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Hypothyroidism and Heart Failure: Epidemiology, Pathogenetic Mechanisms & Therapeutic Rationale

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Abstract

Heart Failure (HF) is a major public health problem and a major cause of morbidity and mortality worldwide. Thyroid hormones (TH) have multiple effects on the heart and cardiovascular system. In recent years, studies have shown that hypothyroidism, including subclinical hypothyroidism, is associated with an increased risk for developing and worsening of HF. This review addresses the relationship between HF and hypothyroidism by highlighting the epidemiology, pathophysiology and management.

Keywords

Heart failure; Hypothyroidism; Subclinical hypothyroidism; Pathogenesis

Introduction

Heart failure (HF) is a clinical syndrome characterized by structural and/or functional impairment of ventricular filling or ejection of blood resulting in insufficient perfusion to meet metabolic demands. There is no single diagnostic test for HF, it is a clinical diagnosis based on history, physical examination, laboratory and imaging parameters [1]. Thyroid hormones (TH) have numerous effects on body systems, especially the heart and cardiovascular system including effects on the relaxation and contractile properties of the heart and are critical in preserving cardiac structure [2]. In recent years, studies have shown that alterations in TH are associated with a wide spectrum of cardiovascular diseases - specifically, hypothyroidism and subclinical hypothyroidism have been reported to be associated with increased incidence and worsening of HF, with and without underlying heart disease [3,4]. The aim of this review is to evaluate the effects of hypothyroidism and subclinical hypothyroidism. We will also discuss the postulated mechanisms that may induce and/or exacerbate HF and highlight the appropriate management strategies.

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Competing Interests

The authors declare that they have no competing interests.

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Prevalence of Decrease T3/HF/Subclinical and Associations (Prevalence of Hypothyroidism/Subclinical Hypothyroidism in HF)

Nearly 10 million people (4.6%) in the United States have hypothyroidism. Most of them are asymptomatic, i.e. with subclinical hypothyroidism (4.3%). In iodine-replete communities, the prevalence of spontaneous hypothyroidism is between 1 and 2%, and it is 10 times more common in women than in men, and particularly prevalent among older women. Studies in Northern Europe, Japan and the USA have found the prevalence to range between 0.6 and 12 per 1000 women and between 1.3 and 4.0 per 1000 in men investigated [5].

Tunbridge et al. conducted a study in Whickham, England to determine the prevalence of thyroid disorders in the community and reported that 7.5% of women and 2.8% of men of all ages had thyroid stimulating hormone (TSH) levels greater than 6 mlU/L. After reviewing 12 studies across different cultures, the Whickham study concluded that primary thyroid gland failure (TSH>6 mlU/L) is 5% in multiple populations [6]. Moreover, in the Colorado Thyroid Disease Prevalence Study, 9.4% of the subjects had a high-serum TSH concentration, of whom 9.0% had subclinical hypothyroidism [7]. Among those with an elevated serum TSH concentration, 74% had a value between 5.1 and 10 mlU/l and 26% had a value > 10 mlU/l. Women had a higher percentage of high serum TSH concentration versus men in each decade of age, and ranged from 4 to 21% in women and 3 to 16% in men.

The National Health and Nutrition Examination Survey, composed of 4392 participants conducted between 1999–2002, noted a 3.7% prevalence of hypothyroidism in the general population. It also demonstrated that the serum TSH concentrations increased with age in both men and women and were higher in whites than in blacks, independent of serum anti-thyroid antibody concentrations [8,9].

Heart failure (HF) has been considered an epidemic and a global health problem, with a prevalence of over 5.8 million in the USA and over 23 million worldwide [10]. The estimates of HF prevalence in developed countries generally range from 1–2% of the adult population [11]. Although the age-adjusted incidence and prevalence of HF are decreasing, the absolute number of patients with HF has drastically increased, secondary to shifts in the global age distribution, increased life expectancy, medical advancement and general population growth [12]. HF incidence has shown signs of stabilization and possible reduction in developed countries based on community-based cohorts, such as Framingham and Olmstead county [13,14]. However, the incidence of HF varies between ethnic groups in the USA. The Multi-Ethnic Study of Atherosclerosis reported the highest incident rates of HF among African-American individuals, intermediate rates among Whites and Hispanic individuals, and the lowest rates among Chinese-American individuals [15].

Ning et al. conducted a meta-analysis including 19,354 subjects with HF, 2173 with hypothyroidism, to clarify the association of hypothyroidism and all-cause mortality and morbidity in patients with HF. The analysis reported that hypothyroidism and subclinical hypothyroidism were associated with increased all-cause mortality even after correction with

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thyroid replacement therapy. Moreover, hypothyroidism and subclinical hypothyroidism were associated with increased risk of hospitalization in HF patients [3].

Pathophysiology of Decrease T3 and Effect on HF

The American College of Cardiology defines HF as a complex clinical syndrome that impairs the ability of the ventricle to fill with or eject blood [16]. In recent years, studies have shown that untreated overt hypothyroidism is an important cause of HF [3,17]. Moreover, persistent subclinical hypothyroidism has been associated with the development of HF in patients with and without underlying heart disease [18].

Thyroid gland produces and releases hormones mostly as the prohormone thyroxine (T4). triiodothyronine (T3), the biological active thyroid hormone, derives from the conversion of T4 by deiodinase enzymes. Three deiodinase enzymes regulate circulating and tissue concentration of THs: type 1 (D1); type 2 (D2), and type 3 (D3). D1 is considered the major peripheral source of circulating T3 and is commonly found in the liver and the kidney, whereas D2 plays a critical role in providing local conversion to T3in the heart, skeletal muscles, brain and pituitary tissues. D3 is involved in the inactivation and degradation of T3 [19]. Due to the necessity of T3 in preserving both cardiac morphology and performance in adult life, the heart is sensitive to reductions in local T3 levels.

Genomic nuclear effects of thyroid hormones initiate most of physiologic effects in humans. T3 binds to specific nuclear thyroid hormone receptors (TRs), which subsequently bind as homodimers or heterodimers to thyroid hormone response elements in the promoter region of some genes [20–22]. There are two isoforms of receptors generated by two TR genes in the heart. TRa1 transcripts binds to T3 with high affinity and acts as a positive regulator, whereas TRa2 acts as a negative regulator as it binds TREs but does not bind to T3 [20–23].

There are many cardiac structures that are transcriptionally regulated by T3, such as sarcoplasmic reticulum calcium ATPase (SERCA2), alpha - myosin heavy chain (αMHC), B1 adrenergic receptors sodium/potassium ATPase, voltage-gated potassium channels, malic enzyme and atrial and brain natriuretic hormone [20,21]. Other cardiac genes are negatively regulated by T3 namely βMHC, phospholamban, sodium/calcium exchanger, TRa1 and adenylyl cyclase type V and VI [20–21]. However, T3 also has non genomic effects on cardiac myocyte and peripheral vascular resistance. These effects involve the transport of ions across the plasma membrane, glucose and amino acid transport and mitochondrial function [21,23].

The effects of T3 allow it to have control on the inotropic and lusitropic properties of the myocardium and have an influence on cardiac growth, myocardial activity and vascular function. As a result, thyroid hormone deficiency is likely responsible for an increased risk of HF events, by causing cardiac atrophy, chamber dilation and impaired myocardial blood flow. (Figure 1)

Cases of hypothyroidism and reversible dilated cardiomyopathy have been reported. Changes in αMHC expression by measuring mRNA, extracted from endomyocardial biopsy, of a hypothyroid patient with dilated cardiomyopathy before and after T4 replacement

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therapy. The administration of thyroid hormone therapy and restoration of euthyroidism produced an increase in αMHC gene expression and reversed the cardiomyopathy [24].

Relation of Decreased T3 and Other Heart Diseases

The total thyroid hormones produced by the thyroid gland is 80% thyroxine (T4) and 20% triiodothyronine (T3), however the concentration of T3 in the plasma is 1/40 of T4. Thyroxine has an intrinsic effect whereas T3 is necessary for all metabolic activities and used by all organs. In general, the effects of low T3 are essentially the opposite of hyperthyroidism, with indirect and direct effects on the heart (Table1) [20,1]. In the previous section the effects of Hypothyroidism on heart failure were explained. In this section we will focus on the effects of low T3 on the cardiovascular system other than heart failure.

The major changes of low T3 on the cardiovascular system are related to decreased cardiac output, cardiac contractility, bradycardia, and increased peripheral vascular resistance. But many other atherosclerotic modifiable risk factors like high concentrations of cholesterol; accelerated atherosclerosis, coronary artery disease and impaired endothelial derived relaxation factor (nitric oxide) are also affected [25,26]. Systemic vascular resistance can increase as much as 50% due to the decrease in arterial compliance [26,27]. In hypothyroidism, as opposed to hyperthyroidism, atrial arrhythmias are rare and ventricular ectopy is common [26]. Low T3 levels by regulatory effects on the expression of numerous ion channels in the heart (B-adrenergic, Na/K ATPase, Voltage-gated K channels, Na/Ca exchanger etc.) [28,29], tend to prolong the cardiac action potential and hence the QT interval. Consequently, attenuated activity on precordial examination if often appreciated predisposes the patient to ventricular irritability and, in rare cases, acquired torsade de pointes [30].

Effect of Treating Hypothyroidism in Heart Failure

Hypothyroidism is a reversible cause of HF. Consequently, thyroid function should be evaluated in patients with HF and non-ischemic dilated cardiomyopathy. The American College of Cardiology guidelines for HF recommend screening for serum thyroid hormones levels for all newly diagnosed HF patients [16]. Hypothyroidism has many effects on the heart's physiology and internal blood supply. Studies have shown the administration levothyroxine (LT4) can actually reverse myocyte apoptosis, improve cardiovascular performance and ventricular remodeling in hypothyroidism [3,31]. Moreover, diastolic dysfunction, impaired ventricular filling and coronary flow improve when euthyroidism is restored. The Cardiovascular Health Study demonstrated that LT4 may decrease the risk of developing heart failure in patients with subclinical hypothyroidism (SHypo) and TSH>10 [4]. Consequently, it appears that replacement doses of LT4 should be considered in patients with SHypo and TSH>10 mU/l to prevent the risk of developing HF.

Additionally, thyroid hormone replacement has been shown to decrease total cholesterol, low-density lipoproteins (LDL) and triglycerides, reduce blood pressure, improve diastolic function, and control heart rate both at rest and during exercise. These documented effects all contribute to a theoretical risk reduction in developing atherosclerosis [20,24,32,33].

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However, a problem that many physicians encounter is the fact that hormonal therapy may precipitate both fatal arrhythmias and/or myocardial ischemic events. Per Somwary et al., 20% of patients with hypothyroidism maybe over treated during replacement therapy leading to increased risk of atrial fibrillation, especially among the elderly [34,35].

Hence, the usual approach (start low, go slow) is to start with the lowest dose of levothyroxine and titrate up until a euthyroid state has been achieved. Despite the improvement in both symptoms and cardiac contractility, close observation is needed when starting thyroid hormonal therapy, particularly in elderly and in those with known coronary ischemia [36,37].

Effect of Subclinical Hypothyroidism on Heart Failure and the need for Therapy?

Subclinical hypothyroidism is a biochemical diagnosis; it is defined as a normal T4 concentration while also having an elevated serum TSH concentration. Many patients usually do not have any symptoms; therefore, it is merely considered a laboratory diagnosis. Its prevalence ranges from 4 to 15 percent in the United States [18]. There have been prospective studies suggesting that the annual rate of progression to overt hypothyroidism ranges from 2 to 4 percent depending on the initial TSH level. Higher TSH levels have been associated with increased cardiovascular disease including heart failure and coronary heart disease. There is some discrepancy about the exact levels related to increased risk, but the general consensus is that levels greater than 10 mU/L are associated with more cardiovascular pathology. The Cardiovascular Health Study revealed that patients with a TSH equal or greater than 10 mU/L had an increased risk of HF and a greater baseline peak E velocity, which is a measurement of diastolic function associated with HF incidence, after adjustment for age, gender, and systolic blood pressure compared to euthyroid participants [4]. However, patients with TSH 4.5 to 9.9 mU/l had no increased HF risk. Increased LV mass, impairment of LV relaxation were also exclusively associated with subclinical hypothyroidism with TSH >10.0 [4]. The Health Aging and Body Composition population-based study showed that patients (aged 70–79 years) with TSH level 7 mU/l or greater had a higher rate of CHF incidence and recurrence compared with euthyroid patients. Among the 127 patients who had HF, 51 had recurrent HF events [38]. Furthermore, in the PROSPER study 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) [39].

When treating a patient with heart failure, that is also found to have subclinical hypothyroidism, there are many discrepancies in regards to starting treatment with levothyroxine. Some studies showed beneficial outcomes when treating with hormone replacement, including decreased blood pressure, LDL, total cholesterol and carotid intima thickness [40]. But other studies have shown no significant reduction on CAD [41]. On the contrary, analysis from a population based cohort study has linked increased cardiovascular mortality in terms of ischemic heart disease and dysrhythmias in patients treated for subclinical hypothyroidism with levothyroxine. This trend has been seen mainly in elderly

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patients (>70 years old). After the European Thyroid Association proposed guidelines in regards to this matter, there has been a general consensus to treat with levothyroxine all those patients <70 years old who have a TSH serum concentration >10 mIU/L. For patients >70 years old with TSH levels <10 mIU/L the guidelines discourage from treating, given higher chances of exacerbating ischemic events and arrhythmias in CAD patients [42].

Studies show that 7 out of 10 elderly women will have subclinical hypothyroidism with nearly the same changes in cardiovascular function, but less marked, than overt hypothyroidism [43]. A study performed in Netherlands comprised of 1149 postmenopausal women demonstrated women with subclinical hypothyroidism where more likely to have a myocardial infarction and a higher frequency of calcification to the aorta [44]. When patients with subclinical hypothyroidism are treated with thyroxine, systolic and diastolic cardiac function improves [45]. Nevertheless, screening and management strategies are still a subject of disagreement, but from the cardiac perspective, treating a patient with high serum thyrotropin and normal serum thyroid hormone concentration, seems to offer a benefit with minimal risks [46,47].

At the present time, there is no randomized clinical trial evaluating the long-term cardiovascular outcomes in patients with subclinical hypothyroidism receiving hormonal replacement with levothyroxine. Further studies are needed to inform guidelines when encountering these patients, especially in the elderly population >65 years old.

Conclusion

In this review, we outlined the epidemiology and the relationship between hypothyroidism and heart failure. We also discussed the pathogenetic mechanisms by which thyroid hormone, directly and indirectly influences cardiac function. Furthermore, we highlighted the rationale for therapy with T4, particularly in those with TSH>10mU/l

It is clear that both overt and subclinical hypothyroidism can have varied but profound effects on cardiac hemodynamics and physiology contributing to cardiac related morbidities. While the cardiovascular effects of subclinical hypothyroidism are clear, the current management guidelines are still debated. Currently, very high TSH levels in an asymptomatic patient are generally treated, but less definitive data is available regarding initiation of therapy. It is also important to note that close monitoring is recommended especially in the elderly. Overall, there is evidence to suggest that treatment of subclinical hypothyroidism can improve cardiovascular outcomes; however, randomized controlled clinical trials in this field are lacking and warranted.

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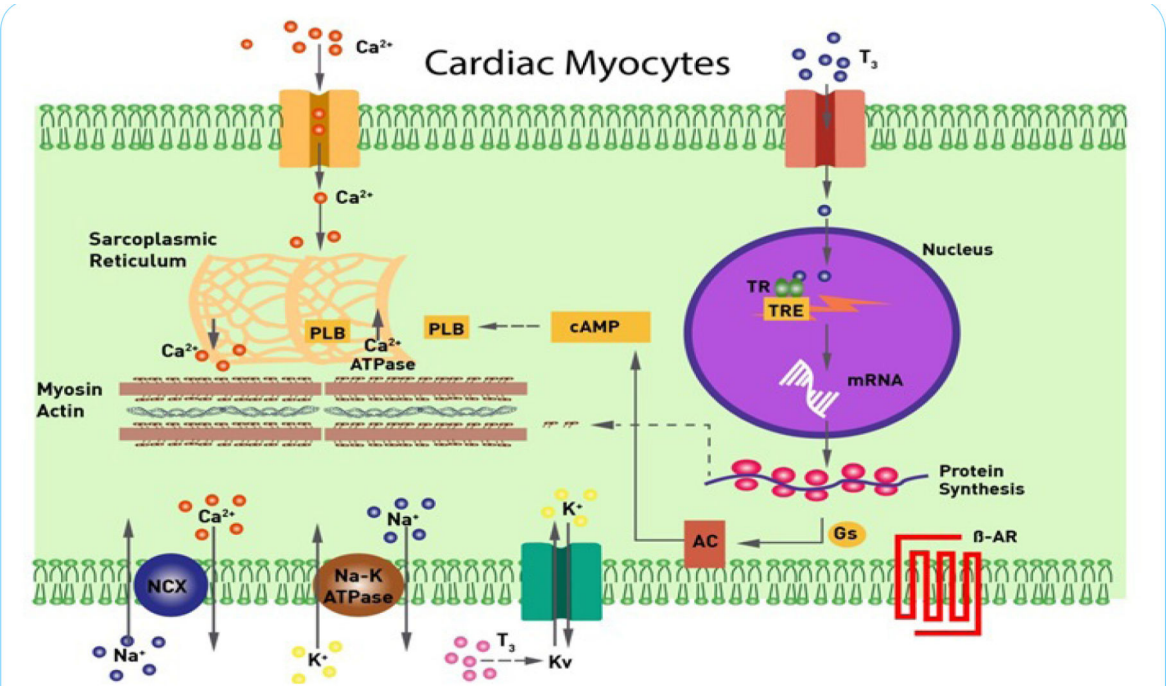

Figure 1:

T3 has both genomic and nongenomic effects on the cardiac myocyte. Genomic effects involve binding of T3 to TRs, which in turn, positively or negatively regulates the transcription of specific cardiac genes. Nongenomic mechanisms include direct modulation of membrane ion channels. AC = adenylyl cyclase; β-AR = β-adrenergic receptor; Ca2+ = calcium ions; Ca2+ ATPase = sarcoplasmic reticulum calcium adenosine triphosphatase; cAMP = cyclic adenosine monophosphate; GS = stimulatory G (guanine nucleotide binding) protein; K+ = potassium ions; Kv = voltage-gated potassium ion channel; mRNA = messenger ribonucleic acid; Na-K ATPase = sodium-potassium adenosine triphosphatase; Na+ = sodium ions; NCX = sodium calcium exchanger; PLB = phospholamban; T3 = triiodothyronine; TR = thyroid hormone receptor; TRE = thyroid hormone response element.

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Table 1:

Effects of Low Triiodothyronine (T3) and on the Cardiovascular system.

Indirect Effect on Cardiovascular Function
Mild hypertension
Narrowed pulse pressure
High serum concentrations of cholesterol
High serum concentrations of creatinine kinase (specifically CK-MM)
Pericardial effusions
Non-Pitting edema (myxedema)
Cardiac arrhythmias (Torsade de pointes)
Accelerated atherosclerosis and coronary artery disease
Increased carotid intimal thickening
Impaired endothelial-dependent vasodilation
Direct Effect on Cardiovascular Function
Increase systemic vascular resistance
Decrease heart rate
Decrease ejection fraction
Decrease cardiac output
Increase isovolumetric relaxation time
Decrease blood volume