Controversy in thyroid disease

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ABSTRACT Effective management for hypothyroidism has been available for a century, thanks to the pioneering efforts of George Murray, who first tested injection of thyroid gland extracts in Newcastle. Radioiodine for the diagnosis and then treatment of Graves' hyperthyroidism was introduced by Hertz and Roberts in Boston, and by Leblond in Paris, in 1943, the same year that Astwood in the USA began to use the predecessors of modern antithyroid drugs. Despite this lengthy history, debate continues as to the most effective management of these common disorders. More use of radioiodine, including its use in euthyroid goitre, is being advocated as its safety is now well established. Recent developments in optimising these treatments will be considered in this brief review.

Treatment of Graves' disease

Graves' disease accounts for around 80% of all cases of hyperthyroidism. Toxic multinodular goitre and toxic adenoma are responsible for most of the remainder and their treatment with radioiodine or, rarely, surgery is usually straightforward. However, there is considerable disagreement between endocrinologists with regard to the best way to deal with Graves' disease, highlighted by the transatlantic differences in approach (Table 1)\(^1\)\(^-\)2.

Antithyroid drugs

Most patients with Graves' disease in the UK are given antithyroid drugs initially\(^3\). Remission lasting one year after stopping antithyroid drugs occurs in 50–60%; after ten years, 40% will remain in remission. There are no reliable markers that predict those who will stay in remission. In general, patients with the most severe hyperthyroidism and the largest goitres will relapse, as will those with the highest levels of thyroid stimulating hormone (TSH) receptor stimulating antibodies at the end of a course of treatment. Although the predictive value of measurement of these antibodies continues to be debated, it is currently of little practical use because the decision to use antithyroid drugs cannot be based on the unknown future behaviour of the antibodies and the results with present assays are not sufficiently sensitive and specific\(^4\).

The standard antithyroid drug in the UK is carbimazole, the precursor of the active metabolite methimazole which is used elsewhere in Europe. Propylthiouracil is preferred in the USA, having the theoretical advantage of blocking deiodination of T4, thus lowering T3 levels preferentially. However, this effect offers no real advantage except in severe thyrotoxicosis (thyrotoxic crisis or storm), and any benefit is offset by the shorter half-life of propylthiouracil (90 minutes) compared with methimazole (6 hours). Single daily dosing is therefore possible with carbimazole once euthyroidism is achieved, and compliance has been further improved by the introduction of 20mg size tablets, reducing the number of tablets in many cases to one or two daily (two 20mg carbimazole tablets have the same antithyroid effect as three 50mg propylthiouracil tablets, thrice daily). The side effect of rash occurring with carbimazole is usually dealt with by substituting propylthiouracil, but more serious side effects should lead to cessation of all antithyroid drugs.

The optimum regimen for antithyroid drugs is unclear, the choice broadly being between a titration regimen and a block-replace regimen (Table 2). No trial has compared 6 months of the block-replace regimen with 18–24 months of titration of dose, especially in terms of patient satisfaction, but it seems likely that the block-replace regimen will achieve remission with fewer clinic visits. Other variations on these two regimens have been suggested, including the use of thyroxine after stopping antithyroid drugs with the aim of 'resting' the thyroid with possible immunological benefits. The striking benefits of this approach in a Japanese trial\(^6\) have not been reproduced in the UK or USA\(^7\), and therefore continued thyroxine after antithyroid drugs can-

Table 1. Differences between the choice of treatment for Graves' disease in Europe and North America: data from Refs 1 and 2.

|                        | Europe | North America |
|------------------------|--------|---------------|
| Initial presentation  |        |               |
| with small goitre      |        |               |
| Antithyroid drugs      | 77%    | 30%           |
| Radioiodine            | 22%    | 69%           |
| Surgery                | 1%     | 1%            |
| Initial presentation  |        |               |
| with large goitre      |        |               |
| Antithyroid drugs      | 32%    | 18%           |
| Radioiodine            | 17%    | 75%           |
| Surgery                | 51%    | 7%            |

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not be recommended. It is unclear why such conflicting results have arisen.

A recent review\(^{a}\) called for regular screening to detect the development of agranulocytosis during the first months of antithyroid drug treatment, but this is not the current practice of UK thyroidologists, and there are no prospective trials which show any benefit from screening\(^{10}\). At present, it is best to give patients a written warning about this side effect, with instructions to stop medication and seek an urgent white cell count if suggestive symptoms occur. If agranulocytosis is confirmed, hospitalisation and broad spectrum antibiotics are the mainstay of treatment. Despite case reports of a benefit from granulocyte colony-stimulating factor, a prospective study\(^{11}\) found that recovery was no quicker when this treatment was given.

Radioiodine

Concerns over the long-term effects of radioiodine have been dispelled by surveys showing little evidence of any adverse effect\(^{12-15}\). The slight increase in mortality after radioiodine treatment, due to thyroid-related causes, hip fracture, stroke and cardiovascular events, almost certainly reflects the impact of hyperthyroidism itself and there is no overall increase in death from cancer. A small excess of deaths from site-specific cancers, including the thyroid\(^{14,15}\), has been reported, but it is difficult to know what, if anything, to make of this. The greater number of deaths from thyroid cancer could relate to the adverse effects of thyroid-stimulating antibodies in Graves' patients with a coincidental thyroid malignancy, as there is some evidence that thyroid cancer is more aggressive in Graves' disease. Alternatively, radioiodine could alter the natural history of thyroid tumours, causing dedifferentiation. This uncertainty makes many endocrinologists wary of using radioiodine in children or adolescents, although any risk must be very small and should be set against the risks of alternative forms of treatment\(^{16}\).

| Table 2. Comparison between block-replace and titration regimens for antithyroid drugs. |
|----------------------------------|------------------|------------------|
| **Titration**                    | **Block-replace**|
| Initial daily dose of carbimazole| 40mg             | 40mg             |
| Subsequent doses                 | Reduce by 5–10mg decrements, to maintain normal free T4 levels | Continue 40mg |
| Thyroxine                        | Not needed       | Add 100\(\mu\)g thyroxine daily when free T4 normal; adjust T4 dose in 25–50\(\mu\)g steps to maintain normal T4 |
| Duration for maximum remission   | 18–24 months     | 6 months         |
| Use in pregnancy                 | Yes              | No               |
| Remission rate                   |                  |                  |
| 1 year                           | 50–60%           | 50–60%           |
| 10 years                         | 40%              | 40%              |

**Key Points**

- Antithyroid drugs are the usual initial treatment for Graves' disease. The duration of treatment required when used in a block-replace regimen is shorter than when given by dose titration.
- Radioiodine is safe, effective and increasingly used as first-line treatment for Graves' disease but caution is needed in patients with severe ophthalmopathy.
- Euthyroid sporadic goitre also responds to radioiodine. It provides an alternative to surgery, once malignancy has been excluded, that avoids the adverse side effects of thyroxine suppressive therapy.
- Two controversial issues that need further clinical trials are the place of screening for thyroid dysfunction, particularly in pregnancy, and the use of triiodothyronine combined with thyroxine in the treatment of hypothyroidism.

Other areas of controversy concern the optimal dose of radioiodine, the combined use of antithyroid drugs, and the effects of radioiodine on ophthalmopathy. A UK national survey for the College in 1992\(^{17}\) found huge variation between centres in the dose of radioiodine administered for fairly well defined clinical situations. Subsequent College guidelines\(^{18}\) have described an optimal strategy as being one that achieves euthyroidism with a moderate rate of hypothyroidism (15–20% two years after treatment and 1–3% thereafter). Dosimetry formulae based on preliminary iodine uptake measurements and scans have gradually fallen out of fashion as a method of determining the precise dose given, with the realisation that innate variations in radiosensitivity prevent accurate prediction of outcome and that such an approach is not cost-effective. Any dosimetry which achieves a low initial rate of hypothyroidism is associated with a high rate of failure to cure hyperthyroidism\(^{19}\). Moreover, fixed dose capsules of radioiodine make administration simpler and safer, but cannot be used to deliver an individually tailored dose. An alternative strategy has been to administer a sufficiently large dose of radioiodine to render the patient permanently hypothyroid\(^{20}\). Proponents of this ablative approach argue that it achieves the most rapid and certain cure of hyperthyroidism while allowing the early hypothyroidism to be dealt with during hospital-based follow-up, thereby avoiding unpredictably late hypothyroidism going untreated. This latter point is less pressing now with the wide availability of computerised follow-up schemes and must be judged against the need to give and monitor thyroxine
replacement at an earlier stage than in patients receiving radioiodine doses based on a semiquantitative approach. Moreover, in practice, a single, fixed ablative dose will not necessarily cure all patients unless such doses are given that outpatient treatment is precluded.

Antithyroid drugs are generally given prior to radioiodine in patients with severe Graves' disease or toxic multinodular goitre to reduce the risk of thyrotoxic crisis (or storm), in which there is rapid worsening of thyrotoxicosis due to the release of stored thyroid hormone from the damaged gland. Typical recommendations are to discontinue antithyroid drugs at least two days prior to radioiodine and to use a higher dose of radioiodine than given to patients not receiving the drugs, as antithyroid drugs confer a degree of resistance to radioiodine.

However, several studies have failed to demonstrate any effect on outcome of pre-treatment with antithyroid drugs, and the reason for any protection provided by these drugs is not clear. A retrospective survey has clarified the situation by showing that pre-treatment with propylthiouracil but not methimazole reduces the cure rate after radioiodine, provided methimazole is stopped five or more days before 131I treatment.

Remarkably, the radioprotective effect of propylthiouracil lasted up to 55 days after stopping the drug. Carbimazole and methimazole, nonetheless, do have a mild radioprotective effect and must be discontinued at least one day before radioiodine to avoid this. As an aside, it is worth mentioning that lithium enhances the effect of radioiodine by blocking release of iodine from the thyroid, and therefore produces faster control of hyperthyroidism. The usefulness of lithium in radioiodine treatment remains to be established.

Although the general safety of radioiodine is now well established, the last decade has seen controversy over a possible adverse effect on the course of thyroid-associated ophthalmopathy. Uncertainty was created by studies that had inappropriate controls or inadequate size to allow for confounding factors, but a definitive study has now clearly shown that radioiodine is followed by the appearance or worsening of ophthalmopathy in 15% of Graves' patients, significantly more than the 3% who had deterioration when treated with methimazole. The worsening is often transient and occurs most frequently in smokers, who are at high risk of developing ophthalmopathy. Any worsening of ophthalmopathy can be prevented by a tapering dose of prednisolone given at the time of radioiodine administration. This adverse effect has undoubtedly influenced the management of patients with ophthalmopathy in Europe, and most endocrinologists would prefer to treat Graves' patients with severe ophthalmopathy with antithyroid drugs rather than with radioiodine. The mechanism behind the worsening is unknown but may relate to the release of thyroid antigens believed to share antigenicity with orbital proteins, and to the associated increase in T cell activation which occurs 1–3 months after radioiodine treatment.

Surgery

Subtotal thyroidectomy is an established and effective treatment for Graves' disease, particularly in young patients with large goitres (Table 1) and severe ophthalmopathy; when there is concurrent nodular disease of uncertain aetiology, and when this treatment is preferred by the patient. It is the most expensive of the three treatments for Graves' disease but only by 30–40% when relapse costs are taken into account. To lower the costs of surgery, inpatient stay has been shortened and some centres offer outpatient thyroidectomy, but the safety of this remains controversial.

Despite repeated evaluations, no factor other than remnant size reliably predicts relapse or hypothyroidism after surgery. Since avoiding recurrence of hyperthyroidism after surgery should obviously be a key priority, total or near total thyroidectomy rather than subtotal resection has been advocated. This operation carries little if any increased risk provided it is undertaken by a skilled endocrine surgeon. It seems likely that total thyroidectomy will be used increasingly, but in fewer centres, so that the necessary expertise can be maintained.

Pregnancy and Graves' disease

Complications of Graves' disease in pregnancy include congestive heart failure, thyrotoxic crisis, preterm delivery, stillbirth, low birth weight, preeclampsia and neonatal thyrotoxicosis, the latter being caused by the transplacental transfer of thyroid stimulating antibodies from the mother. Although impaired fetal growth and a high fetal heart rate (>160/min) suggest the presence of neonatal thyrotoxicosis, there is disagreement over the value of measuring the

| Table 3. Guidelines for the measurement of TSH receptor antibodies in pregnant women with Graves' disease; modified from Ref 32. |
|---------------------------------------------------------------|
| **Mother** | **TSH-R antibody measurement*** |
| Euthyroid after previous treatment with antithyroid drugs | Not needed |
| Euthyroid (on or off thyroxine) after previous treatment with radioiodine or surgery | Either early in pregnancy, with fetal monitoring and repeat antibody measurement in last trimester if initial results positive, or at the beginning of last trimester |
| Hyperthyroid and taking antithyroid drugs | At the beginning of the last trimester |

* Although assays measuring thyroid stimulating antibodies provide the most accurate information, these are not widely available, and TSH-receptor binding assays provide nearly as much information.
maternal level of thyroid stimulating antibodies in pregnant women with Graves' disease. This controversy is compounded by the lack of a readily available assay for thyroid stimulating antibodies. TSH-receptor binding antibodies are often measured as a proxy but the two sets of results do not correlate completely. Ideally, the stimulating antibodies should be measured but the recent guidelines produced by the European Thyroid Association provide justification for the use of TSH-receptor binding antibodies and give useful recommendations for those who care for such patients (Table 3).

Because of the risks to the mother and the fetus, Graves' disease in pregnancy requires treatment with antithyroid drugs by the titration regimen, surgery in the second trimester being the only alternative. Which antithyroid agent should be used? It has generally been thought that propylthiouracil is less likely to cause fetal hypothyroidism than methimazole as there is less placental transfer of propylthiouracil, but in practice there is nothing to choose between the drugs and even low doses of either may cause fetal hypothyroidism. The message is clear: doses must be individually tailored to maintain maternal free T4 in the high normal (or even slightly elevated) range using the smallest possible dose of either drug. Propylthiouracil is also preferred by some endocrinologists because methimazole has been associated with fetal aplasia cutis and choanal atresia. Here the evidence is less good and if there is a true association, the effect of methimazole is weak. Nonetheless, I agree with others in the belief that propylthiouracil is preferable in pregnancy as it has not been associated with any malformation despite widespread use in North America, and, in all other respects, is equally effective. Why take any risk in pregnancy?

**Treatment of hypothyroidism**

*Subclinical hypothyroidism*

During the slow progression of thyroid failure, patients are increasingly recognised who have elevated TSH but normal free T4 levels, so-called subclinical hypothyroidism. As a result of careful population surveys, the relative risks of progression in subclinical hypothyroidism are now well established. There is now a good case to be made for treating patients with a sustained elevation of TSH, normal T4 and positive thyroid antibodies, and for offering a trial of treatment or annual follow-up to those who are thyroid antibody-negative (Fig 1), although there is no unanimity on this nor on which patients should be screened for thyroid failure, clinically overt or otherwise.

The question of screening has now extended into debate over the benefits of screening all pregnant women, provoked by the evidence that elevated TSH levels in the maternal circulation during pregnancy are associated with suboptimal performance in neuropsychological tests administered to their children at ages 7–9. These data confirm what is expected from previous animal and human studies on the importance of thyroid hormones on brain development throughout pregnancy, although much alarm has followed this recently published paper. It is important to appreciate that the effects were small and not apparent in the majority of neuropsychological tests performed, and there are no data yet on any benefits of treatment if sub-

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**Fig. 1 Algorithm for managing subclinical hypothyroidism. In all cases it is important, before proceeding further, to confirm that TSH elevation is sustained by measuring TSH levels 2–3 months after initial measurement. From Ref 35 with permission.**
clinical or overt maternal hypothyroidism is identified in the second trimester, the stage of pregnancy when these samples were taken. As the fetal thyroid develops at week 7 and is fully functional at week 12, it seems most likely that later treatment of a hypothyroid mother will not help, any neurological damage being caused in the first trimester when the fetus is totally dependent on maternal thyroid hormone. Thyroxine treatment would, on this reckoning, only be likely to be useful if offered to hypothyroid women identified pre-conception. Setting up a study to test this, never mind a subsequent screening programme, would be very difficult indeed.

**Thyroid hormone replacement**

There is no doubt that the current assays for TSH have greatly improved the precision with which thyroxine replacement can be monitored, and there is a consensus that the goal of treatment is to lower TSH into the reference range with thyroxine alone, such replacement having no adverse effects

In some patients pre-existing angina may be uncovered by this approach and, if optimising antianginal treatment does not improve matters, it is probably best to accept a lower dose of thyroxine. Patients apparently resistant to thyroxine pose a severe challenge to endocrinologists, but the answer is almost always failure to take thyroxine (Table 4).

Unfortunately, a few patients continue to feel unwell on conventional thyroxine replacement but seem better on doses which lower TSH below the reference range

Continued suppression of TSH increases the risk of atrial fibrillation and – less convincingly – clinically significant bone loss, posing a problem solved by some who titrate thyroxine to bring TSH into the lower half of the reference range, and by others who accept that symptomatic relief with larger doses of thyroxine is preferable to biochemical normality. Why should this be?

T4 is inactive and must be converted to T3 by one of three deiodinase enzymes expressed in a relatively tissue-specific manner. Thus it is possible that thyroxine levels sufficient to satisfy the deiodination pathway in the pituitary, and to be reflected in a normal TSH level, are insufficient to supply T3 at normal levels to other tissues with different deiodination kinetics. The logical extension of this argument is to use triiodothyronine as well as thyroxine in replacement. Such a trial has recently been reported, with 50μg of the normal thyroxine requirement of patients being replaced by 12.5μg of triiodothyronine

Modest improvements in mood and some aspects of neuropsychological function were found when the combination replacement was tested against thyroxine alone, but caution is needed before adopting these results enthusiastically. First, this was a very short study (5 weeks on each treatment) and more sustained benefit must be shown. Second, was there really restoration of euthyroidism by the combination, or were some subjects on thyroxine alone under-replaced?

Under-replacement is suggested by the tissue markers of thyroid hormone action which showed a change with the two treatments. Finally, T3 has a much shorter half-life than T4 and the bolus-like effect of intermittent T3 has the potential for adverse cardiac effects, even if the TSH is kept normal. It is striking that our concepts of this simplest of treatments can still be challenged and that more work is needed despite the intervening century since George Murray's discovery.

**Goitre**

Non-endemic or sporadic goitre affects 5% of the UK population. It is surprising that still so little is known about the pathogenesis of such a common condition and why some goitres progress from a so-called simple or colloid stage to multinodularity and finally toxic multinodular goitre. Most patients do not seek or require treatment but those with cosmetic problems, neck discomfort or dysphagia do require help. Exclusion of malignancy is a *sine qua non* and this is one of the main reasons for operating on retrosternal goitres which cannot otherwise be biopsied. The frequency of malignancy is probably neither increased nor decreased in a typical multinodular goitre.

Non-surgical treatment for goitre has had an uncertain place in management and trials of thyroxine replacement originally gave conflicting results, ranging from 0–60% success

Patient heterogeneity and, most importantly, failure to classify patients biochemically, contributed to this variability: if the aim of thyroxine treatment is to avoid the thyroid growth-stimulating effects of TSH, it is obviously useless to use thyroxine in patients with subclinical hyperthyroidism, where TSH is already suppressed. Controlled trials have shown that thyroxine has a beneficial effect in about 60% of euthyroid patients with sporadic goitre, leading to around a 25% decrease in volume, and this treatment also prevents the appearance of new nodules in multenodular goitre

These changes are modest and are only sustained as long as thyroxine is continued. The adverse cardiac effects of long-term TSH suppression, mentioned

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**Table 4. Reasons for failure of TSH to normalise on conventional thyroxine replacement doses (up to 200μg/day).**

| Reason for Failure |
|-------------------|
| Poor compliance |
| Malabsorption |
| Increased requirements (pregnancy, obesity; target dose is 1.6–1.7μg/kg body weight) |
| Assessment of TSH too soon after starting or increasing thyroxine (allow 6–8 weeks) |
| Tablets out of date |
| Drugs interfering with absorption or metabolism (ferrous sulphate, colestipol, cholestyramine, sulphasalazine, aluminium hydroxide, phenytoin) |
| Anomalous TSH values due to assay artefact |
| Incorrect diagnosis (thyroid hormone resistance syndrome, pituitary tumour) |
above, make many endocrinologists reluctant to use thyroxine treatment for goitre, especially in the elderly.

Radioiodine has been increasingly employed in continental Europe for the treatment of euthyroid, sporadic goitre42. The doses used are often high (600–3400MBq) and hospitalisation is required for patients who receive doses greater than 800MBq. Further work is needed to clarify the optimum dose in terms of both efficacy and patient convenience. Around 70–80% of patients treated with radioiodine have a reduction in goitre size of about 50% two years later. Those with the largest and most nodular goitres have the least benefit, suggesting that maximum benefit from this treatment will be obtained when it is given early, and the goitre is still small43. Unfortunately, it is impossible at an early stage to predict which goitres may cause symptoms or cosmetic problems. The side effects of radioiodine obviously include hypothyroidism, and in a few patients Graves’ disease has paradoxically been triggered, most likely due to the immunological effects of radioiodine, mentioned above in the context of ophthalmopathy. Radiation thyroiditis, causing local tenderness and sometimes fever, is unusual, self-limiting and easily treated with a short course of prednisolone. Acute thyroid swelling, as part of this thyroiditis, leading to tracheal oedema and obstruction, has been a theoretical concern but even very large goitres causing partial airways obstruction can be treated safely using radioiodine44.

On balance, therefore, radioiodine is a safe and effective treatment for symptomatic sporadic goitre. Once the natural reluctance of physicians to use radiation treatment for a benign and non-life threatening condition changes, it is likely that radioiodine will be used more frequently in the UK for euthyroid goitre. Improved patient selection criteria for early treatment will be an important development.

Conclusions

Developments in thyroid disease management continue to provoke controversy. The large numbers of patients with thyroid disease, or at risk of developing it, make any improvements in diagnosis or treatment important, not least in the delivery of the most cost-effective methods. Further work is still needed, particularly to identify a safe, immunologically-targetted treatment for Graves’ disease and ophthalmopathy that avoids hypothyroidism, and to establish the best protocol for screening for thyroid disease.

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