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The clinical impact of thyroid epidemiology

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Introduction

Abnormalities of the thyroid gland have been recorded for nearly four millennia. Approximately 1600 BC, the Chinese were reported to use burnt seaweed to treat enlarged thyroids, a treatment that was still being used by the Romans according to Pliny. Use of thyroid extract was first reported in 1475, and Robert Graves described hyperthyroidism with eye disease in 1835. The importance of iodine was recognised during the early 19th century and thyroxine extract was first used during the late 19th century. Iodine and isolated thyroxine started to be used therapeutically during the early 20th century. In most western countries, thyroxine is now between the second (US) and fourth (UK) most commonly prescribed drug. However, despite this long history, there is still much to learn about the management of thyroid disease.

Prevalence of thyroid disease

Thyroid disease is the most common endocrine disorder. The percentage of people in Tayside, Scotland in 2011 receiving a prescription for thyroxine or anti-thyroid drugs was 5.9%. In addition, there are many patients with euthyroid goitres, which means that thyroid disease is more common than diabetes mellitus (DM), which has a local prevalence of 4.8%. These figures are fairly representative of the UK and Caucasian populations, although type 2 DM (T2DM) is more common in Asian and Oriental ethnic groups.

Similar to DM, the prevalence of thyroid disease is increasing. From 1994 to 2001 across the Tayside region, the prevalence of hypothyroidism and hyperthyroidism increased from 1.9% to 3.2% and from 0.5% to 0.75% of the population, respectively.[1] In women, the incidence of hyperthyroidism increased, whereas the incidence of hypothyroidism increased in men. The increase in prevalence is likely to be the result of better ascertainment and identification of thyroid disease at a younger age,[1] as well as a real increased incidence in some thyroid conditions, and improved life expectancy, as thyroid disease is an increasingly prevalent condition in the older population. Recent data have suggested that iodine concentrations in the population, as measured in teenage girls, have decreased over the past four decades.[2] In the UK, only 32% of the population were deemed to be iodine sufficient, with a urinary iodine concentration of >100 ug/l, whereas one in seven people were moderate to severely iodine deficient (Fig 1). This might be influencing the changing incidence of thyroid disease, as the population was thought to be broadly iodine sufficient 30–40 years ago.

The rates of hyperthyroidism vary across Europe. In areas of chronically low endogenous iodine, such as Denmark, the incidence of hyperthyroidism varies from 0.65 to 0.93 per 1,000 of the population each year, which contrasts with more iodine-sufficient areas, such as Iceland, where the incidence is 0.23 per 1,000 people (Table 1). By contrast, areas of iodine sufficiency appear to have higher rates of primary hypothyroidism.

The high prevalence of thyroid disease in the general population is not generally appreciated. This is partly because the management of frank hyperthyroidism and hypothyroidism is well established; however, the increasing workload in primary and secondary care does need to be recognised. In addition, there is increasing focus from clinicians, and demand from patients, on fine-tuning thyroid replacement therapy, with an uncertainty as to how endogenous subclinical thyroid disease should be managed.

Subclinical hyperthyroidism

Endogenous subclinical thyroid disease is defined when patients who are asymptomatic have an abnormal thyroid-stimulating

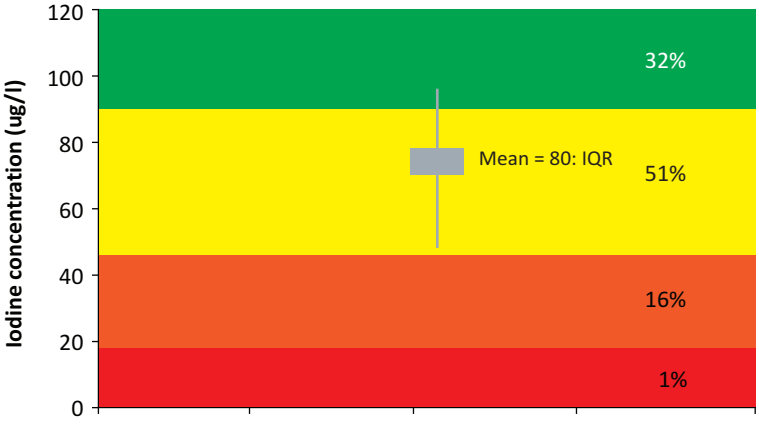

Fig 1. Concentration of urinary iodine in girls aged 14–15 years in 2010 in the UK. N = 737. Green = sufficient iodine; yellow = mild iodine deficiency; orange = moderate iodine deficiency; red = severe iodine deficiency. Predictors of low iodine concentrations were geography, summer sampling, low milk intake and high egg intake.[2]

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Table 1. Reported incidences (per 1,000 of the population) of hyperthyroidism across Europe.

Denmark	0.65–0.93
England	0.1–0.8
Iceland	0.23
Scotland	0.5–0.6
Spain	0.52
Sweden	0.26–0.43

Table 2. Reported incidences of subclinical hyperthyroidism in the UK and USA.

Study	Number of participants	Location	Prevalence
NHANES III[14]	17,353	US	0.70%
TEARS[3]	272,746	UK	0.63%
Birmingham[15]	5,960 (>65 y)	UK	2.10% (>65 y)
Whickham[16,17]	2,779	UK	0.10%

hormone (TSH) level, but serum free T4 and T3 concentrations within the reference range. Patients with subclinical hyperthyroidism (SH) have a low or suppressed TSH and a 'normal' free T4 concentration. The condition is fairly common, with the National Health and Nutrition Examination Survey (NHANES) III study reporting a prevalence of 0.7% in a population of 17,353 patients from the USA, and the Thyroid Epidemiology Audit and Research Study (TEARS) from the UK[3] reporting a prevalence of 0.63% from a population of 272,746 people (Table 2). In Birmingham, a prevalence of 2.1% was reported in people over the age of 65 years, reflecting the fact that the prevalence of SH increases markedly with age.

Many published studies examining outcomes for such patients have combined patients with endogenous subclinical disease and patients taking long-term thyroxine (ie with so-called 'exogenous' subclinical thyroid disease). This approach can be criticised as the clinical background of such patients might be quite different. However, studies following up exclusively patients with endogenous SH have shown an increased mortality in people aged over 60 years.[4] In the classic study, the risk of death from cardiovascular disease (CVD) was increased 2.2-fold and the risk of cerebrovascular disease 2.8-fold. Others have shown a 2–3-fold increased risk of atrial fibrillation (AF)[5,6] and, where sufficiently powered, an increased risk of CVD.[6] Interestingly, in patients with normal TSH concentrations, free T4 concentrations also predict AF. SH also increases the risk of fractures in most but not all studies. The risk of fractures was greater for patients with a TSH <0.1 mU/l compared with those with a TSH between 0.1 and 0.5 mU/l, showing a dose-response effect in the positive studies. The risk appears to be mainly for patients with endogenous SH, and less so for patients taking thyroxine replacement who happen to have a low TSH. A recent study indicated that the relative risk of fracture with SH might be greater for men than for women. An association between SH and dementia is less clear. There might be an association between low TSH concentration and dementia, but low TSH is not associated with a change in cognition. Studies are suggestive that any association is probably not causal.[6]

A key issue in deciding how to manage SH is how commonly does SH lead on to overt hyperthyroidism? The TEARS study identified a cohort of 2,024 patients with stable SH, defined as having SH for at least 4 months. At 7 years of follow-up, 30% of patients with SH had reverted to normal TSH levels, whereas only 0.5% had progressed towards sustained overt biochemical hyperthyroidism,[3] which is similar to other reported values of approximately 1%. Some studies showing higher levels of progression have used a single baseline TSH concentration and, thus, have included many patients who probably had non-thyroidal illness or early frank hyperthyroidism that had been detected an early stage. Therefore, progression towards overt hyperthyroidism is uncommon and should not be a significant factor when deciding whether to treat an individual patient for SH. However, as demonstrated above, SH is associated with significant endpoints in its own right, such as CVD, arrhythmias and possibly fractures.

Subclinical hypothyroidism

Patients with subclinical hypothyroidism have a raised TSH with a normal free T4, and such patients more commonly progress to overt hypothyroidism. Subclinical hypothyroidism is more common than is SH. Numerous studies have reported a prevalence of subclinical hypothyroidism of approximately 5–6%, but this increases to approximately 7–10% in those aged over 60 years. Raised serum TSH and positive anti-thyroid antibodies in women both increase the risk of developing overt hypothyroidism by eightfold, with a 38-fold increase if both are present. Rates of progression to overt primary hypothyroidism increase dramatically when the TSH is greater than 10 mU/l, with a 3–5 year conversion rate of 15–20%. The relative risks are even greater for men.

There is an increased risk of death from coronary heart disease in patients with a serum TSH greater than 7mU/l,[7] and there is a suggestion that this is more pronounced in patients of 65 years or less. Interestingly, the risk for patients with a TSH between 5 and 7 mU/l at baseline was not particularly increased. If the TSH was greater than 10 mU/L in these patients with subclinical hypothyroidism (and therefore by definition a free T4 level in the reference range), the risk of coronary heart disease was nearly doubled. The study potentially included some patients who might have developed overt hypothyroidism during follow-up (treated or otherwise), and might have included some patients with exogenous hypothyroidism; therefore, although this was an important international and very large study (N=55,287), there might have been some confounding variables. However, treatment improves symptoms and cardiovascular risk factors[8] and there is now proof that there are improved cardiovascular outcomes in younger patients.[9]

The relation between age and outcomes in subclinical thyroid disease is intriguing. TSH concentrations in the general population

are not 'normally' distributed, but are skewed to the right. This means that there is a more than expected number of people in the general population with a TSH concentration in the higher range. It has been suggested that this population is represented by certain ethnic groups, or older people.[10] For people over 70 years of age, 70% of those who had a TSH concentration above the reference range for the general population, actually had a TSH below the 97.5% upper confidence interval for their own age (ie what would be considered as normal if age adjusted). This might explain why treatment of subclinical hypothyroidism is more beneficial in those aged less than 70 years. It might also imply that the elderly could be 'over-treated' and this might put them at risk of increased fractures, which has been observed in a recent study.

Thyroid replacement

The dose of long-term thyroxine prescribed to patients is usually determined by achieving optimal symptom control while maintaining serum TSH concentrations within the laboratory reference range (generally between 0.4 and 4.0 mU/l). For most patients, this is successfully achieved, although many patients seem to prefer a serum TSH below 2 mU/l. The TEARS study has previously indicated that this strategy is safe. In a population-based study, there was no increased mortality during 8 years of follow-up for patients with treated primary hypothyroidism or those with treated hyperthyroidism who were established on long-term thyroxine.[11] Other studies showing a small increased mortality risk after treatment with radioactive iodine, demonstrated that the main risk was in those not treated with thyroxine and was associated with patients having a high TSH (ie inadequately replaced).[12] The former study only included patients with stabilised disease 6 months after any treatment for hyperthyroidism to exclude any effects of the intervention itself. There was a small 1.2-fold increased risk of new CVD in patients with treated primary hypothyroidism, and an ongoing risk of incident arrhythmias for patients even after their hyperthyroidism was treated and stabilised.[11]

A few patients prefer doses of thyroxine that result in a serum TSH towards the upper reference limits, but more patients are keen to have higher doses of thyroxine resulting in a low or suppressed TSH. In a further analysis, the TEARS group examined the impact of different levels of TSH concentration on outcomes for patients taking thyroxine. For patients with a suppressed TSH of less than 0.04 mU/l, there was an increased risk of CVD (1.4-fold), arrhythmias (1.6-fold) and fractures (two-fold) compared with patients with a TSH in the reference range.[13] The risks of these endpoints were also increased for patients taking thyroxine with a raised TSH, with rates of 1.9-fold, 1.8-fold and 1.8-fold, respectively. Intriguingly, for patients with a low but not suppressed TSH at 0.04–0.4 mU/l, there was a non-statistically significant trend in all these categories.[13] As the total patient cohort numbered 17,684, and with over 3,700 patients having a low non-suppressed TSH, it is unlikely that any of these non-statistical significant trends are of any clinical significance. This implies that it might be safe for patients to have a low but not suppressed TSH when taking long-term thyroxine replacement. When modelled as a continuous variable, having a TSH at the very lowest end of the reference range at approximately 0.4 mU/l was associated with the lowest cardiovascular morbidity, and a TSH between 0.5 and 1.0m U/l was associated with the lowest fracture morbidity (Fig 2).

Initial data from pregnant patients taking long-term thyroxine show that 19% of TSH assays were raised during pregnancy, and 29% were raised during the first trimester. As thyroid control in early pregnancy is increasingly thought to be important for the neuropsychological development of children, these findings are potentially important and indicate that the management of thyroid replacement therapy in pregnancy should be more aggressive.

Conclusions

In summary, thyroid disease is the most common endocrine disease and its prevalence is increasing. Endogenous SH rarely progresses to overt hyperthyroidism, but is associated with increased mortality, AF, CVD and possibly fractures. Endogenous subclinical hypothyroidism more commonly progresses to overt

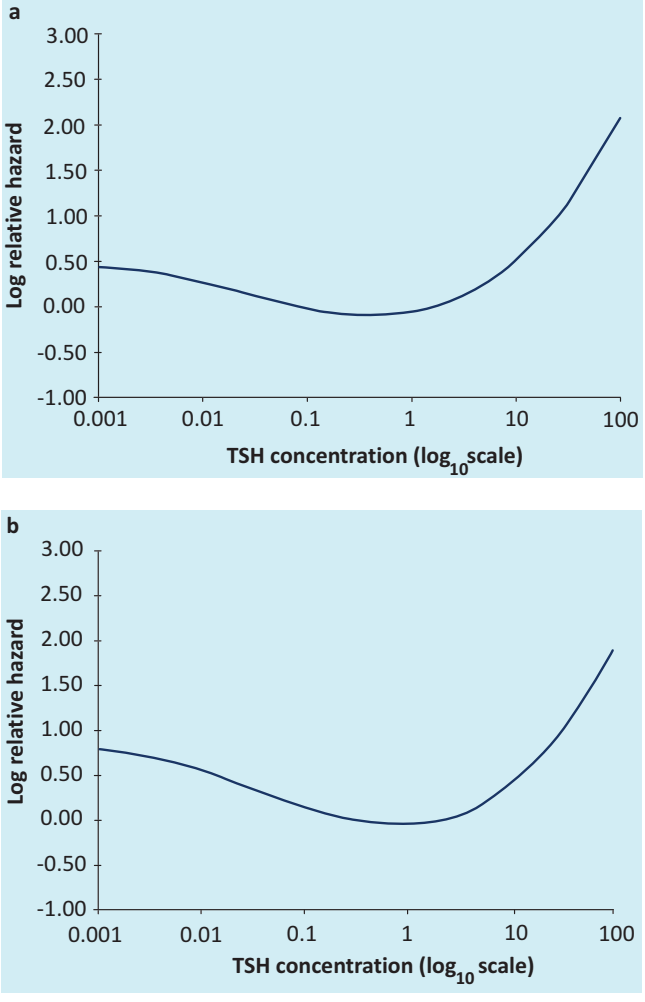

Fig 2. Serum thyroid-stimulating hormone (TSH) concentration and log relative risk for (a) cardiovascular morbidity (CVD) and (b) fractures. Data from Flynn *et al*. 2010.[13]

hypothyroidism; however, when the TSH is greater than 7mU/l, there is an increased risk of CVD and death. Risk of CVD is improved by treatment in younger patients.[9] Patients taking stabilised long-term thyroid replacement have an excellent prognosis if their serum TSH concentration is maintained in the laboratory reference range, and possibly even if their TSH is between 0.1 and 0.4 mU/l. There is increased morbidity for patients with a raised TSH (>4 mU/l) or with a suppressed TSH (<0.1mU/l), but it might be safe for patients taking long-term thyroxine to have a low but non-suppressed TSH in the range of 0.4 to 4.0 mU/l.

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