European Journal of Endocrinology (2012) **167** 609–618 ISSN 0804-4643

REVIEW
MECHANISMS IN ENDOCRINOLOGY

Heart failure and thyroid dysfunction

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Abstract

Context: Heart failure (HF) is a major cause of morbidity and mortality in Europe and in the United States. The aim of this review article was to assess the results of the prospective studies that evaluated the risk of HF in patients with overt and subclinical thyroid disease and discuss the mechanism of this dysfunction.

Evidence Acquisition: Reports published with the following search terms were searched:, thyroid, hypothyroidism, hyperthyroidism, subclinical hyperthyroidism, subclinical hypothyroidism, levothyroxine, triiodothyronine, antithyroid drugs, radioiodine, deiodinases, clinical symptoms, heart rate, HF, systolic function, diastolic function, systemic vascular resistance, endothelial function, amiodarone and atrial fibrillation. The investigation was restricted to reports published in English.

Evidence Synthesis: The outcome of this analysis suggests that patients with untreated overt thyroid dysfunction are at increased risk of HF. Moreover, persistent subclinical thyroid dysfunction is associated with the development of HF in patients with serum TSH <0.1 or >10 mU/l.

Conclusions: The timely recognition and effective treatment of cardiac symptoms in patients with thyroid dysfunction is mandatory because the prognosis of HF may be improved with the appropriate treatment of thyroid dysfunction.

European Journal of Endocrinology **167** 609–618

Introduction

Heart failure (HF) is a principal complication of all forms of heart disease (1). The American College of Cardiology defines HF as a complex clinical syndrome that impairs the ability of the ventricle to fill with or reject blood (2). In fact, it may be caused by a defect in myocardial contraction ('myocardial failure'), by an impairment in ventricular filling with preserved systolic function ('diastolic HF') or by a combination of both (3).

HF is a major cause of morbidity and mortality in Europe and in the United States and is responsible for a high rate of hospitalization (4, 5). Despite progress in treating HF in the last 15 years, the prognosis of this dysfunction remains poor (6). In recent years, untreated overt hyperthyroidism and hypothyroidism have been reported to be common causes of HF (7, 8, 9, 10). Moreover, persistent subclinical thyroid dysfunction has recently been associated with the development of HF in patients with and without underlying heart disease (11, 12, 13). Thyroid dysfunction is a modifiable risk factor in patients who are at risk of HF (7, 9).

The aim of this article was to assess the mechanism by which thyroid dysfunction may increase the risk of HF and to examine the prognosis and the potential improvement or regression of HF with the appropriate treatment of thyroid dysfunction.

Mechanism underlying the effect of thyroid hormone on the cardiovascular system

Besides its metabolic and thermoregulatory tissue effects, thyroid hormone regulates cardiac performance by acting on the heart and vascular system (14, 15). The relationship between thyroid hormone and the cardiovascular system has been extensively demonstrated in numerous experimental and clinical studies (14, 15, 16, 17, 18, 19). This association has been recently confirmed by significant changes in cardiac structure and function in patients with persistent subclinical thyroid dysfunction (11, 12, 13, 14, 15, 16).

Triiodothyronine (T_3) is the biological active thyroid hormone; it is mostly generated by 5′-monodeiodination of thyroxine (T_4) in peripheral tissues (20). The availability of T_3, which is the active form of thyroid hormone in the heart, is controlled by the deiodinases,

DOI: 10.1530/EJE-12-0627
Online version via www.eje-online.org

which regulate cardiac levels of T_3 (19, 20). The heart is particularly vulnerable to the reduction in local T_3 levels because T_3 is essential to preserve both cardiac morphology and performance in adult life (16, 17, 18, 19). In fact, thyroid hormone influences cardiac performance by genomic and non-genomic effects and increases cardiac output by affecting stroke volume and heart rate (14, 15). Many of the physiological effects of thyroid hormone are mediated by its genomic nuclear effects. These effects result from the binding of T_3 to specific nuclear thyroid hormone receptors (TRs), which are encoded by the α and β c-erbA proto-oncogene families (14, 15). TRs act by binding as homodimers or heterodimers to thyroid hormone response elements in the promoter region of some genes (14, 15, 21, 22). In the human heart, two TR genes are expressed and each gene generates two isoforms of receptors (TRα1, TRα2, TRβ1 and TRβ2) (14, 15, 21, 22, 23). TRα transcripts are abundant in the heart. TRα1 binds T_3 with high affinity and is thus a functional receptor involved in the regulation of important physiological functions (23). On the contrary, TRα2 acts as a negative regulator because it binds TREs on DNA but does not bind T_3; therefore, it functions by suppressing TRα1 transcription (23). The occupancy of these receptors by T_3, combined with recruited cofactors, allows the thyroid hormone–receptor complex to bind or release specific sequences of DNA that, in turn, modify the rate of transcription of specific target genes (14, 15).

Several important cardiac structural and functional proteins are transcriptionally regulated by T_3, namely, sarcoplasmic reticulum calcium ATPase (SERCA2), α-myosin heavy chain (αMHC), β1 adrenergic receptors, sodium/potassium ATPase, voltage-gated potassium channels, malic enzyme and atrial and brain natriuretic hormone (14, 15). Furthermore, thyroid hormone regulates the transcription of pacemaker-related genes and hyperpolarization-activated cyclic nucleotide-gated channels 3 and 4 and guanine nucleotide regulatory proteins (24). In addition, T_3 modulates the expression of angiotensin receptors in vascular smooth muscle cells (25). Other cardiac genes are negatively regulated by T_3, i.e. βMHC, phospholamban, sodium/calcium exchanger, TRa1 and adenylyl cyclase type V and VI (14, 15).

The non-genomic effects exerted by TH on cardiac myocyte and peripheral vascular resistance are the effects that do not require the binding to nuclear receptors (26). These effects start very quickly and involve the transport of ions (calcium, sodium and potassium) across the plasma membrane, glucose and amino acid transport, mitochondrial function and a variety of intracellular signalling pathways (15, 26).

Thyroid hormones have a pro-angiogenic effect in adult heart and can stimulate arteriolar growth in normal heart as well as after myocardial infarction (27, 28). The pro-angiogenic actions of thyroid hormones occur via both non-genomic and genomic mechanisms (29). Their angiogenic effect starts at the cell surface integrin receptor ($\alpha_v\beta3$). Integrin $\alpha_v\beta3$ contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen-activated protein kinase and induction of angiogenesis (30). Vascular endothelial growth factor and fibroblast growth factor are implicated in thyroid hormone-induced angiogenesis (31). TRβ is required for angiogenesis during cardiac development (32). Thyroid hormones are powerful regulators of vessel overgrowth in the hypothyroid state; they promote coronary arteriolar and capillary growth (33).

Cardiovascular function in hyperthyroidism

Short-term hyperthyroidism is characterized by a high cardiac output state with a remarkable increase in heart rate and cardiac preload and a reduction in peripheral vascular resistance, resulting in a hyperdynamic circulation (15, 16, 34). Cardiac preload (left ventricular end diastolic volume) is increased as a consequence of the increase in blood volume and the improvement in diastolic function (15, 34). The improvement in diastolic relaxation in the presence of T_3 is due to the down-regulation of phospholamban by increasing its phosphorylation and the upregulation of SERCA2 (35). Moreover, T_3 promotes relaxation of the peripheral vasculature. It decreases systemic vascular resistance indirectly by affecting tissue thermogenesis and directly by acting on vascular smooth muscle cells and endothelial nitric oxide production (14, 15, 36). The reduction in system vascular resistance is responsible for the decrease in renal perfusion pressure and for activation of the renin–angiotensin–aldosterone system (RAS), with a consequent increase in sodium absorption and blood volume (14, 15). Therefore, the hyperthyroid heart increases its performance through the modulation of hemodynamic loads (15, 37). This positive effect on energy metabolism and oxygen consumption improves the left ventricle mechanical efficiency of the hyperthyroid heart by optimizing its cardiac mechanical energetic utilization (15, 37).

In experimental studies, thyroid hormone treatment induced physiological cardiomyocyte hypertrophy by acting on intracellular signalling pathways (38). In humans, long-term exposure to thyroid hormone excess may exert unfavourable effects on cardiac morphology and function because it may increase left ventricular mass, arterial stiffness and left atrial size and may induce diastolic dysfunction, thereby impairing left ventricle performance (9, 39). However, these alterations may be reversible or may improve when euthyroidism is restored because thyroid hormone excess does not induce cardiac fibrosis (9).

Table 1 'High-output' HF in hyperthyroidism.

Congestive circulation may occur with increased cardiac output in the absence of underlying heart disease due to the effects of:
Persistent tachycardia
Increased cardiac preload
Reduced systemic vascular resistance
Elevated ventricular filling pressure
Increased pulmonary arterial pressure

HF in hyperthyroidism

Knowledge regarding the mechanism by which thyroid hormone may induce HF is an important issue for both endocrinologists and cardiologists. Patients with overt and subclinical hyperthyroidism (SHyper) are at increased risk of cardiac death, although the exact mechanism leading to this effect is not well established (40, 41, 42). The increased risk of cardiac mortality might be a consequence of the increased risk of atrial arrhythmias (43) and of the risk of HF in these individuals (10), especially in elderly patients. In particular, thyrotoxic atrial fibrillation has been associated with an increased risk of cerebrovascular and pulmonary embolism (44, 45). Importantly, autoimmune hyperthyroidism has been frequently linked to autoimmune cardiovascular involvement; therefore, pulmonary arterial hypertension, myxomatous cardiac valve disease and autoimmune cardiomyopathy have been reported in patients with Graves' disease (9).

Hyperthyroid patients complain of exercise intolerance and dyspnoea during effort due to the inadequate increase in cardiac output during exercise (9, 37, 39, 46). Thus, impaired exercise tolerance can be interpreted as the first symptom of HF in hyperthyroid patients; it is the sign that the hyperthyroid heart cannot further accommodate the increase in cardiovascular demand during physical exercise (9, 46). The onset of negative changes in the loading conditions, the loss of sinus rhythm or the depression of myocardial contractility may further impair the efficiency of the cardiovascular system in hyperthyroid patients, thereby inducing congestive HF. The development of orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema and neck vein distension may indicate the progression to advanced HF. However, the clinical manifestations and degree of HF in hyperthyroid patients depend on a variety of factors, namely the patient's age, the cause and severity of hyperthyroidism and the underlying cardiac conditions. Many groups have assessed the association of overt hyperthyroidism with HF (47, 48, 49, 50, 51, 52, 53).

Patients with severe hyperthyroidism may develop a 'high-output HF' (47). However, HF is not really the appropriate term because cardiac output is increased, although congestive circulation is present (47). The development of high-output HF in thyrotoxicosis may be due to 'tachycardiac-mediated cardiomyopathy' (54). In young hyperthyroid patients, this condition is not associated with an underlying heart disease and the heart is intrinsically normal. In fact, the symptoms and signs of HF occur in the setting of an increased cardiac output with normal systolic function and low systemic vascular resistance, whereas blood volume is increased due to the chronic activation of the RAS and, consequently, cardiac preload is enhanced (Table 1). Patients with high-output HF may have symptoms such as breathlessness at rest, fatigue and fluid retention with peripheral oedema, pleural effusion, hepatic congestion and increased pulmonary arterial hypertension.

No clinical trials have been conducted regarding treatment of high-output HF in patients affected by hyperthyroidism. Several case reports suggest that treatment with β-blockers and diuretics may improve the congestive circulatory symptoms in these patients (9, 54). On the other hand, an untreated high-output state and undiagnosed hyperthyroidism may lead to ventricular dilatation and persistent tachycardia, which can trigger chronic HF and fatal events (55).

The risk of low-output HF in hyperthyroid patients has been reported to be between 6 and 15% (10, 56, 57, 58, 59). Elderly hyperthyroid patients may develop HF accompanied by a low ejection fraction. In this condition, cardiac output is low, systemic vascular resistance is increased, left ventricular contractility is reduced and left ventricular filling is impaired, whereas blood volume is increased (Table 2). The risk of HF and low ejection fraction is increased in hyperthyroid patients with underlying heart disorders such as coexistent ischaemic, hypertensive or valvular disease and/or atrial fibrillation. About 7–8% of middle-aged hyperthyroid patients may develop atrial fibrillation or flutter; this risk may further increase to 10–20% in elderly patients and up to 20–35% in hyperthyroid patients with coexistent ischaemic heart disease or heart valve disease (9, 43). In a cohort of 591 consecutive patients with hyperthyroidism due to different causes, HF was present in 6% of cases (10). Multivariate analysis showed that atrial fibrillation at presentation was an independent predictor of congestive HF (odds ratio 37.4, 95% CI, 9.72–144.90; $P<0.001$) (10). However, in one study, only 50% of hyperthyroid patients with congestive HF were reported to have impaired left ventricular systolic function (50). Diastolic dysfunction may play an important role in the development of diastolic HF in some hyperthyroid

Table 2 'Low-output' HF in hyperthyroidism.

HF with low cardiac output may occur especially in elderly patients and in patients with underlying heart disease due to the effects of:
Increased cardiac preload
Impaired left ventricular filling
Loss of atrial contribution to atrial fibrillation
Rapid ventricular rate
Increased systemic vascular resistance
Decreased contractile reserve

patients with preserved left ventricular ejection fraction; this condition is usually common at an older age (50). In the same study, increasing age was the only independent predictor for the development of diastolic dysfunction and HF in hyperthyroid patients (50).

HF usually improves in hyperthyroid patients when euthyroidism is achieved. In fact, euthyroidism results in a rapid clinical improvement of cardiac function and symptoms of congestive HF. However, HF may become irreversible in some cases (10). Approximately, one-third of patients may develop hyperthyroid cardiomyopathy (10). Reversible and irreversible dilated cardiomyopathy with a low ejection fraction has been reported in patients affected by autoimmune hyperthyroidism (51). The autopsies in some of these patients have shown findings consistent with idiopathic dilated cardiomyopathy due to an autoimmune origin (60, 61, 62).

Although systemic vascular resistance and diastolic blood pressure are decreased in hyperthyroid patients, the mean pulmonary arterial pressure is usually increased (63). There is a strong relationship between hyperthyroidism and pulmonary hypertension, and hyperthyroid patients may develop right ventricular failure (63, 64, 65, 66, 67, 68, 69, 70). In several case reports, isolated right HF, severe right ventricle volume overload and tricuspid regurgitation have been attributed to hyperthyroidism (52, 53, 64, 65, 66). Recent studies have suggested an autoimmune link between pulmonary arterial hypertension and Graves' disease as a consequence of immune-mediated endothelial damage or dysfunction (9). The proportion of patients with pulmonary arterial hypertension has been estimated to be between 40 and 94% in prospective studies of patients with autoimmune thyroid disease (9). Pulmonary arterial hypertension, resulting in right HF, could be underestimated in hyperthyroidism because it is usually reversible with the achievement of euthyroidism.

HF and amiodarone-induced hyperthyroidism

The administration of amiodarone, an antiarrhythmic agent, may induce thyroid dysfunction (71). Patients with amiodarone-induced thyrotoxicosis (AIT) are at a high risk of developing adverse cardiac events (72). In a recent study, the presence of AIT and impaired left ventricular ejection fraction has been associated with a particularly high risk of developing major adverse cardiovascular events such as cardiovascular mortality, myocardial infarction, stroke and HF or ventricular arrhythmias with a hazard ratio (HR) of 3.18 (72). These results suggest that amiodarone should be used with caution, especially in patients with hyperthyroidism and impaired left ventricular ejection fraction. A recent study showed that more than 70% of major adverse cardiovascular events occurred within 3 months after the diagnosis of AIT (72).

HF and SHyper

Few studies have assessed the risk of HF in patients with SHyper. The Cardiovascular Health Study, a population-based study of healthy people, evaluated the risk of HF in 46 patients with SHyper, with a mean age of 72.6 years, with low or undetectable serum TSH (11). Although statistically significant echocardiographic abnormalities were observed in the 46 patients, no correlation was found between SHyper and the risk of HF.

The onset of SHyper can exacerbate the cardiovascular risk in patients with underlying heart disease (9, 13); it is an independent predictor of cardiac death in patients with congestive HF and especially in subjects with toxic multinodular goitre (13). In the recent Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), SHyper (TSH <0.1 mU/l) was associated with an increased incidence of HF in older patients with a history of cardiovascular disease (12). This prospective European study showed that mild thyroid hormone excess also increases the incidence of HF in patients aged between 72 and 82 years (mean age 75.3 years) at high risk of cardiovascular disease, particularly in the presence of serum TSH <0.10 mIU (12). SHyper might contribute to HF by increasing heart rate and left ventricle size, by impairing diastolic function and by causing atrial fibrillation (37, 39). Interestingly, no link was found between AF and HF in the PROSPER study (12).

The pooled data of six prospective cohort studies were recently analysed in the attempt to clarify the association between SHyper and HF events (73). Among the 648 participants with SHyper, the HR for HF events in age- and gender-adjusted analyses was 1.46 (CI, 0.94–2.27) compared with euthyroid subjects during a median follow-up of 10.4 years. These data suggest that the risk of HF is significantly increased in patients with undetectable serum TSH (HR 1.94, CI, 1.01–3.72) (73).

Prevention and treatment of HF in hyperthyroidism

The timely recognition of overt and SHyper may improve the prognosis of HF in hyperthyroid patients. Therefore, thyroid function tests should be performed in patients without pre-existing cardiac disease who have no other identifiable causes of HF, atrial fibrillation, pulmonary hypertension and dilated cardiomyopathy. In addition, the high morbidity and mortality that occur during the early phase of AIT supports the need for close, serial monitoring of thyroid function in patients receiving amiodarone. Clinical examination, thyroid Doppler ultrasonography, assessment of radioiodine uptake and interleukin-6 may help to identify the causes of hyperthyroidism in patients with HF.

The correction of thyroid dysfunction should be the first procedure carried out in hyperthyroid patients with

HF. Antithyroid drugs may improve thyroid function, although some weeks might be necessary to control thyroid hormone excess (9). Definitive treatment of hyperthyroidism is usually performed to recover cardiac function (42, 74, 75). Nevertheless, a trend towards increased cardiac mortality has been reported in treated hyperthyroid patients (40). Thus, the correct way to treat hyperthyroid patients with HF or cardiac involvement remains to be clarified. Recent data suggest that total thyroidectomy may rapidly restore euthyroidism, thereby improving cardiac function and reducing the risk of mortality in AIT patients with severe left ventricular dysfunction (76).

The prevention of the severe cardiac complications of hyperthyroidism (atrial fibrillation, HF and embolic events) should be considered to counteract the cardiovascular mortality associated with thyroid hormone excess. Doppler echocardiography may be the most useful diagnostic test in the evaluation of hyperthyroid patients with HF. In fact, this technique is used to assess the left ventricular ejection fraction, to evaluate the structure of the LV and to estimate other structural abnormalities such as valvular, pericardial or right ventricular abnormalities that could account for the clinical presentation. Therefore, this technique is mandatory in hyperthyroid patients with suspected heart disease.

Prompt, effective treatment of cardiac manifestations in symptomatic patients with hyperthyroidism is important because cardiovascular complications account for most of the deaths in hyperthyroid patients. The management of HF in hyperthyroid patients is difficult because symptoms of HF may be linked to heterogeneous entities. HF may be the complication of atrial fibrillation or sinus tachycardia and may be improved or resolved when the ventricular rate is slowed or sinus rhythm is restored. In patients with hyperthyroidism and atrial fibrillation, initial therapy should aim at controlling ventricular rate using β-blockers. These drugs should be used early and in doses able to control the heart rate to a nearly normal level in order to improve the tachycardia-mediated component of left ventricular dysfunction.

The treatment of HF in elderly cardiac patients is difficult. Treatment of these patients should aim at improving cardiac hemodynamics, controlling the ventricular rate and preventing thromboembolism in the presence of atrial fibrillation. Hospitalization is required to start routine therapy for HF in patients with known preexisting left ventricular dysfunction and in patients in whom HF does not improve when heart rate is normalized.

Cardiovascular function in hypothyroidism

The transition from the foetal to the adult phenotype heart depends on the increase in thyroid hormone in the perinatal stage (7). Moreover, normal thyroid hormone levels are required in adult life to maintain normal cardiovascular function (7, 17, 18, 19). T_3 controls the inotropic and lusitropic properties of the myocardium, cardiac growth, myocardial contractility and vascular function (14, 15).

Chronic hypothyroidism in adult rats leads to the loss of coronary arterioles and impaired blood flow; it induces maladaptive changes in the shape of myocytes and the development of HF (19). Important changes in cardiac structure and function have been reported in patients with overt and subclinical hypothyroidism (SHypo) with a severity depending on the degree and the duration of thyroid hormone deficiency (14, 15, 16, 77, 78, 79). Hypothyroidism is characterized by a low cardiac output due to the decreased heart rate and stroke volume (15, 16). Systolic and diastolic functions are reduced at rest and during exercise, thus impairing quality of life (80). Cardiac preload is decreased due to the impaired diastolic function and the decreased blood volume (78). Vascular function may also be deranged in overt and mild thyroid hormone deficiency (78, 79, 81). Renal perfusion is decreased with a consequent reduction in glomerular filtration, impaired free water clearance and hyponatremia (15). The cardiac energetic efficiency of the hypothyroid human heart is impaired despite its reduced cardiac oxygen consumption (15). Moreover, important metabolic effects may develop in long-term untreated hypothyroidism (74, 75). An increased cardiovascular risk has been reported in patients with various degrees of hypothyroidism (74, 75). This may be linked to the increased risk of coronary artery disease and HF associated with hypothyroidism (11, 82, 83). In particular, an increased risk of coronary heart disease events and mortality has been reported in young patients affected by SHypo with TSH >10 mU/l (83, 84).

HF and hypothyroidism

Thyroid hormone deficiency may be responsible for an increased risk of HF events (11, 12) (Table 3). Experimental studies have demonstrated that hypothyroidism causes cardiac atrophy due to decreased αMHC expression and increased βMHC expression. Moreover, hypothyroidism leads to chamber dilatation and impaired myocardial blood flow (7, 17, 18, 19).

Table 3 Mechanism of HF in hypothyroidism.

HF may occur in patients with overt hypothyroidism and in elderly patients with subclinical hypothyroidism with TSH >10 mU/l due to the effects of:
Bradycardia
Impaired systolic function
Impaired left ventricular diastolic filling
Increased systemic vascular resistance
Diastolic hypertension
Increased arterial stiffness
Endothelial dysfunction

In an early study, myxoedema and congestive HF were diagnosed in a patient affected by hypothyroidism (86). The manifestations of myxoedema and HF improved during therapy with desiccated thyroid. More recently, cases of hypothyroidism and reversible dilated cardiomyopathy have been reported (87, 88). Changes in myocardial gene expression (αMHC and phospholamban) were documented by measuring mRNA extracted from endomyocardial biopsy specimens of a hypothyroid patient with dilated cardiomyopathy before and after T_4 replacement therapy (88). In this patient, the administration of thyroid hormone with restoration of euthyroidism produced an increase in αMHC gene expression with a trend towards the β-to-αMHC shift, which in turn led to an improvement in cardiac function and reversible cardiomyopathy (88).

Thyroid hormone metabolism is altered in HF, cardiac surgery and myocardial infarction. The conversion of T_4 to T_3 is impaired and a low serum T_3 syndrome may develop in cardiac dysfunction (7, 89, 90, 91, 92). This condition is a strong predictor of mortality in patients with severe heart disease (7, 89, 90, 91, 92). The failing heart develops alterations in gene expression that are similar to those induced in experimental hypothyroidism, suggesting that TH dysfunction may play an important role in the progression of HF (22).

HF in SHypo

A growing body of clinical evidence suggests that SHypo may lead to HF (11, 12, 73, 82). The Health Aging and Body Composition population-based study showed that patients (aged 70–79 years) with TSH level 7 mU/l or greater, who were monitored for 4 years, had a higher risk of HF events than euthyroid patients (82). In the multivariate analysis, the HR was 2.58 (CI, 1.19–5.60) for patients with a TSH level between 7.0 and 9.9 mU/l and 3.26 (CI, 1.37–7.77) for patients with a TSH level of 10.0 mU/l or greater. Among the 127 patients who had HF, 51 had recurrent HF events.

The Cardiovascular Health Study performed routine echocardiography over 6 years of follow-up in 3065 subjects aged 65 years or over to identify the risk of HF (11). Individuals with TSH levels of 10 mU/l had a higher peak E velocity (after adjusting for age, HR, gender and systolic blood pressure), which was associated with incident HF (HR 1.14 for each 0.1 m/s increment; 95% CI, 1.09–1.18; $P<0.001$). During the follow-up, patients with a TSH level of 10 mU/l or greater had a higher risk of HF events with low ejection fraction compared with euthyroid participants (80 vs 45% $P=0.08$; HR 1.88; CI, 1.05–3.34). The risk of congestive HF was not increased among older adults with TSH levels between 4.5 and 9.9 mU/l (11).

These results indicate that SHypo with TSH >10 mU/l is an important risk factor for HF in older adults. These data were recently confirmed by a meta-analysis of six prospective cohort studies for a total of 2068 patients with SHypo (73). In fact, the risk of HF events was increased in patients with TSH levels higher than control values, and there was a statistically significant risk of HF among patients with a TSH level >10 mU/l (HR 1.86; CI, 1.27–2.72). The risk of HF persisted after exclusion of patients with pre-existing HF or pre-existing atrial fibrillation (73).

Some studies suggest that SHypo is a risk factor for cardiac death in patients with chronic HF (12, 94, 95). In PROSPER, patients with persistent SHypo had an increased rate of HF hospitalization compared with euthyroid controls with an age- and sex-adjusted HR of 4.99 (95% CI, 1.59–15.67) (12). In the 38 patients with SHypo with TSH levels above 10 mU/l, the incidence of HF was significantly higher in the age- and sex-adjusted model than in euthyroid subjects (HR, 3.01; 95% CI, 1.12–8.11) (12).

Treatment of HF in hypothyroid patients

Thyroid function should be evaluated in patients with HF and non-ischaemic dilated cardiomyopathy to determine whether hypothyroidism and low T_3 syndrome caused the cardiac disease. In fact, hypothyroidism is a reversible cause of HF. The American College of Cardiology guidelines for HF recommend screening of serum thyrotrophin levels for all cases of newly diagnosed HF (1).

The administration of replacement doses of L-T_4 reduces myocyte apoptosis and is able to improve cardiovascular performance and ventricular remodelling in experimental hypothyroidism (7, 18, 89, 96). This is in line with the results of some randomized and placebo-controlled studies that demonstrated

Table 4 Clinical practice suggestions for the prevention and treatment of HF in patients with thyroid dysfunction.

1. Thyroid function tests are indicated in patients receiving amiodarone and when thyroid dysfunction is considered a possible or concomitant cause of congestive HF, atrial fibrillation, pulmonary hypertension, dilated cardiomyopathy or coronary heart disease (e.g. patients without pre-existing cardiac disease or other identifiable causes of these disorders)
2. Correction of thyroid dysfunction should be the first procedure in patients with HF
3. Definitive treatment should be performed to recover cardiac function in patients with hyperthyroidism
4. Doppler echocardiography is mandatory to assess cardiac function, pulmonary pressure, valve disease and pleural or pericardial effusion in symptomatic patients
5. Prompt, effective treatment of cardiac manifestations should be initiated in patients with thyroid dysfunction to improve cardiac hemodynamics
6. Hospitalization is required to treat HF in patients with pre-existing left ventricular dysfunction or when HF does not improve upon restoration of euthyroidism

improvement of cardiovascular function in patients with mild and SHypo after replacement doses of L-T_4 (74, 75, 79, 97, 98). Diastolic dysfunction due to slowed myocardial relaxation and impaired ventricular filling is reversible after replacement therapy. Moreover, vascular function (systemic vascular resistance, arterial stiffness and endothelial function) and coronary flow reserve may improve significantly when euthyroidism is restored (74, 75, 79, 97, 98). The risk of HF was significantly lower in T_4-treated patients than in untreated patients during the follow-up in the Cardiovascular Health Study (11). Patients with TSH >10 mU/l had an increased risk of HF during the periods of L-T_4 withdrawal than during its use (11). This observation indicates that replacement doses of L-T_4 may reduce the risk of HF. Consequently, it appears that replacement doses of L-T_4 should be considered in patients with SHypo and TSH>10 mU/l to prevent the risk of HF events (74, 75). However, about 20% of patients with hypothyroidism may be over-treated during replacement therapy (99). An increased risk of atrial fibrillation may develop in elderly patients with suppressed serum TSH during L-T_4 therapy (100, 101). The potential adverse effects of iatrogenic SHyper suggest that serum TSH should be normalized according to the age (74); a higher TSH level should be reached during replacement treatment with L-T_4 in elderly subjects (74, 75, 102). Randomized controlled studies are necessary to evaluate the efficacy of L-T_4 administration in preventing the risk of HF and its negative prognosis in patients with overt and SHypo.

Some studies suggest that replacement doses of T_3 may improve cardiovascular remodelling and function in patients with HF and low T_3 syndrome (7, 89). Further studies are necessary to assess the potential therapeutic use of THs and their analogues in treating or preventing HF (103, 104).

Conclusion

This assessment of the mechanisms that may lead to HF in patients with thyroid dysfunction confirms the link between thyroid hormone and cardiovascular function. This, in turn, reinforces the importance of early detection and effective treatment of cardiac abnormalities in patients affected by thyroid disorders (Table 4). Close cooperation between endocrinologists and cardiologists to identify the best treatment options is essential if we are to improve the prognosis of severe cardiac involvement in patients with overt and subclinical thyroid dysfunction.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 22 July 2012
Revised version received 1 September 2012
Accepted 5 September 2012