



How to Manage Treatment of Hypothyroidism in Patients with Cardiac Disease

a report by

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The haemodynamics of hypothyroidism are characterised by increased systemic vascular resistance and decreased blood volume, cardiac output, heart rate and myocardial contractility.¹ As a consequence of these changes, hypothyroid patients have a reduced cardiac index and impaired renal perfusion, as well as low production of renin and aldosterone and subsequent hyponatraemia. Hypothyroidism is further associated with a number of atherosclerotic cardiovascular risk factors, such as hypertension, high total and low-density lipoprotein (LDL) cholesterol, endothelial dysfunction and increased central arterial stiffness.²⁻⁶ Theoretically, all of these factors could be partly responsible for the frequent association between hypothyroidism and ischaemic heart disease. A recent study further indicated that in a group of patients with ischaemic heart disease there was a very high prevalence of hypothyroidism, especially among those who also had elevated total and LDL cholesterol.⁷

Whether ischaemic heart disease is caused by or coincides with hypothyroidism, clinicians are left with a number of patients with both conditions (hypothyroidism and cardiac disease) in whom the initiation of levothyroxine (T4) therapy is indicated. The aim of T4 therapy in hypothyroid patients is to restore the basal metabolic rate, including that of the heart. However, this can inadvertently cause a clinical de-masking of compensated pre-existing ischaemic heart disease by elevating the metabolic demands on the heart, and can even be associated with a reversible coronary dysfunction.⁸

It is generally accepted that elderly patients with coronary heart disease and hypothyroidism should be treated cautiously with thyroid hormone replacement to avoid precipitating or exacerbating angina pectoris, precipitating acute myocardial infarction and precipitating or aggravating ventricular arrhythmias or congestive heart failure.^{9,10} However, there is no solid evidence that mortality and morbidity are reduced by T4 therapy of hypothyroid patients with cardiovascular disease. The evidence reviewed in this article is mainly based on surrogate markers such as improvement in lipid profile, endothelial dysfunction and cardiac performance.¹¹

Treatment of the Hypothyroid Heart with Levothyroxine

Overt hypothyroidism is defined as a serum concentration of thyroid-stimulating hormone (TSH) at or above 10mU/l with a low serum T4 level, and it is generally accepted that such patients should be treated with T4 replacement. Whether mild (or subclinical) hypothyroidism with TSH levels between 4 and 10mU/l should also be treated is more controversial, although recent evidence has indicated a higher mortality and morbidity in these patients.^{12,13} As indicated above, the major cardiac concerns when initiating T4 therapy are the risks of provoking cardiac insufficiency, ischaemia and angina pectoris, tachyarrhythmias, pericardial effusion or high output failure without pre-existing heart

disease.¹⁴ The most important factors in relation to the heart when initiating T4 therapy are duration of hypothyroidism, the age of the patient, the severity of hypothyroidism and whether or not the patient has pre-existing heart disease.

Before starting levothyroxine replacement therapy, it is important to be aware of the fact that the duration and degree of hypothyroidism may influence the degree of ischaemic abnormalities, whereas the haemodynamic changes may have developed even in the early stages of hypothyroidism (see *Table 1*). However, in young hypothyroid patients without a history of heart disease, as well as in patients whose thyroid has been removed by surgery, there is no objection to starting levothyroxine replacement therapy immediately and at full dose. Even very severe short-term hypothyroidism is not associated with an increased incidence of myocardial ischaemia.¹⁵ On the other hand, most hypothyroid patients – particularly the elderly who may also have concomitant heart disease – have developed the hypothyroidism over years, and it is therefore most often advised to initiate replacement very slowly and to carry out titration at long intervals. In patients with ischaemic heart disease it may even be necessary to perform a stress test and/or coronary angiography before starting treatment. In cases of significant stenosis, either medical treatment or surgery should be used to increase the oxygen supply to the suffering cardiac areas before increasing the metabolism by treatment with T4.

The effect of replacement therapy with T4 is an intended increase in or normalisation of basal metabolic rate. The treatment also normalises cardiac output, left ventricular contractile performance and diastolic dysfunction, lowers diastolic blood pressure and increases the blood flow (see *Table 1*).^{2,3,4,11,16} Hypothyroidism is treated with levothyroxine – sodium salt. The replacement dose is usually 100–150µg in women and 125–200µg in men. The intestinal absorption of oral T4 is 80%, the T4 peaks in the serum are reached two to four hours after intake and serum T4 usually remains elevated for six hours after ingestion when the patient is on stable steady-state therapy. The plasma half-life of T4 is approximately seven days, and steady state is achieved six to eight weeks after the initiation of therapy. The long-term treatment goal is to reach the reference range



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of TSH levels between 0.4 and 4.0mU/l and, since the distribution of TSH values in a reference population is logarithmic, preferably at the lower end of the reference range. For a normal TSH, serum T4 is most often found to be at the high end of the reference range, or even above it (for more information, visit www.thyroidmanager.org). Measurement of serum TSH during dose titration is not necessary and can even be misleading because at this stage the pituitary will be very slowly reacting to the increasing T4 levels. The speed of titration is mainly dependent on the cardiac condition; therefore, during titration clinical signs of cardiac symptoms are the most important factor.

Is It Risky to Treat Hypothyroid Patients with Heart Disease?

Even patients with pre-existing angina most often experience a gradual amelioration of symptoms under therapy in the long term, but some may develop a previous unknown ischaemic state or experience worsening angina, or even a myocardial infarction. Keating et al.¹⁷ investigated the effect of T4 on angina pectoris in 1,503 hypothyroid patients: 38% improved with the treatment, 46% showed no change and 16% had more symptoms. Thirty-five patients developed overt chest pain after the start of therapy.

Although many subsequent studies have investigated the consequences of hypothyroidism as well as the consequences of T4 treatment for the heart, no later clinical studies have investigated whether T4 therapy improves or worsens cardiac ischaemia, nor whether T4 therapy changes mortality and cardiac morbidity in patients with hypothyroidism. As mentioned above, the main body of evidence is based on the investigation of surrogate markers such as improvement in lipid profile, endothelial dysfunction and cardiac performance.^{11,12} A very recent case report demonstrated improvement of severe cardiac failure after treatment with T4 in a patient with overt hypothyroidism who was resistant to the usual cardiac inotropic drugs.¹⁸

A challenging problem is the treatment of hypothyroid patients with unstable angina, especially if coronary vascular surgery is indicated. It may be relevant after carefully weighing up the pros and cons in each individual case to treat the cardiac vascular occlusion before starting replacement with T4. Intensifying anti-angina medical therapy is also advised. However, a recent study of hypothyroid patients on stable

Table 1: Treatment of Hypothyroidism with Levothyroxine – Cardiac Concerns and Effects on Risk Factors

Concerns	Effects
Cardiac insufficiency	Normalises cardiac output
Ischaemia and angina pectoris	Normalises left ventricular contractile performance
Tachyarrhythmias	Lowers diastolic blood pressure
Pericardial effusion	Decreases serum cholesterol
High output failure without pre-existing heart disease	Normalises diastolic dysfunction
	Normalises endothelial function

Source: Friis and Pedersen 1987;³ Klein et al 1995;² Biondi et al 2002;¹¹ Klein and Danzi 2007.⁶

levothyroxine therapy concluded that routine thyroxine administration is all that is required for a satisfactory outcome in patients undergoing coronary bypass surgery while on replacement therapy.¹⁹

Conclusions

Although there exist no randomised clinical trials on whether or not to treat patients with pre-existing heart disease and hypothyroidism with T4, and nor is there much epidemiological evidence for improvement of mortality and morbidity with T4 treatment, it can generally be concluded based on numerous studies on surrogate markers that patients with ischaemic or other heart diseases need treatment for hypothyroidism, because levothyroxine is good for the hypothyroid heart. However, treatment should be initiated at a very low dose in these patients and titrated slowly at long intervals. If necessary, possible underlying cardiac disease should first be carefully assessed by stress testing and coronary angiography, and ischaemic cardiac disease should be treated with vascular surgery and/or medication before initiation of T4 therapy. An underlying cardiac disease should also always be treated with the necessary medication such as beta-blockers, calcium antagonists or nitrates concomitant with T4. It is important that patients with heart disease are titrated to TSH levels in the reference range, because overtreatment (with suppressed TSH level)²⁰ as well as undertreatment can damage the heart. Combination treatment with T4/T3 should be avoided in patients with heart problems, since addition of T3 may elicit an unstable thyroid function throughout the day. Furthermore, it is very important to ensure good patient compliance by careful and initially very frequent monitoring, as unstable thyroid function has been demonstrated to be very unfavourable, in particular for the heart.²¹ However, the general opinion among specialists is that the benefits of T4 therapy in hypothyroid patients with cardiac disease outweigh the risks.⁶ ■

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