Thyroid disease and its treatment: short-term and long-term cardiovascular consequences
Faizel Osman*, Michael D Gammage* and Jayne A Franklyn†

Thyroid hormones exert important effects on the cardiovascular system, including effects on cardiac systolic and diastolic function, peripheral vascular resistance and arrhythmogenesis. Hyperthyroidism and hypothyroidism often cause opposing effects on cardiovascular physiology in the short term. Increasing evidence suggests that long-term vascular morbidity and mortality occurs in both overt and subclinical thyroid disease.

Hyperthyroidism
Hyperthyroidism (also known as thyrotoxicosis) is the clinical state resulting from excess production of thyroxine (T₄) and tri-iodothyronine (T₃). The most common cause is diffuse toxic goitre (Graves’ disease), which results from circulating immunoglobulin G autoantibodies that bind to the thyrotrophin (TSH) receptor on the thyroid gland. It is a common disorder with a prevalence of 3% in females and 0.3% in males in iodine replete areas such as the USA and the UK [2]. The next most common cause is autonomous function of one or more thyroid nodules (toxic nodular hyperthyroidism). Hyperthyroidism is known to induce many cardiovascular effects such as sinus tachycardia, systolic hypertension, changes in ventricular systolic and diastolic function and predisposition to dysrhythmias, especially atrial fibrillation (AF) [3••]. Hyperthyroidism is typically treated with antithyroid drugs, radioiodine or surgery, all of which are effective [4]. The availability of effective treatments for thyrotoxicosis has led to the widespread perception that it is a reversible disorder without long-term consequences but increasing evidence suggests that this is not the case, especially in terms of vascular disease.

Short-term cardiovascular consequences
Hyperthyroidism is known to induce many short-term cardiovascular changes in the patient that manifest clinically. Many of these clinical manifestations are due to the ability of thyroid hormones to alter myocardial contractility and the peripheral vasculature. Thyroid hormones are well known to influence heart rate, cardiac output and systemic vascular resistance (Figure 1). In addition, peripheral oxygen consumption and substrate requirements are increased, causing secondary increases in cardiac contractility [3••].

T₃, the biologically active thyroid hormone, affects cardiovascular physiology in many ways. Patients with hyperthyroidism have increased left ventricular systolic and diastolic function, changes that are consistent with influences on the expression of contractile and calcium-regulatory proteins [3••,5•]. The rate of increase in intraventricular pressure during systole, the left ventricular ejection fraction and the rate of blood flow across the aortic valve are all increased in hyperthyroidism [6]. The rates of isovolumic chamber relaxation and left ventricular filling are also increased, as measured by flow across the mitral valve in diastole [7]. Administering β-adrenoceptor antagonists to patients with hyperthyroidism slows heart rate but not contractile performance, confirming a direct effect of thyroid hormone on cardiac tissue [5•]. At rest, the stroke volume index, ejection fraction and cardiac index are significantly increased in hyperthyroidism with a blunted response to exercise, which normalises after restoration of euthyroidism.
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(normal thyroid hormone levels) [8]. Many of these changes reflect direct effects of T₃ on the myocardium. T₃ is known to regulate the rate of transcription of a variety of genes involved in coordinating the electrochemical and mechanical responses of the myocardium (Table 1).

Invasive and non-invasive measurements in patients with hyperthyroidism indicate that systemic vascular resistance is reduced as a result of dilatation of resistance arterioles in the peripheral circulation [9]. This action is due to the direct effect of T₃ on vascular smooth-muscle cells, promoting relaxation. There is increased activation of the renin–angiotensin–aldosterone axis in thyrotoxicosis, which is the result of decreases in systemic vascular resistance and effective arterial filling volume. Erythropoietin secretion is also stimulated by thyroid hormones. These two actions thus increase circulating blood volume [10] and therefore pre-load, which in turn increases cardiac output further.

Increased resting heart rate at day and night is common in hyperthyroidism and thought, at least in part, to reflect changes in autonomic control with increased sympathetic and reduced parasympathetic activity [11]. In the adult population, AF is the most common cardiac rhythm disturbance and, after sinus tachycardia, is the most prevalent dysrhythmia in those with hyperthyroidism. Between 10% and 15% of hyperthyroid patients develop AF [12]. Treatment of thyrotoxicosis has been reported to lead to spontaneous reversion to normal sinus rhythm in nearly two-thirds of patients with associated AF within 8 to 10 weeks. If sinus rhythm has not been restored after three months of treatment, spontaneous reversion to sinus rhythm is rare [13].

Long-term cardiovascular consequences
There have been few population-based studies examining the long-term influence of thyroid disease and its treatment on morbidity and mortality. We recently identified a cohort of 7209 subjects with thyrotoxicosis treated with radioiodine between 1950 and 1989 [14]. The underlying cause of death for the cohort was compared with age-specific mortality data for England and Wales, and standardised mortality ratio (SMR) used as a measure of relative risk. During a follow-up period of 105 028 person-years of risk, 3611 subjects died. This was a significant increase in mortality over the expected 3186 deaths (P <0.00001). This excess mortality was largely accounted for by an excess of deaths due to both cardiovascular and cerebrovascular circulatory diseases (Table 2). Rheumatic heart disease and hypertensive heart disease had the highest mortality ratios, followed by the category ‘other’ circulatory diseases, which included deaths secondary to dysrhythmias (Table 2). This excess mortality was most evident in the first year after radioiodine treatment and declined thereafter.

Hyperthyroidism is a cause of AF, which in turn may exacerbate rheumatic or non-rheumatic valvular disease, ischaemic heart disease or heart failure. The striking increase in mortality due to rheumatic heart disease may have reflected the timing of investigations of hyperthyroidism and rheumatic heart disease in patients presenting with AF. Excess deaths due to hypertensive and other forms of heart disease were confined to those aged 50 years or older, reflecting increasing mortality from heart disease with increasing age and exacerbation of these disorders by hyperthyroidism [15]. The excess mortality from cerebrovascular disease was also most marked in the first year and confined to those who were 50 years or older at the time of initial treatment. Overall mortality was, however, increased for all age groups.

Excess deaths due to circulatory diseases were also reported in 1762 women with thyrotoxicosis who were treated with radioiodine between 1946 and 1964 and followed for an
average of 14 years (SMR = 1.4, 95% confidence interval [CI] = 1.3–1.6; [16]). Another study, which followed 10,552 thyrotoxic subjects for an average of 15 years after radioiodine treatment, also described an excess vascular mortality (SMR = 1.65, 95% CI = 1.59–1.71; [17]). It is likely that dysrhythmias may have contributed to the excess mortality from both cardiovascular and cerebrovascular disease, especially in those with AF in whom predisposition to embolic events is well established [18]. Supraventricular extra systolic complexes have been reported to be more frequent in thyrotoxic patients than in a matched control group before and after treatment [19, 20]. This suggests a continuing arrhythmic substrate despite restoration of biochemical euthyroidism, and effects on myocardial electrical remodelling, especially of the atria, by thyroid hormones.

**Hypothyroidism**

Hypothyroidism affects approximately 1% of the general population and 4% of people aged 60 years or over are on long-term thyroxine therapy [21]. Hypothyroidism has cardiovascular consequences resulting from direct influences of thyroid hormone deficiency on the heart and from adverse effects on circulating lipid concentrations. The most common signs are bradycardia, mild hypertension, a narrowed pulse pressure and attenuated activity on examination of the chest wall (precordial examination) [3••]. Other characteristic but non-specific findings are atrial arrhythmias and heart rate and the presence of atrioventricular conduction blocks are the only dysrhythmias recognised to be associated with hypothyroidism. Unlike hyperthyroidism, atrial arrhythmias are uncommon and ventricular ectopy is common in hypothyroid subjects [3••]. The QT interval and cardiac action potential are prolonged in hypothyroidism which, in turn, predisposes to ventricular irritability and, in rare cases, acquired torsade de pointes (a type of ventricular tachycardia characterised by QRS complexes of varying amplitude). Thyroid hormone is known to exert important effects on cardiac repolarisation, but the underlying mechanisms are poorly understood. Hypothyroidism has been shown to significantly prolong the rate-corrected QT interval and action potential duration of isolated guinea-pig

<table>
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<th>Table 1</th>
<th>Regulation by thyroid hormones of genes (at transcriptional and post-transcriptional levels) that encode cardiac proteins.</th>
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<tbody>
<tr>
<td>Positive regulation</td>
<td>Negative regulation</td>
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<tr>
<td>α-Myosin heavy chain</td>
<td>β-Myosin heavy chain</td>
</tr>
<tr>
<td>SR Ca^{2+} ATPase</td>
<td>Phospholamban</td>
</tr>
<tr>
<td>β1-Adrenoceptors</td>
<td>Adenylate cyclase types 5 and 6</td>
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<tr>
<td>GTP binding proteins</td>
<td>T₃ nuclear receptor α-1</td>
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<tr>
<td>Na+/K+ ATPase</td>
<td>Na+/Ca^{2+} exchanger</td>
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<tr>
<td>Voltage-gated K⁺ channel (Kv 1.5, Kv 4.2, Kv 4.3)</td>
<td></td>
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SR, sarcoplasmic- reticulum.

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<tr>
<th>Table 2</th>
<th>Excess mortality in a cohort of 7209 thyroid patients treated with radioiodine*.</th>
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<tbody>
<tr>
<td>Disease</td>
<td>SMR</td>
</tr>
<tr>
<td>Cardiovascular circulatory disease</td>
<td>1.2</td>
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<tr>
<td>Cerebrovascular circulatory disease</td>
<td>1.4</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>3.2</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>2.1</td>
</tr>
<tr>
<td>Other circulatory diseases†</td>
<td>1.8</td>
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*Data taken from [14]. †Includes deaths secondary to dysrhythmias.
ventricular myocytes by decreasing dofetilide-resistant current densities and, therefore, also prolonging the repolarisation period [26].

Autonomic function in hypothyroidism has been assessed using power spectral analysis and compared with an age-matched and sex-matched control group [27*]. A sharp reduction in the high frequency (parasympathetic) component of the analysis was noted in seven hypothyroid subjects compared with the control group. Conversely, the low frequency (mainly sympathetic) component was significantly higher in hypothyroid subjects in the standing position. Total heart rate variability (expressed as total power spectral density) was significantly lower in hypothyroid patients compared with controls in the lying position [27*]. After T4 therapy, complete normalisation of autonomic parameters was observed suggesting that autonomic dysfunction is reversible in hypothyroidism.

The vast majority of subjects with hypothyroidism have an abnormality of circulating lipids [28]. About 95% of clinically affected subjects are hypercholesterolaemic with isolated hypertriglyceridaemia present in fewer than 5% of affected subjects. The combination, however, is present in 40–70% of hypothyroid patients [29**]. It has been suggested that hypothyroidism may result in accelerated atherosclerosis and coronary artery disease, probably secondary to associated hypercholesterolaemia and hypertension [3••]. Direct evidence for such an effect, however, is lacking.

**Subclinical hyperthyroidism**

Subclinical hyperthyroidism is common in the community, with prevalence in iodine replete areas reported to range from 0.5% to 3.9% in adults of all ages [30] and 11.8% in one study of the elderly [31]. It is defined as a low serum TSH concentration in an asymptomatic subject with normal serum T3 and T4 concentrations [12]. The most common causes of reduced serum TSH in the general population are the ingestion of hyperthyroid medication and isolated hyperthyroidism [32].

Even though the biochemical abnormality is considered ‘mild’ and the condition ‘subclinical’, suppression of TSH in patients taking T4 has been demonstrated to result in higher scores for symptoms and signs associated with thyroid hormone excess than in euthyroid controls. This results in impaired quality of life compared with an age-matched, sex-matched and lifestyle-matched control group [33**]. This study demonstrated significant increases in left ventricular mass, enhanced systolic function and impaired diastolic function compared with the control group (P < 0.05). A non-significant increase in atrial premature beats was also observed on Holter monitoring [33**].

**Risk of developing atrial fibrillation**

A low serum TSH concentration is generally a sensitive marker of thyroid hormone excess. It has been reported to be associated with a threefold higher risk of developing AF in the subsequent decade in an important recent study of 2007 patients aged 60 years or more (from the Framingham Heart Study; [12]). These patients did not have AF at the start of the study and were classified according to their serum TSH level as follows: low (0.1 mU/L), slightly low (>0.1–0.4 mU/L), normal (>0.4–5.0 mU/L) and high values (>5.0 mU/L). During the 10-year follow-up period, 192 subjects (10%) developed AF. The cumulative incidence of AF at 10 years among subjects with low TSH values was 28% compared with 11% among those with normal TSH values (P = 0.005; Figure 2). After adjustment for other known risk factors, the relative risk for developing AF in those with a low TSH was 3.1 (95% CI = 1.7–5.5) compared with those with a normal TSH (P < 0.001).

Other studies have examined the relationship between a low serum TSH concentration and the subsequent development of AF, but these have been small and in selected cohorts. Tenerz et al. [34] found AF developed in 3 of 32 subjects with subclinical hyperthyroidism during two years of follow-up, compared with none of 35 subjects with normal serum TSH concentrations (non-significant difference).

**Excess vascular mortality**

Increased cardiovascular and cerebrovascular mortality has recently been described in a community-based review of subjects with subclinical hyperthyroidism followed over a 10-year period [35**]. The cohort consisted of 1191 subjects aged 60 years and over who were not receiving T4 therapy or anti-thyroid medication. Serum TSH concentration was measured at baseline in 1988–1989. Causes of death were determined for those who died during the follow-up period and compared with age-specific, sex-specific, and year-specific data for England and Wales. Mortality from all causes was found to be significantly increased at 2, 3, 4 and 5 years after initial measurement in those with a low serum TSH concentration (≤0.5 mU/L, n = 71) compared with the expected mortality for the control population of England.
and Wales. The SMR (with 95% CI) at 2 years was 2.1 (1.0–4.5), at 3 years was 2.2 (1.2–4.0), at 4 years was 1.9 (1.0–3.4) and at 5 years was 2.0 (1.2–3.3). This increase in all-cause mortality was largely accounted for by significant increases in mortality due to circulatory diseases. A comparison of those with low serum TSH and the remainder of the cohort also confirmed significant increases in vascular mortality between 2 and 5 years.

**Subclinical hypothyroidism**

A high serum TSH concentration and normal serum thyroid hormone concentrations characterise subclinical hypothyroidism [29••]. The condition is relatively common with a prevalence of between 5% and 15% in the general population [36•]. The occurrence is often associated with the presence of thyroid autoantibodies, especially in females and the elderly [29••]. There is no clear evidence to date that subclinical hypothyroidism causes clinical heart disease; however, it may be associated with increased morbidity, particularly cardiovascular disease, and subtly decreased myocardial contractility [29••]. Using various non-invasive methods for the determination of cardiovascular and respiratory function, different studies have suggested that subclinical hypothyroidism may subtly affect left ventricular systolic and diastolic parameters, as well as cardiorespiratory exercise capacity during maximal work [20••]. Therefore, both cardiac structure and function appear to remain normal at rest, with impaired ventricular function and cardiovascular adaptation to effort being unmasked during exercise.

Assessment of autonomic function using time-domain and frequency-domain analysis of heart rate variability suggests that patients with subclinical hypothyroidism have suppressed parasympathetic activity, which returns to normal after treatment [29••].

Whether mild thyroid deficiency has any demonstrable effect on serum cholesterol concentrations remains controversial. The majority of cross-sectional studies have found no significant differences in total serum cholesterol concentrations either between subclinical hypothyroidism and euthyroid individuals, or before and after T₄ therapy [37,38]. Current evidence suggests that subclinical hypothyroidism affects risk of coronary artery disease only when superimposed on another underlying cardiac or metabolic disorder [20••]. Flow mediated, endothelium-dependent vasodilatation (a marker of endothelial dysfunction) has been shown to be significantly impaired in patients with subclinical hypothyroidism [39]; this may be the first stage for developing atherosclerosis in subclinical hypothyroidism.

**Conclusions**

Thyroid dysfunction is very common in the community. It affects virtually all systems of the body, especially the cardiovascular system. States of thyroid hormone excess and deficiency both have important cardiovascular consequences that are often diametrically opposed to each other.

Both conditions are readily treatable with antithyroid therapy or thyroxine replacement therapy, respectively. However, increasing evidence suggests that there are long-term consequences and cardiovascular consequences may be particularly important. Subclinical thyroid dysfunction (both excess and deficiency) is also associated with long-term cardiovascular consequences. Recognising patients with continuing cardiovascular risk from treated thyroid disease and subclinical disease will allow better targeting for further therapeutic intervention.

**Acknowledgements**

F Osman is supported by a British Heart Foundation Junior Research Fellowship.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Parry C: Palpitation of the heart in connexion with enlargement of the thyroid. *Dis Heart* 1825, 2:111-165.


A comprehensive review of thyroid status and the cardiovascular system. The mechanisms of disease are examined for thyroid hormone excess and deficiency.


A study examining myocyte calcium handling in a rat model of hyperthyroidism.


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A study examining cardiac function and metabolism, using positron emission tomography (PET) and magnetic resonance imaging (MRI), in patients with hypothyroidism before and after treatment. It demonstrated reduced cardiac oxygen consumption in hypothyroidism, which is associated with increased peripheral vascular resistance and reduced cardiac contractility.


A study examining the reversibility of prolongation of electromechanical delay and impairment of early diastolic relaxation as measured by radionuclide ventriculography. Reversible prolongation of contraction without major changes in global systolic function and a reduction in early active cardiac relaxation were demonstrated.


Study examining the effects of hypothyroidism on the sympathetic and parasympathetic nervous system, before and after treatment. The results suggest that thyroid deficiency is associated with an increased sympathetic influence on the autonomic cardiovascular system.


A review focusing on the cardiovascular effects of thyroid hormone deficiency and the possible mechanisms involved.


A study assessing the clinical impact of subclinical hyperthyroidism by examining quality of life in 23 patients and comparing with age-matched and sex-matched controls. Quality of life was found to be reduced.


Study examining the long-term vascular mortality in patients with subclinical hyperthyroidism followed over a 10-year period. A low TSH in subjects aged 60 or more was found to be associated with increased mortality, especially from cardiovascular causes.


A study that used doppler echocardiography and videodensitometric analysis to examine whether subclinical hypothyroidism induces cardiovascular alterations. Altered myocardial shortening and contractility (e.g. increased isovolumic relaxation time, pre-ejection and ejection times) were found in subclinical hypothyroidism, these may be reversed by thyroxine therapy.

