Editorial

Hypothyroidism, thyroxine treatment, and the heart

Hypothyroidism is a common condition; surveys indicate that approximately 1% of the general population and 4% of people 60 years and older are prescribed thyroxine long term.[1] Hypothyroidism has cardiovascular consequences resulting from both direct influences of thyroid hormone deficiency on the heart, and adverse effects on circulating lipid concentrations. Furthermore, with the advent of improved tests of thyroid function, it has become clear that even when patients with hypothyroidism are treated with thyroxine long term, about half have serum thyrotrophin concentrations above or below the normal range, indicating a degree of under or over treatment with thyroxine. Although little importance has been attached to these minor biochemical abnormalities, recent evidence suggests that they may have considerable clinical significance.

Cardiovascular effects of untreated hypothyroidism

Hypothyroidism is associated with sinus bradycardia, 24 hour ambulatory studies revealing decreases in resting, mean, and maximal heart rates.[2] These reductions in heart rate and atrioventricular conduction blocks are the only dysrhythmias recognised to be associated with hypothyroidism, which may itself reduce the likelihood of ventricular dysrhythmias.[3] An increase in diastolic blood pressure is also well described in hypothyroidism, and may be present in as many as 20% of subjects.[4] This diastolic hypertension is in turn associated with an increase in peripheral vascular resistance. Myocardial contractility is impaired with a reduction in resting left ventricular ejection fraction; diastolic function may also be impaired, contributing to a reduction in cardiac output,[5] and in a few cases to the development of heart failure. Pericardial effusions, demonstrated by echocardiography, are frequent in marked thyroid hormone deficiency, although tamponade is rare.

Untreated hypothyroidism is associated with hyperlipidaemia, specifically with increases in circulating concentrations of total and low density lipoprotein cholesterol, and decreases in high density lipoprotein cholesterol.[6] It is often stated that ischaemic heart disease is more frequent in patients with hypothyroidism; this may be the case, but evidence in support of this view is scanty. A necropsy study demonstrated more coronary atherosclerosis in hypertensive hypothyroid patients than in hypertensive euthyroid subjects, but no difference was found between normotensive hypothyroid and euthyroid groups.[7] A further necropsy study reported more "severe" coronary atherosclerosis in hypothyroid than euthyroid subjects, but neither study demonstrated a difference in prevalence of myocardial infarction.[8] This suggests that hypothyroidism may protect against myocardial ischaemia, a view which in the past led to the use of radioiodine in the treatment of angina.

Effects of thyroxine treatment

Many of the cardiovascular abnormalities of hypothyroidism are corrected by thyroxine replacement therapy. Increases in heart rate occur within days of beginning thyroxine therapy. A fall in diastolic blood pressure is found in many, and abnormalities of ventricular systolic and diastolic function are also corrected by thyroxine replacement.[5]

Despite these clear benefits, it is well known that angina and myocardial infarction may be precipitated by the initiation of thyroxine replacement treatment (even in low dose) in those with underlying coronary artery disease[9] (whether this is evident clinically or electrocardiographically)—this association was described more than 70 years ago. For this reason, a recent United Kingdom consensus statement for good practice in the management of hypothyroidism recommends that in older patients, especially those with ischaemic heart disease, the initial dose of thyroxine should be 25 μg and increased every three to four weeks by 25 μg increments.[10] There is little evidence that triiodothyronine treatment is better than thyroxine in patients with ischaemic heart disease, although there is a theoretical benefit should angina worsen and thyroid hormone replacement be stopped because the half life of triiodothyronine is shorter than that of thyroxine. While it is reported that up to 15% of patients starting thyroxine therapy will sustain a myocardial infarction within two years, it is also clear that chest pain improves or resolves in up to half of patients with this problem.[11] Nonetheless, 40% of patients with angina are unable to tolerate full replacement doses of thyroxine.[12] It has been shown that the presence of untreated or partially treated hypothyroidism does not affect adversely the outcome of coronary artery surgery or angioplasty, so there should be a low threshold for proceeding to angiography. In those considered unsuitable for surgery or angioplasty, adequate doses of thyroxine may not be achieved, even if the daily dose of thyroxine is 25 μg or less, with gradual incremental increases every few weeks.

Significance of minor abnormalities of thyroid function

Prevalence studies have shown that "subclinical" thyroid dysfunction (defined biochemically as increases or decreases in serum thyrotrophin concentrations in association with normal circulating thyroxine concentrations) is common in the general population, especially in people older than 60. Abnormal serum thyrotrophin concentrations are also reported in about half of those in the community prescribed thyroxine long term. We have previously demonstrated that 20% of patients in the community taking thyroxine have a serum thyrotrophin concentration above the normal range, indicating either poor compliance or inadequate dose prescription; a similar pro-

portion has suppression of serum thyrotrophin, indicating a degree of over treatment.[13] The question of whether these biochemical abnormalities are associated with significant cardiovascular consequences, either via direct actions of thyroid hormones on the heart or via changes in the circulating lipid profile, is a controversial issue.

Subclinical hyperthyroidism (low serum thyrotrophin with normal thyroxine) secondary to thyroxine therapy has been reported to be associated with an increase in nocturnal heart rate and electrocardiographic abnormalities such as shortening of the pre-ejection period systolic time interval; a recent study has also demonstrated enhancement of left ventricular systolic function in this condition.[14] We and others have also demonstrated in echocardiographic studies that subclinical hyperthyroidism due to thyroxine therapy is associated with an increase in left ventricular mass index, a marker of left ventricular hypertrophy.[15] In a study recently published in *Heart*, we reported that thyroxine treatment, in doses that reduced serum thyrotrophin to below normal, had no effect on blood pressure, heart rate, left ventricular systolic function, or stroke volume index, but was associated with an 18·4% increase in left ventricular mass index compared with controls.[15]

Untreated thyrotoxicosis was associated with a similar effect on left ventricular mass index (in addition to effects on heart rate and systolic blood pressure), but in those patients antithyroid treatment rapidly abolished any difference from controls.[15] It is notable that the β adrenergic blocker bisoprolol has been shown to be effective in abolishing this increase in left ventricular mass index in subjects on thyroxine, as well as abolishing diastolic dysfunction.[16] The significance of the demonstrated degree of left ventricular hypertrophy in patients prescribed thyroxine long term (and the role of simultaneous β blocker therapy) remains unknown, but given the evidence that left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality, at least in the setting of hypertension, these findings are of concern.

A further area of controversy is the risk of dysrhythmias in patients with subclinical hyperthyroidism. A serial study of 25 patients with hypothyroidism starting thyroxine therapy demonstrated no new onset of significant ventricular or supraventricular arrhythmias.[17] Nonetheless, a much larger and more recent study based upon the Framingham population in the United States revealed that subjects with a low serum thyrotrophin concentration are at threefold higher risk of developing atrial fibrillation over a 10 year period.[18] While most of the subjects with low serum thyrotrophin in that population were not taking thyroxine, these findings raise the question of whether subclinical hyperthyroidism secondary to thyroxine therapy is similarly associated with an increased risk of atrial fibrillation, with attendant consequences in terms of cardiovascular morbidity and mortality.

The possible effects of thyroxine therapy on cardiac mass and arrhythmia risk raise concerns regarding adverse influences of mild thyroxine excess on cardiac risk; however, the effect of thyroxine therapy on the lipid profile may confer a beneficial effect on cardiovascular risk. Some studies of thyroxine treatment of mild or subclinical hypothyroidism have shown little or no effect on the lipid profile.[6] It is notable that our own data have indicated a marked impact of thyroxine treatment on total and low density lipoprotein cholesterol concentrations when sufficient thyroxine is given to suppress serum thyrotrophin to below normal—that is, when subclinical hyperthyroidism is induced.[19]

Thyroid status and cardiovascular morbidity and mortality

There have been few epidemiological studies of the long term cardiovascular consequences of hypothyroidism and its treatment with thyroxine, especially in doses which reduce serum thyrotrophin to below normal. A study of 29 women treated long term with thyroxine indicated no difference in rates of cardiovascular morbidity or mortality compared with controls.[20] A larger study of 1180 patients treated with thyroxine (about half of whom had low serum thyrotrophin) revealed an increased risk of hospital admission for ischaemic heart disease among those younger than 65 years, but no difference among those with normal and suppressed thyrotrophin.[21] The findings from the latter study do not clearly establish that mild thyroid hormone excess was itself the cause of an increase in ischaemic heart disease, not least because half of the subjects included in the study had a previous history of overt hyperthyroidism, which may itself have represented the major risk factor. Nonetheless, these findings, and those summarised above, indicate the need for further epidemiological investigation of the consequences of hypothyroidism and its treatment on cardiovascular risk.

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