Levothyroxine and the Heart

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Thyroid hormone deficiency has been associated with multiple changes in cardiovascular structure and function in recent studies. A strong relationship has been reported between overt and subclinical hypothyroidism with serum TSH ≥10 mIU/L and adverse cardiovascular outcomes, suggesting the necessity of replacement doses of Levothyroxine. The potential benefits of replacement therapy remain an active area of research in euthyroid patients with heart failure.

1 Introduction

Hypothyroidism is a common condition of thyroid hormone deficiency which can lead to increased cardiovascular mortality when untreated. Overt hypothyroidism is defined by thyroxine concentrations below the reference range and a serum thyrotropin (thyroid-stimulating hormone, TSH) measurement that is outside an appropriate reference range (typically between 0.4 and 4.0–4.5 mIU/L, defined in a population of subjects without thyroid disease) [1, 2]. Subclinical hypothyroidism occurs where there is elevation of TSH despite the level of free thyroxine (FT4) being within the normal reference range. Patients with a serum TSH ≥10 mIU/L have a severe form of subclinical hypothyroidism, whereas patients with subclinical hypothyroidism and TSH <10 mIU/L are described as having a "mild" form of this condition, according to European guidance [1]. This chapter considers the effects of hypothyroidism and levothyroxine (LT4) replacement therapy on the heart and cardiovascular system.

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G. J. Kahaly (ed.), *70 Years of Levothyroxine*,
https://doi.org/10.1007/978-3-030-63277-9_7

Table 1 Overview of observational studies of the associations between thyroid status and cardiovascular health that recruited at least 1000 subjects

Refs.	Cardiovascular outcome in patients with hypothyroidism
Population based (without known thyroid dysfunction and with/without CHD at baseline)	
[3–5]	No association between SCH or overt hypothyroidism and MACE
[6]	SCH and overt hypothyroidism associated with higher all-cause mortality and increased risk of MACE (but mortality was lower for TSH 5–10 mIU/L)
[7]	SCH increased risk of mortality in acute CHD
[8]	SCH associated with increased prevalence of CHD, and higher than expected rate of MACE
[9]	SCH increased the risk of all-cause and CV mortality
[10]	SCH increased risk of stroke in adults
[11]	SCH increased total and CHD mortality
[12]	Increased 10-year CVD risk score in people with SCH vs. euthyroid
Patients with or at risk of heart failure (HF)	
[13]	Higher TSH associated with more severe CHF presentation
[13, 14]	Higher TSH associated with adverse clinical outcomes in patients with HF
[15]	Hypothyroidism predicted adverse clinical outcomes, but the association was not independent and disappeared after adjustment for other covariates
[16]	Low FT3 associated with higher risk of developing HF after myocardial infarction
[17]	Hypothyroidism increased the 5-year risk of death in patients with LVEF <35%
[18]	TSH ≥10 mIU/L increased the risk of new-onset HF, increased LV mass, and decreased diastolic function in patients free of HF at baseline
[19]	SCH increased the risk of HF in older subjects at elevated CV risk

2 Overview of the Adverse Effects of Thyroid Dysfunction on the Heart

Many observational studies have evaluated cardiovascular function in people with hypothyroidism and Table 1 summarises the results of some large, recent studies [3–19]. The findings of these studies were variable, probably because of differences between populations in terms of the severity of hypothyroidism, the age of the patients, and the presence of comorbidities. Nevertheless, expert opinions reported a significant association between hypothyroidism with serum TSH ≥10 mIU/L and adverse cardiovascular outcomes [20, 21]. A systematic review demonstrated multiple effects of subclinical hypothyroidism on the heart that were consistent with reduced diastolic or systolic cardiac left ventricular performance, and some of its key findings are summarised in Table 2 [21, 22]. In contrast, a meta-analysis found that the presence or absence of anti-thyroid peroxidase antibodies neither increases nor reduces the risk of adverse cardiovascular outcomes in people with subclinical hypothyroidism [23].

Table 2 Overview of the effects of subclinical hypothyroidism and levothyroxine replacement therapy on the heart, from a systematic review

	Left ventricular diastolic function			LV systolic function		Lipid profiles		
	A wave	E/A ratio	IRT	PEP	PEP/ET	Total cholesterol	LDL-cholesterol	HDL-cholesterol
Effect of subclinical hypothyroidism	↑	↓ or ↔	↑	↑[a]	↑[a]	↑ or ↔	↑ or ↔	↑ or ↔
Effect of LT4 replacement	↓	↑	↑	–	↓	↓ or ↔	↓ or ↔	↔↑

Changes in parameters reflect those seen in most (not necessarily all) studies: ↑ = increased; ↓ = decreased; ↔ = variable effects

E/A early-to-late transmitral peak flow velocity ratio, *ET* ejection time, *IRT* isovolumic relaxation time, *LV* left ventricular, *PEP* pre-ejection period. Compiled from information presented in Refs. [21, 22]

[a]Usually increased when measured using Doppler ultrasound (usually no effect when measured using Weissler's method)

Results of studies that evaluated the relationships between thyroid status and the lipid profile have also been variable although there is some evidence that more severe increases in TSH are associated with a more adverse change in the lipid profile [22]. Effects of the hypothyroid state on "non-traditional" cardiovascular risk factors (e.g. markers of haemostasis or systemic inflammation) were variable although there was some support for a possible action of hypothyroidism in exacerbating atherosclerosis [22].

The association of hypothyroidism with adverse cardiovascular outcomes appears to be stronger and most consistent for people with heart failure [24–26]. A recent (2019) meta-analysis of 14 studies (21,221 patients) found a significant association between hypothyroidism (including the subclinical form) and major prognostic outcomes associated with heart failure, such as cardiac death and/or hospitalisation [27]. A pooled analysis of prospective cohort studies showed that the risk of heart failure events (any physician-diagnosed acute heart failure event, or hospitalization or death related to heart failure) increased as the level of TSH increased above a euthyroid range defined as a TSH level of 0.45–4.49 mIU/L [28]. The hazard ratio (HR) for heart failure events for TSH 7–9.9 mIU/L vs. the euthyroid state was 1.65 (95%CI 0.84–3.23). TSH levels associated with hyperthyroidism also increased the risk of heart failure events in this analysis. Elsewhere, 12 years of prospective follow-up of 3,044 elderly (age ≥65 years) subjects with subclinical hypothyroidism showed that a TSH level >10 mIU/L was associated with an almost doubled risk of developing new heart failure HR 1.88; 95%CI 10.5–3.34) [18]. On the other hand, cardiovascular diseases such as heart failure may themselves lead to an altered thyroid function [29]. Low circulating T3 levels are a common finding in patients with heart failure and contribute to adverse outcomes in this condition [25].

3 Effects of Levothyroxine Replacement Therapy on the Cardiovascular System

3.1 Effects on ECG Parameters

Hypothyroid patients have abnormal heart rate variability compared with euthyroid controls, which can be corrected by an adequate LT4 replacement therapy [30]. Ambulatory ECG recording showed that long-term LT4 replacement appears to avoid the bradyarrhythmias commonly associated with hypothyroidism [31]. Moreover, LT4 treatment may reduce QT interval dispersion in patients with subclinical hypothyroidism, reducing the risk of malignant cardiac arrhythmias [32].

3.2 Effects of L-Thyroxine on Cardiovascular Structure and Function

Subclinical hypothyroidism appears to represent a mild form of thyroid failure that displays early signs of the cardiovascular dysfunction associated with hypothyroidism [33, 34]. The impairment in systolic and/or diastolic performance observed in patients with subclinical hypothyroidism, compared with healthy controls, has been shown to reverse during treatment with LT4 for periods of up to 1 year (Table 2) [21]. Such effects have been observed in young adults but not in elderly subjects in some randomized trials [35–37].

An overview of these and other studies in populations with subclinical hypothyroidism are summarised in Table 3 [32, 35–51]. Markers of atherosclerosis or arterial stiffness improved in some studies [39, 52]. A further cross-sectional analysis demonstrated an improvement in atrial volume [53]. Another randomised trial showed that treatment with LT4 improved cholesterol levels in people with subclinical hypothyroidism [39]. In addition, patients with mild subclinical hypothyroidism without associated cardiovascular risk factors have a coronary endothelial dysfunction that appears in response to a physiological stimulus [54]. A meta-analysis found an improved lipid profile and reduced carotid intima-media thickness (a marker of the overall burden of atherosclerosis) in patients with subclinical hypothyroidism [38]. Finally, treatment with LT4 may reduce cardiovascular risk in patients with diabetes: increased prevalence of thyroid dysfunction in patients with diabetes (and *vice versa*) suggests that there may be pathogenetic links between these conditions [55].

Thus, clinical evidence has associated overt and severe subclinical hypothyroidism with indices of increased cardiovascular risk, including dyslipidaemia, impaired cardiac function (especially during diastole) and impaired vascular function [56]. Evidence of potentially beneficial cardiovascular effects of LT4 replacement therapy on these parameters has led some experts to propose intervention with LT4 in patients with mild subclinical hypothyroidism and elevated cardiovascular risk factors. However, until more reliable evidence is available from randomised,

Table 3 Clinical evaluations of the cardiovascular effects of levothyroxine substitution in people with subclinical hypothyroidism

Ref.	Design/dur. of LT4	*N*	Précis of main findings
(a) Effects of LT4 replacement therapy on lipid profiles and markers of atherosclerosis			
[38]	MA up to 1 year	543	LT4 replacement improved total and LDL-C and reduced markers of vascular disease (carotid atherosclerosis and arterial stiffness
[39]	RCT 6 months	49	Patients with SCH had higher cholesterol, LDL-C and ApoB vs. 33 euthyroid controls (LDL-C was proportional to the TSH level). Randomisation to LT4 resulted in reduced cholesterol and LDL-C, with no change in Lp(a); there were no significant changes on placebo.
[40]	O, 7 months	30	Blood pressure and augmentation index (measure of arterial stiffness) decreased on LT4 therapy; reduced augmentation index was associated with reduced LDL-C
[41]	O, 6 months	33	In patients with CHD, LT4 treatment improved the lipid profile in patients with shorter duration of CHD, lower BMI and higher cholesterol at baseline.
(b) Effects of LT4 replacement therapy on cardiac function			
[37]	RCT, 18 months	185	No significant difference for LT4 vs. placebo for changes in LV ejection fraction, E/E' ratio or other parameters relating to diastolic functional; no significant interactions relating to gender, baseline TSH, pre-existing HF, and treatment duration
[35]	RCT, 6 months	42	Increased early diastolic velocity and ratio of early/late diastolic velocities and reduced isovolumetric relaxation time was observed after 6 months of LT4; no change was seen in untreated patients
[36]	RCT, 1 year	20	LT4 associated with reversal of impairments (vs. euthyroid controls) in pre-ejection/ejection time ratio, peak A, isovolumic relaxation time, cyclic variation index (myocardial viability); no significant changes on placebo.
[42]	O, 6 months	30	Significant increase in indices of LV contractility (ejection fraction, fractional shortening, myocardial performance index) and end diastolic LV diameter in children; no change in LV end systolic volume or diastolic function (E/E' ratio).
[43]	O, 6 months[a]	31	Adverse changes in parameters of systolic and diastolic function in SCH (compared with 32 euthyroid control children) were partially reversed on LT4 replacement therapy.
[44]	O, 5 months[a]	54	Parameters relating to systolic and diastolic function were within normal range in newly diagnosed SCH patients but were significantly adverse compared with 30 euthyroid controls; LT4 replacement partially reversed these changes.
[45]	O, 12 months	26	Impairments (vs. 13 healthy controls) in systolic and diastolic cardiac function parameters (LV ejection fraction, diastolic relaxation, compliance to ventricular filling) reversed after LT4 therapy.

(continued)

Table 3 (continued)

Ref.	Design/dur. of LT4	*N*	Précis of main findings
[46]	O, 6 months[a]	53	Multiple indices of systolic/diastolic right ventricular function were impaired vs. 25 euthyroid controls; LT4 associated with improved isovolumic acceleration (no change in systolic wave velocity, early/late velocity or myocardial precontraction times.
[32]	O, 16 weeks	16	Treatment with LT4 reduced the QT interval of the ECG, and its temporal dispersion (QT interval dispersion was proportional to the TSH level).
(c) Effects of LT4 replacement therapy on clinical outcomes			
[47]	RT, mean 38 months	257	LT4 replacement for ≥180 days (vs. <180 days) predicted significantly lower risk of acute coronary syndromes or stroke, but no effect on peripheral vascular disease in patients with diabetic neuropathy (average follow-up 38 months).
[48]	RT, median 6 years	162,369	Increased risk (HR [95%CI]) at TSH >10 vs. 2–2.5 mIU/L of IHD (1.18 [1.02–1.38], $p = 0.03$), HF (1.42 [1.21–1.67], $p < 0.001$), or mortality (2.21 [2.07–2.36] $p < 0.001$) in an LT4-treated cohort (97% received LT4 during follow-up)
[49]	RCT, mean 5.6 years	1192	No significant difference for LT4 vs. no LT4 treatment (adjusted IRR [95%CI]) for risk of all-cause death (1.17 [0.90–1.52), MACE (1.08 [0.80–1.45]), or hospital admission (0.94 [0.71–1.24]) in patients with CHD.
[50]	RCT, mean 5.0 years	12,212	No significant effect of LT4 vs. no LT4 on IRR [95%CI] for MI (1.08 [0.81–1.44]), CV death (1.02 [0.83–1.25]), all-cause death (1.03 [0.90–1.19]); suggestion of benefit for all-cause death in patients aged <65 years (0.63 [0.40–0.99]).
[51]	RCT, mean 7.6 years	4735	Fewer IHD events (HR [95%CI]) with LT4 treatment in younger (40–70 years) patients (0.61 [0.39–0.95]) but not in older (≥70 years) patients (HR 0.99 [0.59–1.33]) in the primary care setting.

Diagnoses of subclinical hypothyroidism are as described in source publications according to clinical guidance at the time and have not been reviewed against current guidance

Abbreviations for study designs: *DB* double blind, *MA* meta-analysis (individual studies included in this analysis are omitted here for conciseness), *O* observational/cohort study, *R* randomised, *RT* retrospective. Other abbreviations: *BMI* body mass index, *CHD* coronary heart disease, *HF* heart failure, *IHD* ischaemic heart disease, *IRR* incidence rate ratio, *LV* left ventricular, *MACE* major adverse cardiac events, *ACH* subclinical hypothyroidism, *TSH* thyroid-stimulating hormone (thyrotropin)

[a]Months with euthyroid function established on LT4 replacement therapy

controlled trials, intervention with LT4 should be considered on an individual, case-by-case basis, balancing the patient's potential for progressive thyroid failure with the need to protect the cardiovascular system [56].

An increase in left ventricular mass with a consequent diastolic dysfunction can be observed during long-term therapy with TSH-suppressive doses of LT4 [57, 58]. The addition of a β-blocker can ameliorate the potentially adverse effects of

prolonged TSH suppression and be useful in patients with high-risk differentiated thyroid cancer [58]. The role of LT4 in the management of thyroid cancer is discussed in chapter, "Levothyroxine and Cancer" of this book.

3.3 Effects of LT4 on Major Adverse Cardiovascular Events

So far, only retrospective studies have evaluated the effects of LT4 treatment on cardiac endpoints in patients with subclinical hypothyroidism (Table 3c). The results of these studies, however, are variable. Two studies showed no significant effects of LT4 replacement on the risk of myocardial infarction, or on cardiovascular and all cause death [49, 50]. Intriguingly, there was a suggestion of a greater potential for cardiovascular benefit of LT4 therapy in younger than in older patients [51, 52]. A smaller study suggested some cardiovascular benefit for a longer rather than a shorter duration of LT4 treatment [47].

A large database analysis in a population with hypothyroidism, of whom 97% received LT4 during a median follow-up of 6 years, showed that treatment with LT4 *per se* was insufficient to protect the cardiovascular system if TSH was not normalised [48]. Specifically, under-treatment with LT4 (TSH >10 mIU/L) in this study was associated with increased risk of ischaemic heart disease (HR 1.18 [1.02–1.38], $p = 0.03$), heart failure (HR 1.42 [1.21–1.67], $p < 0.001$), or death (HR 2.21 [2.07–2.36], $p < 0.001$), compared with euthyroid subjects (TSH 2–2.5 mIU/L). A further, register-based study showed that every 6 months of elevated TSH was associated with increased risk of mortality in LT4-treated individuals, with identical risks (HR 1.05 [1.03–1.08], $p < 0.0001$) for TSH >4 IU/L or TSH >10 IU/L, compared with euthyroid controls (this study is not shown in Table 3, as it did not report cardiovascular outcomes) [59].

Treatment with LT4 for more than 1 year reduced the risk of developing CHD, compared with no LT4 treatment, in a large retrospective analysis from Taiwan [60]. The effect of LT4 therapy on clinical outcomes was also measured in a retrospective study on 12,283 patients with atrial fibrillation [61]. The adjusted risk of mortality was lower in women treated with LT4 (hazard ratio [HR] 0.78 [95%CI 0.68–0.91]), but not men (HR 0.87 [95%CI 0.69–1.10]) compared to those untreated. There was no significant effect of LT4 treatment on rates of myocardial infarction, stroke, or heart failure in this study. A large ($N = 87,902$) retrospective study saw no difference in cardiovascular outcomes between patients receiving a branded or generic preparation of LT4 [62].

3.4 Effects of LT4 in Patients with Heart Failure

A retrospective analysis of a large database of patients with heart failure from Denmark ($N = 224,670$) compared outcomes in non-users of LT4 and in 6,560 patients using LT4 at the start of the analysis, and in 9007 who subsequently

received LT4 therapy [63]. Both groups of LT4 users were at increased risk of all-cause death, cardiovascular death, or MACE, compared with non-users. However, the risk of myocardial infarction was increased in patients already taking LT4 at baseline but reduced in patients who started LT4 during the follow-up period.

Large, randomized clinical trials of LT4 replacement therapy powered for determination of effects on clinical outcomes are lacking in populations of euthyroid subjects with heart failure and hypothyroidism. A placebo-controlled evaluation of LT4 treatment in 20 subjects with cardiac insufficiency secondary to idiopathic dilated cardiomyopathy demonstrated improvements in multiple measures of cardiac function, including LV ejection fraction, cardiac output, LV diastolic dimensions, systemic vascular resistance, and functional capacity [64, 65]. Another small ($N = 28$) study involved randomization of patients with severe symptoms of heart failure (New York Heart Association class III–IV) to LT4 supplementation or to no treatment for 1 month [66]. Significant improvements were seen in LV ejection fraction and isovolumic relaxation time in the LT4 group. An uncontrolled evaluation of LT4 in 10 patients with severe LV systolic dysfunction and cardiogenic shock demonstrated significant improvements in cardiac index, pulmonary capillary wedge pressure, and mean arterial blood pressure at times up to 36 h after treatment [67]. LT4 treatment also contributed to stabilization of the condition of 9/10 of these patients, allowing for surgical intervention (heart transplant or insertion of a mechanical device to assist the heart).

Administration of T3 in patients with heart failure has also been demonstrated to improve cardiac performance in patients with severe heart failure, in some [68, 69] but not all [70] studies. Although current guidance for the management of thyroid dysfunction (see chapter, "Pharmacodynamic and Therapeutic Actions of Levothyroxine") does not support the therapeutic use of preparations of T3, these findings are consistent with a role for thyroid dysfunction within the pathophysiology of heart failure, and with the importance of the low T3 syndrome in this setting [25]. The therapeutic use of T3 in patients with heart failure remains within the research domain, for now, and further clinical studies are needed in this area.

4 Conclusions

Hypothyroidism, including the severe form of subclinical hypothyroidism in which TSH is ≥10 mIU/L, has been associated with multiple negative changes in the structure and function of cardiovascular tissues and adverse cardiovascular outcomes. Some studies have shown that intervention with LT4 to correct hypothyroidism can result in a reduced risk of MACE although the results of studies are conflicting. Randomized clinical trials are needed and yet problematic in patients with overt hypothyroidism because management guidelines clearly state that all patients with this condition must be treated with LT4.

A potential role for LT4 therapy remains an active area of research in patients with subclinical hypothyroidism. It is particularly important to correct hypothyroidism

and the more severe form of subclinical hypothyroidism in these patients [20, 21, 25]. Elderly patients with hypothyroidism may be especially challenging to manage, as they are more likely than younger patients to present with one or more cardiovascular comorbidities. For all patients, careful tailoring of the LT4 dose in hypothyroid patients should be performed to ovoid over-treatment and possible adverse effects on the cardiovascular system.

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