Management of Primary Hypothyroidism

Primary hypothyroidism is an insidious condition with a significant morbidity and often subtle and non-specific symptoms and clinical signs.

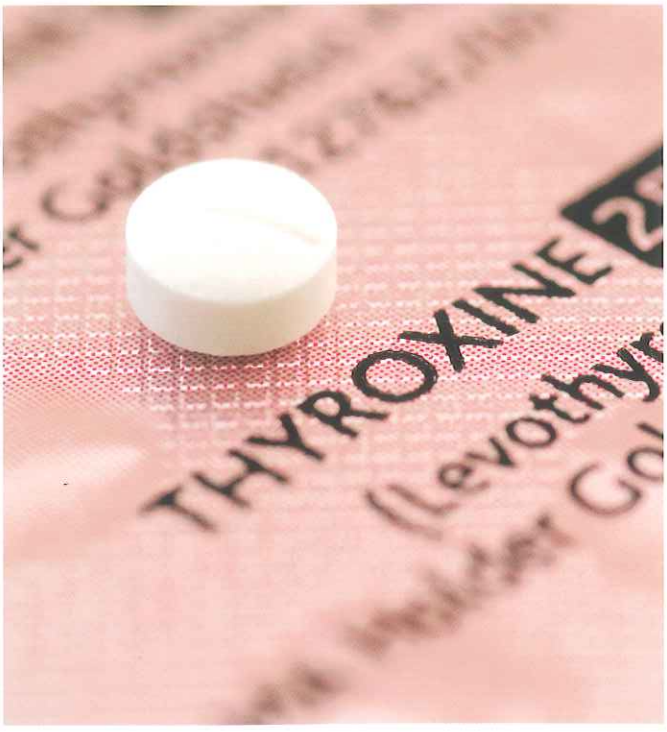
The earliest biochemical abnormality is an increase in serum thyroid-stimulating hormone (TSH) concentration associated with normal serum free thyroxine (T4) and triiodothyronine (T3) concentrations. This 'subclinical hypothyroidism' is followed by a decrease in serum free T4 concentration, which leads to overt hypothyroidism, at which stage most patients have symptoms and benefit from treatment.

In the UK, the prevalence of spontaneous hypothyroidism is between 1% and 2%. It is ten times more common in women than in men, and more likely to affect older women. The cause is either chronic autoimmune disease or destructive treatment for hyperthyroidism with either radioiodine or surgery, which may account for up to a third of all cases of hypothyroidism.

Every day over one million people in the UK take the thyroid hormone levothyroxine sodium (L-T4), but few are aware of the controversies that have surrounded the treatment of hypothyroidism for over a century. From the first injections of sheep thyroid in 1891 to academic rivalry surrounding the identification of T4, and the ongoing debate over the advantages of combining L-T4 with liothyronine (L-T3), boosting a sluggish thyroid has never been straightforward.

The goal of therapy is to restore patient wellbeing and normalise serum TSH levels. Most patients respond well, but a minority experience persistent symptoms despite adequate biochemical correction, and caring for these individuals is challenging.

A 19th century English physician, George Murray, first



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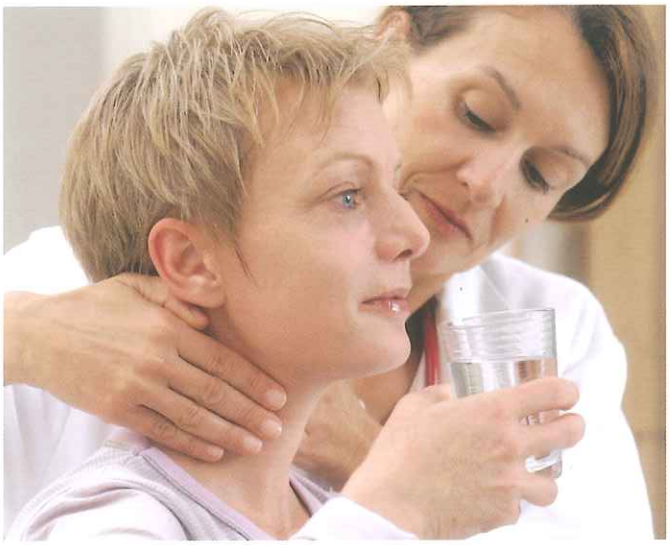

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suggested injecting patients with myxoedema (severe hypothyroidism) with extract of sheep thyroid, but he initially received little support from the medical establishment. However the beneficial effects he achieved with sheep thyroid in a 46 year old woman in 1891 aroused considerable interest, even when his third and fourth patients died of heart failure.

Fortunately, the first patient survived for nearly 30 years and continued to use sheep thyroid extract, initially by injection and later orally. As animal thyroid gland use became more widespread, chemists set about extracting the vital ingredient responsible for overcoming symptoms of hypothyroidism.

The US chemist Edward Kendall first succeeded in isolating 7g of T4 from 3,000kg of pig thyroid gland in 1914. Charles Harington, a British chemist then synthesised the hormone and corrected Kendall's description of its chemical formula a decade later. Harington also recognised that although T4 occurred naturally as an equal mixture of the levo and dextro forms of the chemical, it was the levoform that had greater physiological activity. A commercial product was launched by Glaxo in 1949.

Synthetic forms of L-T4 have been prescribed since the 1950s and were introduced without randomised controlled trials. Evidence subsequently appeared of potential harm from L-T4 over-replacement, including atrial fibrillation and bone loss, particularly in post-menopausal women. More accurate serum TSH measurement has led to patients now being prescribed lower doses of L-T4 than in earlier decades, with more closely matched serum TSH, T4 and T3 levels.

The healthy thyroid produces mainly T4 and much smaller amounts of the physiologically more active T3. Approximately 80% of T3 is provided by conversion of T4 to T3, with the remaining 20% of T3 coming direct from the thyroid. In contrast, people with hypothyroidism are treated with T4 alone, so all of their T3 is produced as a result of conversion from T4.

It has been suggested that one reason why some people are not happy with L-T4 treatment is that they are not

getting their supply of T3 in a physiological way, as all of it is coming from the conversion from T4.

Some practitioners have advocated going back to using pig thyroid extracts, but the balance of T4 and T3 that patients get from these is far from natural. The pig thyroid produces T4 and T3 in a ratio of 4:1, compared with the ratio of 14:1 in human thyroid. Setting aside the issue of the "unnatural" ratio of thyroid hormones in pig tissue, would patients be better off with potentially more physiological combination treatment with synthetic human L-T4 and L-T3 than with L-T4 monotherapy?

In 2013 the European Thyroid Association (ETA) reviewed 1,355 patients in 13 randomised controlled trials of L-T4 + L-T3 versus L-T4 monotherapy. Study design, duration of treatment and dose ratio of T4 to T3 were variable. In studies that considered quality of life, cognition, mood and symptoms, combination therapy was no better than monotherapy in nine out of 12 studies, but better in three.

Data was analysed from six trials in which patients were asked to state a preference for treatment, and 48% preferred combination treatment, 27% preferred monotherapy and the rest had no preference. The ETA concluded that there was insufficient evidence to show that combination treatment is more effective than monotherapy, and recommended that endocrinologists should rule out autoimmune disease associated with thyroid autoimmunity, reassure patients about their condition, and support them in coming to terms with a chronic disease requiring life-long medication.

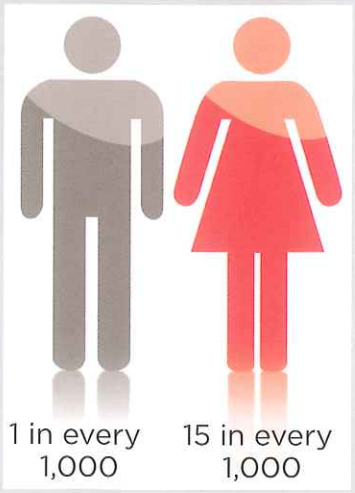
If symptoms still persist for six months or more, endocrinologists may consider combination treatment on an experimental basis. When this is appropriate, the ETA suggests that treatment should be started in L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight, and that L-T3 should be divided in two doses.

The GP Quality and Outcomes Framework (QOF) targets for thyroid in England encourage regular monitoring of patients with hypothyroidism. This may demonstrate greater fluctuations in thyroid levels than previously realised, and a tendency for micromanagement of L-T4 dosing in primary care, whether or not this is indicated by a patient's symptoms.

Delivering individualised, patient-centred care and shared decision making is key with primary hypothyroidism.

People now have high, sometimes unrealistic expectations about how energetic they should feel, but that does not mean that tiredness and symptoms such as "brain fog" should be ignored. L-T4 is considered the most perfect hormone replacement that has yet been devised for endocrine conditions, but there are undoubtedly people who fall outside the current treatment model.

Who's affected?



In the UK, it affects 15 in every 1,000 women and 1 in 1,000 men.

Around 1 in 3,500-4,000 babies are born with an underactive thyroid (congenital hypothyroidism). All babies born in the UK are screened for congenital hypothyroidism using a blood spot test when the baby is about five days old.

Source: www.nhs.uk/conditions/Thyroid-under-active

Animal-derived products that contain T4 and T3 are not physiological and are not the answer in the longer term, but we do need to find ways to ensure that all our patients with hypothyroidism feel the full benefits of replacement therapy.

The British Thyroid Association (BTA) is to publish a statement on current best practice for the management of primary hypothyroidism, updating the previous 2013 Royal College of Physicians (RCP) statement and reviewing recent hypothyroidism guidelines from the American Thyroid Association (ATA) and ETA.

L-T4 therapy offers a safe, rational, and simplified approach to the correction of hypothyroidism, and treatment results in improved physical and psychological well-being for the vast majority of patients. However, the management of patients with a sub-optimal clinical response remains challenging.

The benefits of combination therapy with LT-4 and LT-3 are still unproven and the potential for harm exists with unregulated use of unapproved therapies. Future randomised controlled trials will be of value, especially on the use of combination therapy in patients with specified genetic or clinical characteristics. Strategies to improve medication adherence, optimise drug delivery, and standardise thyroid hormone formulations will ultimately improve patient outcomes.

Delivering individualised, patient-centred care and shared decision making is key with primary hypothyroidism. The BTA hopes that this statement will support clinicians in implementing evidence based strategies in the management of the disease. ■

Reference

Okosieme O, Gilbert J, Abraham P, et al. (2015) Management of Primary Hypothyroidism Statement by the British Thyroid Association Executive Committee. Clinical Endocrinology in press.

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