Thyroid disease and its treatment: short- and long-term consequences

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ABSTRACT – Thyroid dysfunction is common, with up to 5% of the population affected by hyper- or hypothyroidism. Short-term effects of overt thyroid dysfunction are well recognised: for example, effects of hyperthyroidism on pulse rate or blood pressure and effects of hypothyroidism on lipids. There is now also increasing evidence for long-term morbidity and mortality associated with thyroid dysfunction. This includes an increased likelihood of cardiovascular and cerebrovascular mortality in subjects with previous thyrotoxicosis treated with radioiodine, and of osteoporotic fracture of the femur in those with previous thyrotoxicosis. Subclinical or mild thyroid dysfunction may also be associated with long-term effects, with evidence for increased risk of atrial fibrillation in those with subclinical hyperthyroidism. Treatment for thyroid disease may also cause long-term problems. The cancer risk associated with therapeutic radioiodine for hyperthyroidism has been investigated extensively. Our own studies reveal no increase in cancer diagnoses or deaths, apart from a small increase in thyroid cancer risk which may be associated with the underlying thyroid disease.

Cardiovascular effects of thyroid dysfunction

Thyroid hormones regulate many of the body’s functions. Thyroid disease is common, with a prevalence in women of hyperthyroidism of 2.7% and hypothyroidism of 1.9%[1]. The cardiovascular effects of overt hyperthyroidism have been recognised since the first description of the condition by Parry in which he noted ‘palpitation of the heart in connection with enlargement of the thyroid’[2]. Cardiovascular symptoms (e.g., palpitation and shortness of breath) and signs (e.g., resting tachycardia) are well recognised features of thyroid hormone excess. Several cross-sectional studies which have compared cardiovascular findings in subjects with hyperthyroidism and controls have reported increases in daytime and nocturnal heart rate, systolic and mean 24-hour blood pressure, and left ventricular (LV) fractional shortening and ejection fraction determined by echocardiography[3][4]. Furthermore, IV mass index, a marker of IV size, is also increased in subjects with thyrotoxicosis[5]. These findings reflect several mechanisms, including direct effects of thyroid hormones upon transcription of major contractile protein genes such as those encoding the myosin heavy chains[6], as well as indirect effects mediated via interaction with the sympathetic nervous system and effects upon the systemic vasculature[7].

Although cross-sectional studies of selected subjects have shown that effective antithyroid treatment reverses the influences of hyperthyroidism upon heart rate, blood pressure and IV systolic function and size[3], it is clear that some patients are exposed to longer-term cardiovascular complications. Atrial fibrillation is reported to occur in 15% of those with hyperthyroidism, and examination of the literature indicates that increasing age (and hence pre-existing cardiac morbidity) predisposes to the development of atrial fibrillation[8]. Increasing age also reduces the rate of spontaneous reversion to sinus rhythm after antithyroid treatment[9].

In view of the potential adverse effects of thyroid hormone excess upon cardiovascular morbidity and mortality, long term as well as short term, we set out to examine the vascular consequences of overt hyperthyroidism in 7,209 subjects treated with radioiodine for hyperthyroidism between 1950 and 1989[10]. The vital status of the cohort was determined on 1st March 1996, and cause of death ascertained in those who had died.

The underlying cause of death (coded to ICD9) was compared with age-specific mortality data for England and Wales, with standardised mortality ratio (SMR) used as a measure of relative risk. During a follow-up period of 105,028 person-years of risk, 3,611 subjects died, the expected number of deaths being 3,186 (p <0.00001). Significant increase in risk of death was observed for all categories of heart disease (240 excess deaths) (rheumatic heart disease: SMR 3.2, 95% confidence intervals (CI) 2.5–4.2; hypertensive disease: SMR 2.1, 95% CI 1.6–2.7; ischaemic heart disease: SMR 1.1, 95% CI 1.0–1.1) and for cerebrovascular disease (159 excess deaths; SMR 1.4, 95% CI 1.2–1.5). Excess mortality due to cardiovascular and cerebrovascular causes affected all age groups and was most common in the first year after radioiodine therapy. Cardiovascular mortality was highest in those aged over 50 years at treatment because of increased event frequency with increasing age. Higher cumulative dose of radioiodine was a risk factor for mortality due to all causes and mortality from circulatory diseases and fracture[11]. Excess mortality in this cohort may have reflected an adverse influence of
hyperthyroidism itself, a specific adverse effect of radioiodine or of subsequent hypothyroidism and its treatment with thyroxine.

The relationship between risk of death and time from treatment (ie the highest death rate was observed during the first year after treatment when thyroid dysfunction is at its worst) and the relationship between mortality and dose of radioiodine (an indirect marker of the severity of hyperthyroidism) strongly suggest that hyperthyroidism itself is the major factor determining adverse outcome. This probably arises through influences on cardiac rate, rhythm and function, as well as exacerbation of any underlying valvular, hypertensive or ischaemic heart disease. We hypothesise that excess vascular mortality in subjects with a history of thyrotoxicosis is related to the prevalence of unrecognised vascular disease, and that this mortality could be reduced by identifying those at risk and subsequent targeting of therapeutic intervention.

**Effects of thyroid dysfunction on bone metabolism**

The association between osteoporosis and overt hyperthyroidism was recognised over 100 years ago in a case report describing multiple vertebral crush fractures in a young woman with thyrotoxicosis9. Thyroid hormones exert direct effects upon bone formation and resorption, thyroid hormone excess resulting in net bone loss. Treatment of hyperthyroidism results in an increase in bone mineral density (BMD)7, but even effective antithyroid therapy may not restore BMD, and hence fracture risk, to that of control subjects without a past history of thyrotoxicosis9. In a cross-sectional study comparing women treated for hyperthyroidism with radioiodine and age-matched controls, we found that femoral neck and lumbar spine BMD was significantly reduced in the postmenopausal group, although in the premenopausal group BMD was similar in patients and controls11. These findings suggest that it is the postmenopausal oestrogen-deficient woman who is at particular risk of potential adverse effects of hyperthyroidism upon bone metabolism.

There have been few population-based studies examining the risk of osteoporotic fracture (as opposed to measurements of BMD) in subjects with hyperthyroidism. Our study7, however, provided evidence for a marked increase in mortality from fracture of the femur in subjects with hyperthyroidism treated with radioiodine (SMR 2.9, 95% CI 2.0–3.9), findings in agreement with an earlier prospective study which described a relative risk of 1.8 for fracture associated with previous hyperthyroidism12.

**Radioiodine treatment and cancer risk**

The three main treatment modalities employed in hyperthyroidism are thionamide drugs, partial thyroidectomy and radioiodine. Radioiodine is increasingly regarded as the treatment of choice for most cases of hyperthyroidism, including Graves' hyperthyroidism which has relapsed after drug therapy, and toxic nodular hyperthyroidism13. None the less, both patients and doctors remain concerned about the long-term safety of radioiodine therapy, especially in terms of cancer risk14. These concerns have been heightened by reports of a marked increase in thyroid cancer incidence among children exposed to iodine-131 after the Chernobyl reactor accident15.

Several studies of cancer risk in patients treated with radioiodine for hyperthyroidism have been reported, but with conflicting results. There was no significant excess risk of leukaemia in a large cohort of Swedish subjects exposed to iodine-131, either during diagnostic scanning or treatment of hyperthyroidism or thyroid cancer16. The same study reported findings for solid tumours in those within the cohort who had been treated with radioiodine for hyperthyroidism17. Overall cancer incidence was increased (standardised incidence ratio (SIR) 1.06, 95% CI 1.01–1.11) and analysis of a subgroup of 10-year survivors revealed significantly greater risks for cancers of the stomach, kidney and brain. Furthermore, the risk of stomach cancer was reported to increase with both time and increasing doses of radioactivity16. However, other studies comparing cancer risk in patients treated for hyperthyroidism with radioiodine or surgically18–20 failed to reveal any difference in cancer incidence or mortality at these or other specific sites. In contrast, a recent analysis of patients treated with radioiodine in centres throughout the US from 1946–1964 has also reported an increase in thyroid cancer mortality21. The small size of most published studies and the relatively low incidence of thyroid cancer have made it difficult to make a convincing case for an increase in thyroid cancer incidence after radioiodine therapy.

In view of these conflicting findings, and persisting concerns regarding the risk of cancer among those treated with radioiodine, we again used our computerised database to identify 7,417 subjects treated with radioiodine for hyperthyroidism from 1950–1991 to investigate both cancer incidence and mortality22. Details of all cancer diagnoses and deaths from 1971–1991 were obtained from the UK Office for National Statistics, and findings compared with age-, sex- and period-specific cancer incidence and mortality data for England and Wales. During 72,073 person-years of follow-up, 634 cancer diagnoses were made.

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**Key Points**

- **Thyroid dysfunction is common.**
- **Hyperthyroidism is associated with increased vascular mortality long-term and increased risk of fracture of the femur.**
- **Radioiodine therapy does not increase cancer incidence or mortality, although there is a small associated increase in risk of thyroid cancer.**
- **It is unclear whether mild thyroid dysfunction has adverse effects on the vascular system or on bone.**
compared with an expected number of 761 (SIR 0.83, 95% CI 0.77–0.90). The relative risk of cancer mortality was also less in the cohort (observed cancer deaths 448, expected 499; SMR 0.90, 95% CI 0.82–0.98). The reduction in cancer risk reflected significant decreases in the incidence of cancers of the pancreas, bronchus and trachea, bladder, and lymphatic and haemopoietic systems. Mortality from cancers at each of these sites was also reduced, but was significant only for bronchus and trachea. There were significant increases in incidence and mortality for cancers of the small bowel (SIR 4.81, 95% CI 2.16–10.72; SMR 703, 95% CI 3.16–15.66) and thyroid (SIR 3.25, 95% CI 1.69–6.25; SMR 2.78, 95% CI 1.16–6.67), although the absolute risk of these cancers was small. The reduction in overall cancer incidence and mortality is reassuring for those treated for hyperthyroidism with radioiodine. While the absolute risk of cancers of the small bowel and thyroid was low, an increase in relative risk for these malignancies demands long-term vigilance in those receiving radioiodine, especially those in younger age groups at the time of treatment.

Subclinical thyroid dysfunction and risk of vascular and bone metabolic disease

Subclinical hyperthyroidism is defined biochemically as a reduction in serum thyrotrophin (TSH) in association with normal circulating concentrations of thyroid hormones. This biochemical pattern is a frequent and persistent finding in those who either have a past history of overt hyperthyroidism or who have goitre. Reduction in serum TSH is also a frequent finding in those taking thyroxine (T4) replacement therapy. A recent survey in several local general practices of subjects taking T4 revealed that 20.6% had a serum TSH below the normal range, consistent with a degree of overtreatment.

Cross-sectional studies of BMD measurements in subjects taking T4 have yielded conflicting results, some suggesting an adverse effect of T4 treatment upon BMD – and hence upon fracture risk – while others, including our study of 49 subjects treated long term with large doses of T4 because of a past history of treatment for thyroid cancer, have failed to show an adverse effect of T4 therapy. These conflicting results have reflected relatively small study sizes and poor matching of patients and controls in terms of factors such as menopausal status and, most importantly, past history of overt hyperthyroidism. A recent meta-analysis of studies of T4 treatment in doses which suppress serum TSH to below normal has suggested that subclinical hyperthyroidism secondary to T4 treatment does not result in excess bone loss in premenopausal women, but that in postmenopausal women there is a statistically significant excess annual bone loss of 0.91%. It remains to be proven whether this is translated into an increase in fracture risk. The one population-based prospective study of factors predisposing to fracture revealed that an apparent excess risk of fracture of the femur in those taking T4 was no longer evident when a past history of thyrotoxicosis was taken into account.

The long-term vascular consequences of subclinical hyperthyroidism secondary to T4 therapy also remain unclear. We, and others, have reported that doses of T4 sufficient to suppress serum TSH to below normal result in a number of cardiovascular effects, including an increase in LV mass index. LV hypertrophy represents an independent risk factor for later cardiovascular morbidity and mortality, so adverse long-term effects might be predicted in a proportion of subjects taking T4. No study has fully addressed this possibility, but investigation of the Framingham population revealed that a low serum TSH (whether or not secondary to T4 therapy) is a risk factor for the development of atrial fibrillation. In the UK, 5% of subjects over 60 years are taking T4, many in doses sufficient to suppress serum TSH to below normal, so it is clear that a better understanding of the long-term consequences of this therapy is crucial, especially in terms of vascular and bone metabolic disease.

Effective treatments for thyroid dysfunction are clearly readily available, but increasing realisation of the long-term consequences of thyroid diseases and their treatments could have an important impact upon the health of the population.

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