF was analysed in 8711 participants from 5 cohorts. The study results showed that endogenous subclinical hyperthyroidism is associated with an increased risk of coronary heart disease mortality, and incident AF, with highest risks of coronary heart disease mortality, AF and HF when TSH level is lower than 0.10 mIU/L.

However, all these alterations may be reversible or may improve with the achievement of euthyroidism, because an excess of thyroid hormone does not induce cardiac fibrosis. Actually, the goal of thyroid dysfunction treatment is to restore the euthyroid state and avoid potential side effects.

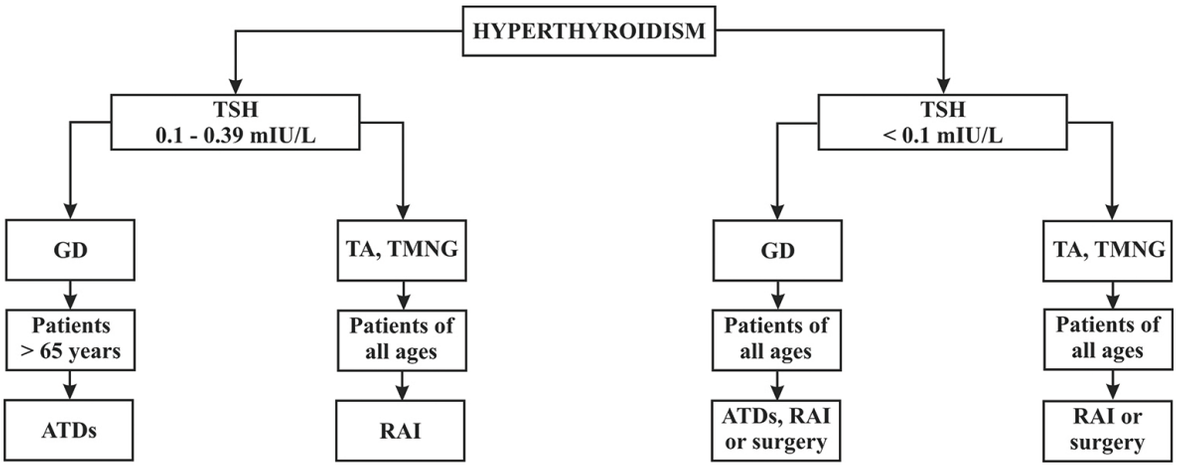

Figure 3. Algorithm for the treatment of hyperthyroidism in patients with atrial fibrillation and/or heart failure. TSH: thyroid-stimulating hormone; GD: Graves' disease; TA: toxic adenoma; TMNG: toxic multinodular goitre; ATDs: antithyroid drugs; RAI: radioactive iodine.

An algorithm for the treatment of hyperthyroidism in patients with AF and/or HF is presented in **Figure 3**. The first-line therapy in patients older than 65 years of age with hyperthyroid-

ism, due to Graves' disease, should be the treatment with anti-thyroid drugs (carbimazole or its metabolite methimazole) in order to obtain spontaneous conversion to sinus rhythm. Ablative therapy (surgery or RAI) is the best treatment option in patients with hyperthyroidism, due to toxic adenoma (TA) or toxic multinodular goitre (TMNG), and concomitant heart disease, as can be seen in **Figure 3**. RAI therapy is much safer than it sounds and has no associated complications [40]. Also, ablative therapy may be recommended for patients with Graves' disease if the treatment with anti-thyroid drugs fails [32]. Nevertheless, HF may become irreversible in some cases of autoimmune hyperthyroid cardiomyopathy with a low ejection fraction [41].

4. Impact of hypothyroidism on heart failure

As shown in **Table 2**, in hypothyroidism, cardiovascular effects are diametrically opposed to hyperthyroidism and cardiac output declines by 30–50% [33]. Hypothyroidism is associated with bradycardia, reduced pulse pressure, cold intolerance, mild diastolic hypertension, and fatigue.

Significant changes in cardiac structure and function have been reported in patients with hypothyroidism, with a severity depending on the degree and length of thyroid hormone deficiency [42–48]. Overt hypothyroidism affects approximately 3% of the adult female population. Overt and subclinical hypothyroidism results in an increased SVR with a reduced cardiac output, a reduction in heart rate, an increased prevalence of hypertension, changes in cardiac natriuretic hormones, changes in lipid profile, accelerated atherosclerosis, damage of the physical and intellectual capacities, and an impaired quality of life. Hypothyroidism is a risk factor of HF in the general population. Several similarities have been observed between acute hypothyroidism and HF, including: decreased cardiac output; decreased cardiac contractility and an altered gene expression profile (alteration in myosin heavy chain isoform expression and alterations in the activity of the sarcoplasmic reticulum Ca^{2+} pump that are induced by its interactions with phospholamban, a reversible inhibitor). In most cases, these changes are the result of reduced T3 level (<3.1 pmol/L), the physiological T3 therapy improving cardiac function.

A systematic review and meta-analysis to clarify the association of hypothyroidism and all-cause mortality, as well as cardiac death and/or hospitalization in patients with HF, was conducted by Ning et al. [49]. They included 13 articles that reported relative risks estimates and 95% confidence intervals for hypothyroidism with outcomes in patients with HF. The authors found hypothyroidism associated with increased all-cause mortality as well as cardiac death and/or hospitalization in patients with HF.

Multiple cardiac effects of hypothyroidism have been reviewed by Biondi and Cooper [50]. Left ventricular diastolic dysfunction was found at rest and exercise in subclinical hyperthyroidism by Doppler echocardiography and radionuclide ventriculography. The isovolumetric relaxation time is prolonged and filling rate is impaired compared with controls. Actually, the most common cardiac abnormality in subclinical hypothyroidism is left ventricular diastolic

dysfunction, characterized by slowed myocardial relaxation, and impaired ventricular filling. Impaired left ventricular systolic function is not commonly reported, but was identified using more sensitive techniques [50]. Cardiac effects due to subclinical hypothyroidism are less serious but somewhat similar to those seen in overt hypothyroidism, suggesting a continuum in the impact of thyroid hormone on the heart. Overt hypothyroidism is usually associated with grade I diastolic dysfunction, but grade II diastolic dysfunction, called "pseudonormal filling dynamics", can also be found [51].

There are also data showing that hypothyroidism results in an increased AF susceptibility (HR = 1.23; 95% CI: 0.77–1.97) [36], quite similar to hyperthyroidism, but affecting other atrial electrophysiological parameters than hyperthyroidism. Hypothyroidism alters cardiac ion channel expression and function, decreases heart rate, and prolongs sinus node recovery time and atrial ERP. In hypothyroid patients, increased atrial interstitial collagen may contribute to longer atrial ERP and lead to increased conduction heterogeneity, thus favouring re-entry formation and AF vulnerability. On the other hand, ion channel remodelling and dispersion may enhance AF arrhythmogenesis.

L-T4 replacement therapy reduces myocyte apoptosis and is able to improve cardiovascular performance and ventricular remodelling in hypothyroidism [52, 53]. It is important to recognize that normal cardiovascular hemodynamic restoration can take place without a significant increase in resting heart rate in the treatment of hypothyroidism. Treatment and management of subclinical and overt hypothyroidism should be tailored to each patient. L-T4 dose varies according to age, weight, severity, and duration of hypothyroidism and cardiac condition of the patient. Treatment of subclinical and overt hypothyroidism with appropriate doses of L-T4 has shown benefits in restoring of normal TSH values (after 6–12 months of substitution therapy). In hypothyroidism, systolic and diastolic functions (left ventricular predominantly) are affected. For patients with systolic and diastolic HF and in the elderly (>70 years), a small dose of L-T4 should be started, 25 or 50 mcg daily. The dose of L-T4 should be increased by 25 mcg/day every three to four weeks until a full replacement dosage is reached. This treatment should be individualized and permanently monitored, the aim being to reach a stable serum TSH around 1–5 mIU/L. A special attention should be given to the oldest old subjects (>80–85 years) with elevated serum TSH ≤ 10 mIU/L. These patients should be carefully followed with a wait-and-see strategy, generally avoiding hormonal treatment [54].

5. Perspectives and conclusions

Thyroid dysfunction is a common clinical problem that has key role in regulating the cardiovascular system and may contribute to the clinical course of CAD, HF, and arrhythmic events. Actually, interrelations between thyroid function and cardiovascular system are manifold. Changes in euthyroid status may induce cardiovascular abnormalities and various cardiovascular pathologies may alter thyroid function. Also, cardiac medication can unbalance or impair thyroid function. These things have to be taken into account in the

assessment and treatment of cardiovascular disease. Thus, thyroid function tests are needed in patients receiving amiodarone and when thyroid dysfunction is considered a possible or concomitant cause of HF.

Secondary cardiovascular events require an early diagnosis to prevent complications and establish a therapeutic conduct, with restoration of euthyroid status. An echocardiogram is necessary to detect ventricular, valvular, and atrial disease. The use of Doppler echocardiography is mandatory to assess cardiac function, pulmonary pressure, valve disease, and pleural or pericardial effusion in symptomatic patients with thyroid dysfunction. It is desirable to use newer echocardiographic methods such as 3D echocardiography or speckle tracking echocardiography for a more accurate assessment of myocardial function, offering a comprehensive approach and a better assessment in the early stages of cardiac dysfunction in patients with impaired thyroid.

Many authors have reported that thyroid dysfunction correction spontaneously converts AF to sinus rhythm in up to two-thirds of patients [36]. Unfortunately, one-third of patients remain in AF despite euthyroid state restoration, radiofrequency (RF) catheter ablation being the only therapeutic option. Normalization of thyroid function prior to the RF ablation reduces the risk of recurrence. Also, recommendations for antithrombotic prophylaxis are the same as for patients without thyroid disease. If thyroid dysfunction persists (i.e. thyrotoxicosis), despite an appropriate treatment, administration of a β-blocker (i.e. β-blockers are useful in cases of thyroid storm) is recommended to control the rate of ventricular response. The β-blocker will be replaced by a non-dihydropyridine calcium channel antagonist (diltiazem or verapamil) if contraindications exist.

The management of thyroid dysfunction in patients who receive left ventricular assist device (LVAD) or cardiac transplantation has not been directly addressed by recent guidelines. Thyroid disease is not a contraindication to transplantation, but is a risk factor. That is why, restoration of the euthyroid state should be the first-step prior LVAD or cardiac transplantation. Unfortunately, drugs administration such as amiodarone and anti-coagulants presents a management dilemma.

In conclusion, correction of thyroid dysfunction should be the first procedure in patients with coexisting cardiac impairment, in order to improve cardiac hemodynamics [24]. Despite message currently taught, thyroid hormones are too dangerous to treat patients, in the last few years, clinical and experimental evidence suggests that thyroid may be a target for HF treatment, thyroid hormone therapy improving clinical outcomes in HF [55–59]. It has been proven that thyroid hormones have anti-apoptotic, anti–inflammatory, anti-fibrotic and anti-remodelling effects, promoting angiogenesis and regeneration [57]. L-T4, L-T3, or thyroid hormone analogue diiodothyropropionic acid (DITPA) have been tested in patients with HF, but unfortunately, the protocols used for thyroid hormones administration were much different, affecting the results. However, preliminary data suggest that thyroid hormone therapy in patients with HF is safe, the benefits being substantial. Further studies are necessary to confirm, highlight, and explore the full potential of the therapeutic use of thyroid hormones in treating and/or preventing HF.

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