Thyroid dysfunction on the heart: clinical effects, prognostic impact and management strategies

Giulia Mattesi[1], Sara Di Michele[2], Donato Mele[1], Ilaria Rigato[1], Riccardo Bariani[1], Andrea Fiorencis[1], Marco Previtero[1], Abdullah Al Sergani[3], Loira Leoni[1], Barbara Bauce[1], Valeria Pergola[1]

[1]Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua Medical School, Padua, Italy; [2]Cardiology Division, San Filippo Neri Hospital, Rome, Italy, [3]King Faisal Specialist Hospital and Research Centre, The Heart Centre, Riyadh, Saudi Arabia

Abstract

Thyroid hormones have a considerable influence on cardiac function and structure. There are direct and indirect effects of thyroid hormone on the cardiovascular system, which are prominent in both hypothyroidism and hyperthyroidism. In this review, we discuss how thyroid dysfunction impacts cardiovascular pathophysiology and the underlying molecular mechanisms.

Correspondence: Giulia Mattesi, Department of Cardiac, Thoracic and Vascular Sciences and Public Health, University of Padua, Via Giustiniani 2, 35128 Padua, Italy.
E-mail: giulia.mattesi@aopd.veneto.it

Key words: hyperthyroidism; hypothyroidism; heart failure; atrial fibrillation.

Contributions: GM, VP, contributed to the design of the work and drafted the manuscript; SDM, MP, AF, AAS, LL, IR, RB, DM, BB, revised the manuscript. All authors have read and agreed to the published version of the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Conflicts of interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: This research received no external funding.

Received for publication: 7 November 2021.
Accepted for publication: 8 March 2022.

Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2022; 92:2145
doi: 10.4081/monaldi.2022.2145

Introduction

The thyroid gland secretes two active hormones: thyroxine (T4) and triiodothyronine (T3). There are direct and indirect effects of thyroid hormones on the cardiovascular system, in both hypothyroidism (HypoT) and hyperthyroidism (HyperT) [1]. This paper aims to describe the clinical effects, the prognostic impact and the screening and management strategies with regard to different patterns of altered thyroid hormones that can be found in cardiac patients.

Recognition and treatment of cardiac disease in patients with thyroid dysfunction

The timely recognition and appropriate treatment of cardiac disease in patients with thyroid dysfunction is mandatory because it has a significant prognostic impact [2,3]. A combination of low serum T3 level and thyroid-stimulating hormone (TSH) within normal range or slightly decreased is called low T3 syndrome, that is a typical pattern of altered thyroid hormone metabolism described in patients with heart diseases. Low T3 status has been demonstrated to be a strong prognostic predictor of death and might be a promising therapeutic target in heart failure patients [4-6]. In HypoT there is a reduction in the heart rate (bradycardia), myocardial contractility (due to a reduced expression of Ca^{++}-ATPase of sarcoplasmic reticulum), and cardiac output. Sometimes pericardial effusions manifest as result of increased vascular permeability. The presence of metabolic disturbances, which ends in cholesterol levels rise, and the altered diastolic pressure increase the risk of coronary artery diseases. Other signs include cardiomegaly, weak arterial pulses, muffled heart sounds, pleural effusion. Angina is rare, even if in the presence of coronary artery disease, because of low oxygen demand, and symptoms may appear when normal thyroid function is restored [7]. Conversely, excess thyroid hormone is associated with symptoms and signs such as palpitations, tachycardia, reduced exercise tolerance, exertional dyspnoea, and atrial fibrillation (AF) [1]. An untreated high-output state owing to HyperT can lead to persistent tachycardia, ventricular dilation, and eventually heart failure (HF), that can result in fatal events [2]. HyperT causes complications such as AF and high-output HF, which can lead to dilated cardiomyopathy in late stages. In a study by Mitchell *et al.*, abnormal thyroid function was associated to a higher risk of mortality in HF patients [3]. The underlying mechanism seems to be the

shift in the synthesis of myosin heavy chain protein from the β to the α form, which makes myocardial contraction less efficient and increases heat production. The direct effects of T3 and the indirect effects of excess lactate production (enhanced tissue thermogenesis) on vascular smooth muscle reduce systemic vascular resistance by 50-70% and the afterload, thus increasing blood flow, particularly to skin, muscle, and heart. The preload rises because blood volume is extended, owing to increased angiotensin converting enzyme and erythropoietin serum concentrations, resulting in increased renal sodium absorption and red cell mass. In HyperT, the left ventricular ejection fraction (LVEF) at rest is high but, paradoxically, it significantly falls during exercise because of the increase in afterload by the additional burden of exercise on a heart working close to its maximum capacity [1]. When euthyroidism is restored, it is noted an anticipated increase in LVEF on exercise at the same workload and heart rate. This sort of reversible "cardiomyopathy" could explain the reduced exercise tolerance of HyperT patients [1]. Beta-adrenergic blockade (to decrease heart rate) and diuretics (to reduce congestion) are important aspects of medical management [7]. Correction of the thyroid dysfunction is also crucial, although the most appropriate treatment method is still debated. Anti-thyroid drugs can improve thyroid function but normally require weeks to control thyroid hormone excess. Frequently, definitive treatment with radioactive iodine ablation or thyroidectomy is performed to recover cardiac function [2,8].

Although HF secondary to HyperT has been traditionally considered a reversible cause of cardiomyopathy [9-11], some reports have demonstrated that cardiovascular symptoms and signs, abnormal haemodynamic, and cardiac arrhythmias can be persistent. This is probably because patient characteristics such as age, comorbidities, and risk factors for cardiac dysfunction can significantly affect the individual response to treatment of thyrotoxic cardiomyopathy.

Heart failure

Recent studies demonstrated that multiple hormone deficiencies (MHD) are common in HF because of excessive activation of neurohormonal pathways, such as sympathetic, renin-angiotensin-aldosterone, and cytokine systems on one side, and concomitant reduction of anabolic hormonal axes on the other side. Particularly, thyroid hormones, together with the somatotropic axis [growth hormone (GH) and insulin-like growth factor-1 (IGF-1)] and anabolic steroids (testosterone and DHEA-S), are downregulated in HF [4]. The presence of MHDS is more pronounced in HF with reduced ejection fraction (HFrEF) rather than in HF with preserved ejection fraction (HFpEF) [4,12]. While its prognostic implication in HFpEF has yet to be established, it is well known its impact in HFrEF [4,12]. MHDS has been associated with increased all-cause mortality and cardiovascular hospitalization. About low T3 syndrome, it has been related to worse cardiovascular performance and increased mortality in HF; thus, it should be considered an important therapeutic target to improve clinical status [4].

Cardiac failure is rare in HyperT, and generally occurs in the context of AF with rapid ventricular response in old patients suffering of a pre-existing heart disease. However, even if uncommon, high output HF is a well-established complication of severe thyrotoxicosis. HF occurs because of the above-mentioned haemodynamic changes caused by high levels of thyroid hormone, that reduces myocardial contractile reserve precluding further increases in cardiac function on exercise. HyperT patients can experience congestive HF without a history of previous cardiac injury. This condition characterized by a paradoxically enhanced cardiac output and contractility due to thyroid hormone excess has been erroneously called "high-output HF" [13]. Symptoms of high-output HF are dyspnoea on exertion, fatigue, peripheral fluid retention with lower limbs oedema, pleural effusion, hepatic congestion, and pulmonary artery hypertension (PAH) [14]. True HF manifests as altered cardiac systolic and diastolic function and pulmonary congestion, as a result of severe and chronic HyperT, tachycardia, and AF [7,14,15]. More precisely, thyrotoxic cardiomyopathy is defined as myocardial damage caused by toxic effects of excessive thyroid hormone. At a molecular level, it is characterized by altered myocyte energy production, intracellular metabolism, and myofibril contractile function. At a macroscopic level, main features are left ventricular hypertrophy, dilation of the heart chambers, diastolic dysfunction, PAH, heart rhythm disturbances, primary AF, and heart failure [16].

In the contest of HypoT, HF is rare in absence of other cardiac diseases, and it is mainly related to severe cases of myxoedema [7].

Pulmonary hypertension

Excess thyroid hormone is common among patients with PAH (approximately 20%) [10]. Though the exact mechanism of PAH in HyperT is unknown, a causal relationship is suggested by its reversibility when the euthyroid state is restored [17]. An autoimmune-mediated process of pulmonary vascular remodelling has been suggested [18]. All PAH patients should be screened for hyperthyroidism, and all HyperT patients complaining of dyspnoea should be screened for PAH [19].

Atrial fibrillation

Palpitations are a common symptom of HyperT. Between 10% and 25% of HyperT patients have AF, especially males aged 60 and older. In younger patients under 40 years of age, AF is uncommon, except if there is a longstanding severe thyrotoxicosis or concomitant structural heart disease [20]. Thus, early thyroid hormone analyses in patients with AF is particularly important [21]. However, in elderly patients, AF may be present even in the absence of a marked elevation of T3 and T4 serum levels: a slight increases of thyroid hormones within their respective reference ranges in association with a suppressed serum TSH concentration (subclinical hyperthyroidism) may be enough to trigger AF in susceptible individuals [22]. In the Framingham study, for example, a low serum TSH was associated with a threefold increase in the incidence of AF among clinically euthyroid elderly subjects, 28% of whom developed AF during 10 years of follow up [23]. In one series, 13% of patients with "idiopathic" or "lone" AF attending a cardiology clinic were found to have altered thyroid function. Therefore, the discovery of an unexplained AF should also prompt a measurement of thyroid hormones [24].

The type of AF is usually persistent instead of paroxysmal [25]. The risk factors for AF in patients with hyperthyroidism do not differ from those in the general population: older age, male gender, coronary artery and valvular heart diseases, congestive heart failure [25]. Other factors also have been associated with the presence of AF in HyperT, including obesity, chronic kidney disease, proteinuria, serum-free T4 concentration, and transaminase

concentrations [26]. Notably, while high free T4 levels have been associated with an increased risk of AF, this is not the same for TSH levels [27]. Multiple mechanisms underlying the development of AF have been suggested, such as elevated left atrial pressure that leads to increased left ventricular mass and impaired ventricular relaxation [28], ischaemia due to cardiac supply/demand mismatch [29], and enhanced atrial ectopic activity [23]. AF begins with ectopic beats originating from the pulmonary veins, and persists through a pathway of re-entry [21]. Moreover, HyperT is associated with coagulation anomalies, such as shortened activated partial thromboplastin time, increased fibrinogen levels, and increased factor VII and factor X activity, all of which confer an enhanced thrombotic risk in these patients [25]. Conversely, HypoT may lead to a hypo-coagulable state with an increased risk of bleeding [30]. In addition, thyroid dysfunction potentially affects responses to oral anticoagulation [31].

The management of hyperthyroid AF is 3-fold: i) treatment of the underlying HyperT; ii) symptoms control; and iii) anticoagulation to avoid stroke.

i) Fortunately, in most (55% to 75%) of patients with AF due to HyperT without other underlying heart disease, rhythm will return sinus after few months from beginning of treatment of their thyrotoxic state [7]. Sixty percent will revert spontaneously to sinus rhythm within a few weeks of normalization of blood tests of thyroid function; in roughly half of the rest, electrical cardioversion will be effective in restoring the sinus rhythm if serum TSH levels are normal or raised at the time of the procedure. Failure to achieve stable sinus rhythm is most likely in those who received a late diagnosis, who are usually patients with mild form of the disease caused by a small multinodular goitre with isolated increase in serum T3 levels (T3 toxicosis) and in whom other useful diagnostic features, such as ophthalmopathy or major weight loss, have been missed.
ii) Hyperthyroid AF typically is not controlled by digoxin effectively, because of an increased renal clearance and volume of distribution of the drug. While waiting for a response to HyperT treatment, non-selective β blockers are the drugs of choice to reach an adequate rate control; non-selective propranolol offers the further advantage of reducing the peripheral conversion of T4 to T3 [7]. HyperT is a pro-thrombotic condition that alters responses to oral anticoagulation, and whether traditional anticoagulation strategies are safe and effective to treat patients with AF and thyroid disease is still debated.
iii) The risk of systemic embolization is increased in hyperthyroid AF, being quantified from 2-20% in cross sectional studies. Age over 50 and valvular or hypertensive heart disease confer the greatest risk. Whether younger patients with no structural heart abnormalities benefit from anticoagulation is a matter of debate, but if transoesophageal echocardiography exclude atrial thrombus, it seems more prudent to withhold anticoagulation. As the development of a dense hemiplegia complicating a readily reversible metabolic disorder is a clinical disaster, anticoagulation with warfarin (target international normalized ratio (INR) 2–3:1) in all patients with hyperthyroid AF seems to be prudent. To note, since HyperT is associated with an enhanced sensitivity to warfarin, anticoagulant control may be challenging [31]. An analysis from the Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trial demonstrated that apixaban was superior to warfarin in patients with and without a history of thyroid disease for the efficacy combined end point of ischaemic or haemorrhagic stroke or systemic embolism and for the safety end point of major bleeding [32].

Subclinical hyperthyroidism and heart

Subclinical hyperthyroidism is defined by the presence of subnormal serum TSH level together with serum free T4 and T3 concentrations within the standard reference ranges [33]. Its prevalence varies from 0.6% to 16% [34]. Notably, persistent subnormal TSH values has to be confirmed within 2 to 3 months from first measure [35]. Subclinical hyperthyroidism is further distinguished into two categories: “Grade 1”, with mildly low but measurable serum TSH levels (0.1-0.45 mIU/L), and “Grade 2”, with even lower concentrations of serum TSH (<0.1 mIU/L). Subclinical HyperT can be exogenous or endogenous. The main exogenous cause is represented by TSH suppressive therapy in patients affected by thyroid carcinoma. Among endogenous aetiologies, autoimmune (lymphocytic) thyroiditis, characterized by the presence of circulating antiperoxidase antibodies, is the most common. This disorder may be associated with coronary artery disease. Indeed, in one *post-mortem* study, lymphocytic thyroiditis was evidenced in 20% of men and 50% of women with fatal myocardial infarction and only 10% of men and women who died from other causes [12]. Major endogenous causes are the same observed in overt HyperT: mild Graves’ disease, multinodular goitre, and autonomous functioning thyroid nodule.

Several studies have demonstrated the adverse effects of subclinical HyperT on cardiovascular health, especially in the elderly. Nanchen *et al.* documented a higher incidence of HF hospitalizations in older patients with subclinical HyperT, particularly in those with “Grade 2” subclinical HyperT [36]. Other studies found a significant correlation between AF and subclinical HyperT and observed an opposite relationship between TSH level and the risk of AF [37]. More importantly, a large retrospective study reported that subclinical HyperT was significantly associated with all-cause mortality and cardiovascular events, with HF as the leading cause of increased major adverse cardiac events [38]. Therefore, the European Thyroid Association indicates treating “Grade 2” subclinical HyperT in patients older than 65 years and to consider treating milder grades if heart disease or other significant comorbidities or risk factors are present [35].

Over replacement with thyroxine?

There is some concern that administering thyroxine in a dose which suppresses serum TSH may provoke significant cardiovascular problems, including abnormal ventricular diastolic relaxation, a reduced exercise capacity, an increase in mean basal heart rate, and atrial premature contractions [17]. Apart from an increase in left ventricular mass index within the normal range, these observations have not been verified [18]. Moreover, there is no evidence, despite the findings of the Framingham study, that a suppressed serum TSH concentration in a patient taking thyroxine in whom serum T3 is unequivocally normal is a risk factor for AF.

Influence of heart disease on thyroid function tests

Acute or chronic heart diseases such as myocardial infarction or congestive cardiac failure may alter thyroid function tests for a variety of metabolic and technical reasons. In these circumstances, peripheral monodeiodination of T4 to T3 is reduced, determining

the so called "low T3 syndrome" and, varying between different assays, serum concentration of free T4 can be normal or increased. During illness, concentrations of TSH can be reduced by central inhibition mechanisms or by drug effects (such as dopamine), while it may rise into the hypothyroid range during recovery. Moreover, some patients with non-thyroidal illness express certain inhibitors in the serum, and possibly also the tissues, that interfere with thyroid hormones physiology. In a large series of hospitalized patients was demonstrated that a low serum TSH concentration as well as raised TSH of greater than 20 mU/l were more likely to be caused by non-thyroidal illness than hyper- or HypoT respectively [39]. In the light of this difficulty of relying upon serum TSH measurements, some would suggest requesting thyroid function testing only if there is good evidence of thyroid disease (i.e., goitre, ophthalmopathy or unexplained AF). Despite all these efforts, there will be occasional patients in whom it is not possible to make an unequivocal diagnosis of thyroid illness, thus a trial of anti-thyroid drugs for three months would be recommended. The biochemical changes (that is, low TSH and low T3) occurring during disease or starvation can be interpreted as an adaptive response to save calories and protein; however, whether chronic illness can produce the potentially harmful entity of "tissue HypoT" is still unknown [40]. Although at present thyroid hormone treatment is not indicated in patients with significant non-thyroidal illness, this has become a debated issue. This is also because some studies showed that in patients with chronic cardiac failure treatment with intravenous T3 or oral T4 improve cardiac output and systemic vascular resistance [41].

Assessment of thyroid function before and during amiodarone treatment

Amiodarone is a very effective antiarrhythmic drug used for the treatment of atrial and ventricular arrhythmias. Due to its high iodine content, it can cause dysthyroidism: HypoT (amiodarone-induced hypothyroidism, AIH), or HyperT (amiodarone-induced thyrotoxicosis, AIT). To reduce the risk of dyshyroidism is recommended before starting treatment with amiodarone to examine patients for the presence of preexisting thyroid disease, Hashimoto's thyroiditis, goitre, or Graves' ophthalmopathy, and to measure serum T3, T4, TSH, anti-peroxidase (microsomal) and, if possible, TSH receptor antibodies [7]. Iodine released from amiodarone metabolism can inhibit thyroid function and if the effect persists it can cause amiodarone induced HypoT. In 2018, the European Thyroid Association published guidelines concerning amiodarone-related thyroid dysfunction management [42]. In case of HypoT, amiodarone withdrawal is not necessary, but the patient should be treated with L-thyroxine therapy, whereas subclinical forms might be followed without treatment [7]. Replacement therapy does not compromise the antiarrhythmic effect. Conversely, the management of patients with amiodarone induced HyperT can be more difficult. HyperT can manifest as type 1 AIT, that is a type of iodine-caused hyperthyroidism occurring in nodular goitres or latent Graves' disease; and type 2 AIT, caused by a destructive thyroiditis in a normal thyroid gland. AIT 1 is treated with antithyroid drugs that may be combined for a few weeks with sodium perchlorate to accelerate control of the thyroid gland. Oral glucocorticoids are recommended as first-line treatment of AIT 2. Notably, while AIT 2 patients are followed up without treatment once euthyroidism has been restored, AIT 1 patients should be treated as other forms of spontaneous hyperthyroidism, and elective thyroidectomy or radioiodine treatment should be done. If cardiac conditions deteriorate rapidly, emergency thyroidectomy may be required for all forms of AIT. The decision to continue or to stop amiodarone in AIT should be tailored in relation to cardiovascular risk stratification and taken jointly by specialist cardiologists and endocrinologists [42]. Measurement of T3, T4, and TSH levels should be measured three and six months after starting amiodarone treatment and every six months thereafter, as well as during the first year after the treatment is interrupted (Figure 1). To note, the best indi-

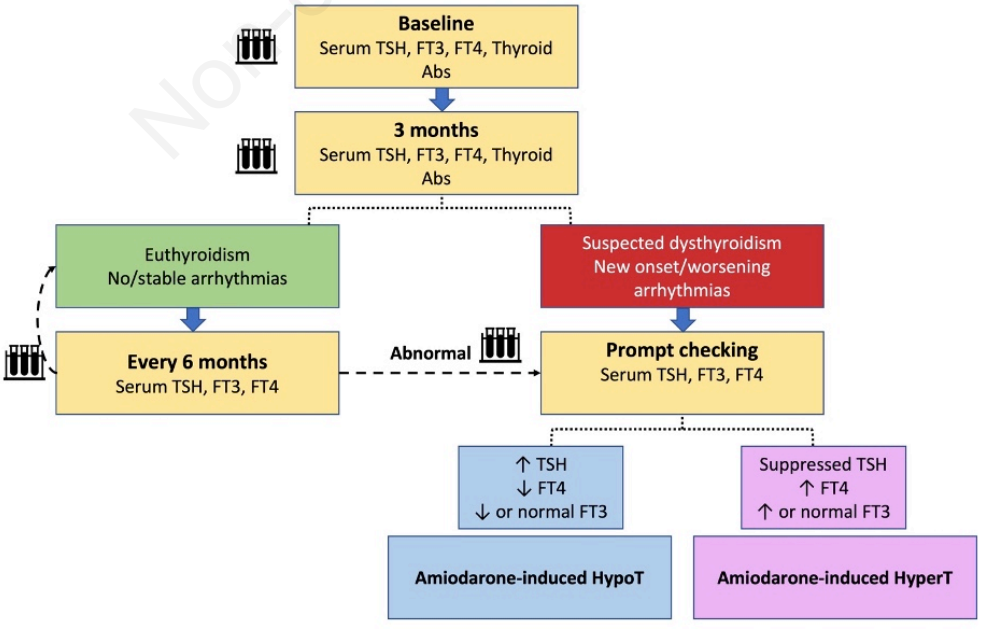

Figure 1. Scheme about the screening of thyroid during amiodarone treatment.

cator of HyperT is serum T3 concentration. In some cases, a test of carbimazole for 6-8 weeks may be required to determine whether the patient is hyperthyroid or not [43].

Conclusions

Hypo- and HyperT cause prominent cardiovascular effects. Low T3-syndrome has been shown to have a substantial impact on prognosis of HF patients. HyperT has been associated with high cardiac output and left ventricular hypertrophy in the early stage and biventricular dilatation and congestive HF in the late stage. AF and PAH also add to the increased morbidity of untreated HyperT. Early and effective treatment of thyroid dysfunction is key in reversing the hemodynamic and cardiovascular abnormalities associated with it.

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