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Citation for final published version:

Taylor, Peter N. , Medici, Marco M., Hubalewska-Dydejczyk, Alicja and Boelaert, Kristien 2024. Hypothyroidism. The Lancet 404 (10460) , pp. 1347-1364. 10.1016/S0140-6736(24)01614-3

Publishers page: [https://doi.org/10.1016/S0140-6736\(24\)01614-3](https://doi.org/10.1016/S0140-6736(24)01614-3)

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Hypothyroidism

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Hypothyroidism, the deficiency of thyroid hormone, is a common condition worldwide. It affects almost all body systems and has a wide variety of clinical presentations from being asymptomatic to, in rare cases, life threatening. The classic symptoms of hypothyroidism include fatigue, lethargy, weight gain, and cold intolerance; however, these symptoms are non-specific and the diagnosis is typically made on biochemical grounds through serum thyroid function tests. The most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis), although other causes, including drugs (such as amiodarone, lithium, and immune checkpoint inhibitors), radioactive-iodine treatment, and thyroid surgery, are frequent. Historically, severe iodine deficiency was the most common cause. Reference ranges for thyroid function tests are based on fixed percentiles of the population distribution, but there is increasing awareness of the need for more individualised reference intervals based on key factors such as age, sex, and special circumstances such as pregnancy. Levothyroxine monotherapy is the standard treatment for hypothyroidism; it is safe and inexpensive, restores thyroid function tests to within the reference range, and improves symptoms in the majority of patients. However, 10% of patients have persistent symptoms of ill health despite normalisation of thyroid function tests biochemically and a substantial proportion of patients on levothyroxine have thyroid-stimulating hormone concentrations outside the reference range. Ongoing symptoms despite levothyroxine treatment has led to some patients using liothyronine or desiccated thyroid extract. Taken together, these factors have led to intense debate around the treatment thresholds and treatment strategies for hypothyroidism. In this Seminar, we review the epidemiology, genetic determinants, causes, and presentation of hypothyroidism; highlight key considerations and controversies in its diagnosis and management; and provide future directions for research.

Introduction

Thyroid hormones act on almost all body systems and have profound and diverse physiological effects, as evidenced by their role in induction of metamorphosis in amphibians¹ and regulation of breeding in ducks and songbirds.² In humans, thyroid hormone deficiency, known as

hypothyroidism, is common worldwide.³ Although hypothyroidism can be asymptomatic with modest clinical effects, if left untreated, it can result in substantial morbidity and ultimately death. Due to the variable nature of symptoms and an absence of clear symptom specificity,⁴ hypothyroidism is largely a bio-chemical diagnosis. Both the diagnosis and monitoring of treatment response relies on the use of thyroid function tests. Modest changes in circulating thyroid hormone levels (free tri-iodothyronine [FT3] and free thyroxine [FT4]) result in larger inverse changes in the pituitary hormone thyrotropin (thyroid-stimulating hormone [TSH]) concentration. Consequently, TSH is the accepted main marker of thyroid status.⁵ Since the 1970s, levothyroxine has been the mainstay of treatment. The current primary goal of hypothyroidism treatment is thus to normalise TSH concentrations.⁶ Most cases are diagnosed and routinely managed in primary care rather than by endocrinologists.

Most cases of hypothyroidism are classified as primary hypothyroidism arising from failure of the thyroid gland to produce sufficient thyroid hormone. Overt hypothyroidism is defined as both a TSH concentration above and an FT4 concentration below the laboratory reference range. Subclinical hypothyroidism is defined as a TSH concentration above the reference range and FT4 concentrations within the reference range.

At present, the TSH threshold for the initiation of levothyroxine treatment is contentious, and initiation at elevations in TSH concentrations marginally above the reference range has been observed in recent years.^{7,8} This treatment approach and widespread thyroid function testing has resulted in levothyroxine being one of the most commonly prescribed medications in the world.⁸ For most patients, levothyroxine monotherapy provides a satisfactory replacement of thyroid hormone. However, 25–40% of patients on long-term levothyroxine treatment have a TSH concentration below or above the reference range.^{7,9,10} A proportion of individuals on levothyroxine have substantial and persistent dissatisfaction¹¹ due to ongoing symptoms of hypothyroidism despite restoration of biochemical euthyroidism, which has led some patients to use liothyronine or desiccated thyroid extract (DTE). However, systematic reviews and meta-analyses of 18 trials of combination levothyroxine–liothyronine replacement found no clear benefit over levothyroxine monotherapy.^{12,13}

Reference ranges might be dynamic rather than static. Compelling arguments can be made for age-specific and pregnancy trimester-specific reference ranges.^{6,14} In older individuals (>65 years), the reference range for TSH is shifted towards higher values, with the 97.5th percentile of the confidence interval for serum TSH in healthy older people being around 7.5 mIU/L.³ Although higher serum TSH values might occur naturally, as part of the ageing process,^{15–17} this effect could be highly pertinent to the management of older individuals, particularly as symptoms such as tiredness and fatigue are common, but are not strongly predictive features of hypothyroidism.⁴ Thus, older individuals could be inappropriately started on levothyroxine. TSH concentrations in healthy individuals oscillate around a narrow point,¹⁸ which is strongly influenced by their genetic architecture.^{19,20} Although the effect is modest, misclassification of abnormal thyroid function or restoration to euthyroidism can occur when stricter targets are used in pregnancy.²¹ Recent meta-analyses have identified clinically relevant TSH and FT4 concentrations in pregnancy,²² and the need for assay and trimester-specific reference ranges.²³

Epidemiology Globally, most cases of primary hypothyroidism are due to the autoimmune thyroid disease known as Hashimoto's thyroiditis. Historically, severe iodine deficiency was a common cause, although its prevalence is fortunately declining.³ Hashimoto's thyroiditis is characterised by slow, progressive thyroid failure due to lymphocytic infiltration and immune-mediated destruction of the thyroid gland.²⁴ Raised concentrations of antibodies to

thyroperoxidase antibodies (TPO-Ab) are a defining feature of Hashimoto's thyroiditis and are present in approximately 11% of the general population.¹⁵ In subclinical hypothyroidism, TPO-Ab positivity is an important risk factor for progression to overt disease.²⁵ The incidence of Hashimoto's thyroiditis has been steadily increasing,²⁶ although the cause is incompletely understood. Hashimoto's thyroiditis is thought to arise from a combination of genetic susceptibility and environmental factors (eg, iodine excess, pregnancy and sex steroids, selenium deficiency, and radiation exposure).²⁷ Chemokines also play a role in the development of Hashimoto's thyroiditis²⁸ and increasing evidence suggests that both genetic and environmental factors modulate epigenetic factors to synergistically increase the risk.²⁹ Additionally, iodine deficiency influences DNA methylation in several genes linked to immune regulation and thus increases the risk of hypothyroidism.

In iodine-sufficient countries, the prevalence of overt hypothyroidism is approximately 1–2%.^{3,31–33} Hypothyroidism (subclinical and overt) is approximately 10-times more common in women than men,³¹ and in older individuals the prevalence is as high as 7% in individuals aged 85–89 years³⁴ when age-related reference ranges are not used.

The prevalence of hypothyroidism (subclinical and overt) ranges from 0.2% to 5.3% in Europe^{3,35–37} and 0.3% to 3.7% in the USA,¹⁰ depending on the definition used and the population. Longitudinal data from the UK suggest an incidence rate of spontaneous hypothyroidism of 3.5–5.0 per 1000 women and 0.6–1.0 per 1000 men.^{31,38} Data on the effect of genetic ancestry on hypothyroidism risk are scarce, although the NHANES III study identified that the overall prevalence of hypothyroidism was 4.6%.¹⁵ The prevalence was markedly lower in individuals of African Caribbean descent (1.7%).¹⁵ Whether this difference is due to variability in genetic architecture, social factors such as access to biochemical testing, or dietary differences such as differing iodine intake is unclear.

At the individual level, hypothyroidism is more common in patients with other autoimmune diseases than in the general population, including rheumatoid arthritis, type 1 diabetes, Addison's disease, and coeliac disease,²⁶ and can also occur as part of the rare autoimmune polyendocrine syndromes. Individuals with Down syndrome and Turner's syndrome also have higher risk than the general population.^{39,40} Hypothyroidism can be iatrogenic following definitive treatment for hyperthyroidism, or after surgery for goitre or thyroid cancer and nodules.

There is flawed evidence from single-cohort studies, with potential for residual confounding, that lifestyle factors might influence disease prevalence of hypothyroidism. Current smokers had a 50% lower prevalence of subclinical hypothyroidism and a 40% lower prevalence of overt hypothyroidism compared with non-smokers.⁴¹ Moderate alcohol intake has also been associated with a reduced risk of hypothyroidism.⁴²

Genetic epidemiology

Hashimoto's hypothyroidism is a complex disorder caused by a combination of multiple genetic and environmental factors. Twin studies have estimated that approximately 65% of variance is determined by genetic factors.⁴³ Studies from the 1970s on genetic determinants often involved a candidate gene approach, which analysed a small number of variants located within specific genes selected based on their known function. Therefore, only a handful of genetic variants have been consistently identified since the 1970s, including variants in HLA classes I and II, CTLA4, PTPN22, IL2RA, TSHR, and FCRL3.⁴⁴ Since the beginning of the 21st century, genome-

wide association studies (GWASs) have allowed the study of associations of approximately 1 million independent genetic variants with a trait of interest across the entire genome with a hypothesis-free approach. The largest thyroid GWASs have focused on variations in thyroid hormone concentrations in the general population, identifying over 100 genetic variants associated with TSH or FT4 concentrations, or both.^{45–47} A GWAS on TPO-Ab status and concentrations identified significant associations with variants in TPO, ATXN2, BACH2, MAGI3, and KALR.⁴⁸ In a follow-up study, these variants were, together with others, combined in a polygenic risk score, which was shown to be associated with the risk of developing both subclinical and overt hypothyroidism.⁴⁹ In this study, compared with individuals in the lowest quartile for genetic risk score, those in the highest quartile had a higher odds of subclinical hypothyroidism (odds ratio [OR] 1.80; 95% CI 1.27–2.55) and a higher odds of overt hypothyroidism (1.89; 1.24–2.87).⁴⁹ In 2019, a GWAS on autoimmune thyroid disease included 30234 cases and 725172 controls from Iceland and the UK Biobank.⁵⁰ The majority of autoimmune thyroid disease cases were Hashimoto's thyroiditis. This study is currently the largest GWAS on autoimmune thyroid disease, and identified⁸⁴ novel genetic variants and provided a rich resource for successful in-vitro studies, unravelling the intricacies of thyroid hormone regulation and disease.^{45,50}

There is an ongoing debate whether subclinical hypothyroidism should be treated or not, as clear answers from clinical trials are missing a greater understanding of the genetic architecture of thyroid status, and might prove to be essential. To see benefit in terms of reductions in cardiovascular events, large studies with substantial follow-up times are needed, and progression to overt disease might also occur in the control group, making meaningful conclusions difficult. The best available literature encompasses epidemiological associations between subclinical hypothyroidism and various clinical endpoints;⁵¹ however, such observational studies are susceptible to confounding, reverse causation, and other biases, which can lead to incorrect causal inference. In mendelian randomisation the effect of an exposure (eg, thyroid function) on an outcome (eg, cardiovascular disease) is evaluated using genetic variants associated with the exposure as the instruments.⁵² As genetic variants can affect an outcome (via exposure), but not vice versa, an association between the genetically estimated exposure and outcome can provide strong support for the causality of the observed association. Although in the past decade many mendelian randomisation studies on variation in normal-range thyroid function have been performed, few focused on the effects of subclinical hypothyroidism as, until recently, only a small number of genetic variants associated with altered risk of developing Hashimoto's thyroiditis had been identified.^{44,50}

Variation in individual thyroid hormone transport and metabolism genes has been suggested to affect hypothyroidism treatment efficacy, such as variation in the type 2 deiodinase, which we refer to in the levothyroxine–liothyronine combination therapy section. However, the combined effects of variation in multiple genes probably have a more substantial impact. These polygenic risk scores are now studied in many fields in medicine in the prediction (prevention), diagnosis, and management of complex diseases.⁵³ The current polygenic risk scores focusing on thyroid function^{45,49} are too limited by their discriminatory power to be used in clinical practice. However, given the important role of genetic factors in Hashimoto's thyroiditis,⁴³ more genetic variants could be identified in future studies with large international consortia, such as the ThyroidOmics Consortium. These genetic variants, together with other clinical markers, could personalise the clinical diagnosis and management of patients with hypothyroidism.⁶

Causes

Hypothyroidism might be primary (due to inadequate production from the thyroid gland), secondary (due to TSH deficiency in the pituitary gland), tertiary (due to thyrotropin-releasing hormone deficiency in the hypothalamus), or peripheral (extrathyroidal; including consumption of thyroid hormone or genetic mutations inducing thyroid-hormone resistance; panel 1). Secondary and tertiary hypothyroidism are often referred to as central hypothyroidism, and both central and extrathyroidal hypothyroidism account for less than 1% of cases worldwide.⁵⁴ Chronic autoimmune thyroiditis (Hashimoto's thyroiditis) is the most common cause of hypothyroidism in iodine-sufficient countries.

Congenital hypothyroidism

Affecting around 1 in 3000 newborns worldwide, congenital hypothyroidism is the most common neonatal endocrine disorder and one of the most common preventable causes of intellectual disability.⁵⁵ 65% of primary congenital hypothyroidism is due to defects in thyroid development, including athyreosis, ectopy, hemiagenesis, and hypoplasia. In these cases, other organ systems are frequently affected as the genes involved often play a central role in key developmental embryogenic processes that affect multiple tissues.^{55,56} In the remaining 35% of primary congenital hypothyroidism cases, thyroid development and differentiation are normal, but one of the key steps in thyroid hormone production is impaired (ie, thyroid dyshormonogenesis), such as iodine uptake or organification; or thyroglobulin synthesis, storage, or release. Central congenital hypothyroidism is less common than primary congenital hypothyroidism and, in most cases, is part of combined pituitary hormone deficiencies, which cause isolated, central congenital hypothyroidism, except for biallelic mutations in the β subunit of TSH and the thyrotrophin-releasing hormone receptor. Although genetic causes identified for primary congenital hypothyroidism are primarily due to thyroid dysgenesis (<5%) and dyshormonogenesis (~50%), progress in genotyping techniques (ie, next-generation sequencing) has facilitated the discovery of various novel candidate genes and variants.^{55,56} Such studies strongly suggest that congenital hypothyroidism can frequently be due to the carriage of multiple genetic variants with modest individual effects, but with substantial effects when carried together.^{57–59} This oligogenic-origin hypothesis for congenital hypothyroidism could explain the sporadic occurrence, and the variable expression and penetrance of congenital hypothyroidism.^{55–57}

Most cases of primary congenital hypothyroidism are detected by neonatal TSH screening, which is universal in most countries. To prevent treatment delay, an abnormal screening result should be immediately followed by confirmatory routine thyroid function testing. Depending on the severity of the TSH (and reflex FT4 measurement) abnormalities, treatment should be started as soon as possible or thyroid function should be retested within a short time interval to prevent intellectual disability.⁶⁰

Iodine deficiency and iodine excess

Since the early 1990s, the prevalence of iodine deficiency has declined dramatically worldwide; 88% of the global population now has access to iodised salt and only 21 countries are currently considered iodine deficient.³³ Severe, but not mild-to-moderate, iodine deficiency results in hypothyroidism.⁶¹ Increased awareness of the importance of iodine status and potential deleterious effects of even mild-to-moderate iodine deficiency in pregnancy on cognitive development in offspring has increased iodine fortification in many countries. There is, however, growing evidence of an increase in the frequency of thyroid autoimmunity following iodisation programmes.^{62–65} Analysis of fortification programmes in Denmark revealed that even a cautious

iodisation approach was associated with an increase in TPO-Ab from 14.3% to 23.8%.⁶⁶ In the past 20 years, several studies have assessed the incidence of thyroid dysfunction following the introduction of effective iodine prophylaxis, with long-term follow-up. In 2020, results of a representative cross-sectional study⁶⁷ were published 20 years after universal salt iodisation had been implemented in China due to mild-to-moderate iodine deficiency. The results showed that following iodine prophylaxis, the incidence of thyroid autoantibodies decreased to similar levels as before iodine prophylaxis was implemented, indicating that the effect of early iodine-induced thyroid autoimmunity was transient.⁶⁷ Similarly, in a study from Denmark, the incidence of hyperthyroidism only increased in the 7–8 years after intervention and its incidence decreased to preintervention levels during follow-up.⁶⁸

Pregnant women are particularly at risk of developing iodine deficiency due to increased thyroidal demands and increased urinary excretion.^{69,70} The impact of maternal iodine deficiency on the developing fetus in pregnancy can be profound, and iodine deficiency remains one of the most common preventable causes of intellectual disability in children. Severe iodine deficiency results in a spectrum of disorders in offspring, which includes severely impaired neurological development, ranging from a decline of approximately 15 intelligence quotient points to profound intellectual disability, hypothyroidism, goitre, and impaired growth.^{71,72} Additionally, correction of moderate and severe iodine deficiency results in better clinical outcomes, including reduced neurological impairment and infant mortality.⁷³ Nevertheless, the evidence for the benefit of iodine prophylaxis during pregnancy in areas of mild-to-moderate iodine deficiency on maternal thyroid function, and neurological and behavioural development of the offspring remains unclear.⁷⁴

However, a sudden, large increase in iodine intake or exposure can result in inhibition of organification in the thyroid, and reduced formation and release of thyroid hormone, known as the Wolff–Chaikoff effect.⁷⁵ This effect can be used to normalise thyroid function before surgery in thyrotoxicosis but can cause unexpected hypothyroidism following exposure to iodinated contrast agents. Monitoring for thyroid dysfunction is usually not required after imaging studies that use such agents, but physicians need to be aware that these agents potentially cause hypothyroidism, which is usually mild and transient;⁷⁶ hyperthyroidism might also occur, usually in people with an abnormal thyroid gland, such as multinodular goitre.

Iatrogenic hypothyroidism

A total thyroidectomy will result in the need for immediate thyroid hormone replacement. A retrospective analysis of patients who underwent partial thyroidectomy identified that within 5 years a quarter of patients required levothyroxine, with a mean daily maintenance levothyroxine dose of 1.34 µg/kg.⁷⁷ Following thyroid lobectomy, not all patients require levothyroxine. The need for levothyroxine following lobectomy is variable due to the varying definition of hypothyroidism and length of follow-up in studies, with most reporting hypothyroidism rates of between 9% and 64%.^{78–80} Higher TSH and lower FT4 concentrations presurgery, or positive thyroid antibodies, are associated with increased risk of postoperative hypothyroidism.⁸¹ One study showed that most new-onset hypothyroidism was observed during routine screening at 3 months, 6 months, and 1 year after surgery.⁸² 72% of patients were diagnosed by 1 year and 96% by 2 years. Quality of life was lower in patients who required levothyroxine following surgery and the need for levothyroxine had a greater negative impact than the extent of surgery.⁸³

Following radioactive iodine, it can take time for patients to develop hypothyroidism and close monitoring is required. In a large study of 812 patients following radioactive iodine treatment for

Graves' disease, abnormal thyroid hormone levels were common and hypothyroidism occurred in 80.7% of patients within 12 months.⁸⁴ Toxic multinodular goitre and solitary toxic nodules tend to result in a lower incidence of post-treatment hypothyroidism than Graves' disease. In a retrospective study, 153 patients with toxic multinodular goitre received radioactive iodine with a follow-up period of up to 12 years; at the end of follow-up, 27.4% of patients had developed hypothyroidism (2.7% overt) with a mean time to hypothyroidism of 2.7 years.⁸⁵

Several drugs can also cause hypothyroidism. Historically, amiodarone and lithium were the most notable and in the past decade, immune checkpoint inhibitors (ICIs) have been observed to cause hypothyroidism. Amiodarone-induced hypothyroidism is usually mild and easier to manage than amiodarone-induced hyperthyroidism;⁸⁶ nevertheless, it is important to recognise and treat as it is associated with adverse cardiovascular outcomes if left untreated long term.⁸⁷ The generally accepted main principles of management include maintenance of amiodarone treatment, levothyroxine treatment in overt (but not subclinical) amiodarone-induced hypothyroidism, and close monitoring to avoid overtreatment and worsening cardiac arrhythmias in cases of spontaneous remission.⁸⁶ Diagnosis of amiodarone-induced hypothyroidism can be challenging because high serum TSH and low FT4 concentrations, and especially low FT3 concentrations, might reflect non-thyroidal illness in patients with severe cardiac or other non-thyroidal disorders. Additionally, amiodarone impairs thyroxine to tri-iodothyronine conversion, commonly leading to increased FT4 and decreased FT3 concentrations, which can challenge effective levothyroxine dosing. Therefore, as in every patient with primary hypothyroidism treated with levothyroxine, the treatment goal should be normalisation of serum TSH concentrations.

Lithium therapy causes overt hypothyroidism in 5–15% of treated patients.⁸⁸ In a study of laboratory data, lithium use increased the risk of hypothyroidism by more than two-fold (OR 2.31; 95% CI 2.05–2.60; $p < 0.001$).⁸⁹ Alemtuzumab, which is increasingly used in the treatment of multiple sclerosis, has also been associated with a high prevalence of hypothyroidism.⁹⁰ Finally, tyrosine kinase inhibitors can result in an increased risk of hypothyroidism, with up to 27% of treated patients requiring levothyroxine during their treatment.⁹¹ Unlike with amiodarone-induced hypothyroidism, the management of hypothyroidism caused by tyrosine kinase inhibitors is more straightforward and should be approached in a similar manner to other causes of hypothyroidism.

The emergence of ICIs has substantially improved the management of advanced cancers. They are used in a variety of common cancers, including melanoma, nonsmall-cell lung cancer, renal cell carcinoma, and head and neck cancers.^{92,93} ICIs can induce autoimmune side-effects that appear to have a preponderance for the hypothalamic–pituitary–thyroid axis.⁹² Primary hypothyroidism is observed more frequently in patients taking anti-PD-1 and anti-PD-L1 monoclonal antibodies, whereas secondary hypothyroidism is more common in patients taking antiCTLA4 antibodies.⁹² For patients who develop aggressive thyroiditis, this might reflect a better response to treatment with ICIs and an increase in overall survival time.^{57,59} When managing hypothyroidism from ICI treatment, it is crucial to exclude hypoadrenalism before levothyroxine is initiated, as ICIs can also cause hypoadrenalism, which correction of hypothyroidism would worsen.

External-beam radiotherapy for head and neck cancers is another cause of iatrogenic hypothyroidism. The incidence of primary hypothyroidism after radiotherapy for head and neck cancers is around 20–30%,⁹⁴ with a higher incidence in women than men.⁹⁵ Hypothyroidism can also occur after radio frequency ablation of benign thyroid nodules. Although this effect is rare,

it is more common in people with positive thyroid antibodies,⁹⁶ and the incidence of subclinical hypothyroidism is subsequently around 6% after 1 year.⁹⁷ Hypothyroidism is rare following ethanol ablation; for example, a case series of 125 patients did not identify any individuals to have developed hypothyroidism.⁹⁸

Secondary and tertiary central hypothyroidism A key feature of central hypothyroidism is inappropriately non-elevated TSH concentrations with a low level of FT4. Concomitant measurement of FT4 with TSH in thyroid function testing protects against central hypothyroidism being missed. FT4 concentrations are usually only tested in addition to TSH concentrations when there is clinical suspicion of hypothyroidism. Biochemical monitoring of levothyroxine replacement in central hypothyroidism should use FT4 and not TSH concentrations. Central hypothyroidism is rare; its prevalence is estimated to be around 1 in 80 000 people to 1 in 120 000 people and is roughly equal in males and females.⁹⁹ In children, central hypothyroidism most commonly arises due to craniopharyngiomas or previous cranial irradiation for brain tumours, haematological malignancies, or genetic causes.¹⁰⁰ In adults, it is most commonly due to pituitary macroadenomas or pituitary surgery or irradiation,⁹⁹ with pituitary apoplexy, Sheehan's syndrome, and infiltrative disease being more rare causes.¹⁰¹ As indicated, various drugs can cause central hypothyroidism, such as high doses of intravenous glucocorticoid therapy, dopamine agonists, and somatostatin analogues. Importantly, the increased use of ICIs to treat various cancers is expected to result in an increased incidence of central hypothyroidism, especially due to CTLA4 inhibitors.

Peripheral hypothyroidism Peripheral hypothyroidism is exceedingly rare and requires highly specialist input to diagnose and a strong index of clinical suspicion, especially as serum thyroid hormone levels do not show the classic hypothyroidism pattern. Tissue-specific hypothyroidism can occur as part of resistance to thyroid hormone receptor α , which is characterised by marked effects consistent with profound hypothyroidism in bone, and neurological and gastrointestinal systems, including dysmorphic facies, skeletal dysplasia, impaired growth, anaemia, constipation, intellectual deficit, and dyspraxia, despite normal or near-normal serum thyroid function.^{63,65,102,103}

Consumptive hypothyroidism is extremely rare; it can occur in patients with gastrointestinal stromal tumours and other vascular fibrotic tumours, and is caused by overexpression of type 3 deiodinase.

Symptoms and signs

There is a wide spectrum of disease presentation, ranging from mildly abnormal blood test results in an asymptomatic patient to myxoedema coma, which is a rare endocrine emergency with a mortality rate of 25–70%.¹⁰⁴ Myxoedema is fortunately uncommon nowadays due to widespread thyroid function testing and a low threshold for initiating levothyroxine therapy.⁷ Striking features of myxoedema coma are hypothermia, bradycardia, altered mental status, profound lethargy, and ultimately multiorgan failure and death.¹⁰⁴ In rare cases, severe, prolonged primary hypothyroidism can lead to pituitary hyperplasia and subsequent insufficiency of other pituitary hormones.

Patients will more commonly present with features suggestive of possible hypothyroidism that prompt thyroid function testing (panel 2). The most common symptoms of hypothyroidism in adults are lethargy, fatigue, cold intolerance, weight gain, hoarse voice, and dry skin.⁴ There is some evidence that patients who report more symptoms and more recently developed

symptoms are more likely to have hypothyroidism.¹⁰ A higher number of symptoms was also weakly correlated with higher TSH concentrations.⁴ Symptoms are often non-specific, which might reflect pathology unrelated to thyroid status. For instance, 70% of euthyroid controls have one or more symptoms linked to hypothyroidism, whereas 15% of patients with hypothyroidism are asymptomatic or only have one hypothyroidism-related symptom.¹⁰⁵ The cardiovascular effects of hypothyroidism usually predominate: hypothyroidism results in bradycardia, decreased cardiac systolic function and cardiac output, diastolic hypertension, increased vascular resistance,¹⁰⁶ and higher total cholesterol and LDL cholesterol.

Routine screening of the general population is not recommended by the UK-based National Institute for Health and Care Excellence (NICE) guidance, which recommends that thyroid function test screening should only be offered to individuals with newly diagnosed type 1 diabetes or other autoimmune diseases, poor growth in childhood, and in those on drugs that can result in thyroid dysfunction, such as lithium.¹⁰⁷ This approach is a compromise between the Canadian guidance, which recommends against screening for thyroid dysfunction in asymptomatic, non-pregnant adults,¹⁰⁸ and the American Thyroid Association guidance, which recommends aggressive case finding in patients with associated autoimmune diseases, first-degree relatives with autoimmune diseases, previous neck irradiation, and those with psychiatric disorders even in the absence of classic hypothyroid.¹⁰⁹

It is generally recommended not to test for thyroid dysfunction during an episode of acute illness or severe psychiatric distress unless thyroid dysfunction is the expected cause, as spuriously abnormal thyroid function results—with typically low concentrations of free thyroid hormones—are common in individuals who are unwell.¹⁰⁷

Diagnosis

TSH is the preferred marker of thyroid status.⁵ A typical TSH reference range is 0.4–4.0 mIU/L. If an elevated TSH concentration is found, the thyroid function test should be repeated to confirm the result, because marginally elevated TSH levels can spontaneously return to the reference range without treatment in up to 50% of cases.¹¹⁰ However, there is growing evidence that the TSH level when levothyroxine is initiated is steadily falling,^{7,111} with a median TSH value at levothyroxine prescription of around 7.0 mIU/L. Therefore, many people treated with levothyroxine have a TSH concentration at the top of, or 1–2 mIU/L above, the reference range.

TSH levels show circadian variation, with higher concentrations noted towards the evening.^{112,113} Large population studies have also shown that there are seasonal variations in TSH concentrations, with higher TSH in winter and spring than in summer and autumn.¹¹⁴ However, these fluctuations only have a marginal effect in clinical practice. In mild and severe hypothyroidism, TSH secretion exhibits both amplified burst mass and basal secretion,¹¹² which might explain the marked variation observed in TSH levels in the same individual.

There are many factors for interpreting thyroid function tests (figure 1). Most commercially available TSH and FT4 assays are immunoassays. The reference ranges for these assays are statistically defined as levels between the 2.5th and 97.5th percentile in an apparently healthy population. These reference ranges are not epidemiological and do not consider the risk of adverse outcomes or symptoms. There is increasing evidence that variation in thyroid status within the reference range is a risk factor for disease burden.^{115–118}

Normal thyroid status varies with age. Cross-sectional studies generally show higher TSH upper limits in younger children (<5 years) compared with older children (≥5 years), with a gradual

decline in TSH concentration towards adult age (15–18 years),^{119–124} and lower FT3 with higher increases in FT4 concentrations from age 4 years.^{125–128} Longitudinal analysis has shown variation in the same individual in the first years of life and sex can influence reference ranges.¹²⁹ In older children, there is marked, sexually dimorphic variation in thyroid hormone parameters throughout puberty.^{124,130} Overall, there is considerable variation between reference ranges by the platform used and age, with weight, sex, and genetic architecture also having an effect.¹¹⁹

Several large cross-sectional studies in iodine-replete populations without thyroid disease have reported higher TSH concentrations in older individuals.^{15,17,19,20} NHANES III reported the 97·5th percentile for TSH exceeded 7·0 mIU/L in individuals older than 80 years,^{15,16} even after exclusion of TPO-Ab-positive individuals, which widens TSH reference ranges, particularly the upper range. In a large laboratory database study,⁵ the TSH–FT4 relationship differs with age, with older people having higher TSH concentrations at any given FT4 level than younger individuals. This shift in the normal TSH distribution to a higher range in older individuals might represent a normal part of ageing,^{15–17,131} with the upper 97·5th percentile of the CI for serum TSH in healthy older people being around 7·5 mIU/L.³ Thus, there is potential for older individuals to be inappropriately started on levothyroxine treatment. This might have adverse effects as epidemiological studies suggest survival advantages both for low thyroid hormones and high TSH concentrations within the normal reference range in older individuals.^{34,132} Therefore, it has been suggested that the upper limit of TSH should be 7·0 mIU/L for people older than 80 years.¹³³ Furthermore, in individuals with genetically higher TSH concentrations there is enhanced longevity.¹³⁴ Older adults with low FT4 concentrations within the normal range exhibit better mobility and fitness levels compared with those with normal FT4.¹³⁵ For example, a large, individual patient data meta-analysis showed that high TSH levels within the normal population range was associated with a lower risk of stroke,¹³⁶ whereas another meta-analysis identified that the 20–40th percentiles of FT4 and the 60–80th percentiles of TSH were the optimal ranges of thyroid function, based on having lower risk of cardiovascular disease and mortality.¹³⁷

A healthy individual's thyroid hormone level is largely genetically determined. Taken together, there is a growing need for age-specific reference ranges to prevent overtreatment in older individuals with the potential risk of adverse outcomes from unnecessary treatment with levothyroxine.

Although interpretation of thyroid function tests relevant to hypothyroidism is usually straightforward, there are some potential pitfalls (figure 1). Assay interference should be suspected when results do not fit with the clinical presentation. The presence of antianimal antibodies can cause patients to have falsely high TSH levels and interfere with FT4 immunoassays. Equilibrium dialysis, and liquid chromatography with tandem mass spectrometry are more resistant to this analytical interference, and as they become more available and analysis standardised, fewer results will be discordant to the clinical picture.¹³⁸ Macro TSH might be the cause of 1% of cases of subclinical hypothyroidism and is a rare condition caused by the binding of TSH to plasma proteins (usually immunoglobulins), which results in falsely elevated TSH measurements but normal T3 and T4 levels, mimicking subclinical hypothyroidism, which might lead to inappropriate levothyroxine treatment. Drugs such as heparin can also falsely elevate FT4 levels.¹³⁹ Supplements containing biotin can also interfere with thyroid function tests in platforms using biotin–streptavidin reporting systems (eg, OCD Vitros5600 and Beckman Coulter UniCel DXI 800) and cause abnormal results.¹⁴⁰

Non-thyroidal illness can also result in spurious thyroid function test results and is characterised by low concentrations of free thyroid hormones (usually FT3 and in severe cases FT4), with TSH concentrations usually within the normal range or slightly low. Non-thyroidal illness can occur in many unwell patients and is present in almost all critically ill patients, including those with severe psychiatric illness.¹⁴¹ Non-thyroidal illness arises from changes to thyroid hormone metabolism and to the response of thyroid hormone transporters and receptors, resetting the hypothalamo–pituitary–thyroid axis, and leading to downregulation of thyrotropin-releasing hormone.

Although thyroid function changes due to critical illness are associated with worse outcomes and thus have prognostic significance, there is no robust evidence that thyroid hormone replacement therapy is beneficial in critically ill patients.¹⁴¹ The recovery phase might result in substantial elevations in TSH concentrations (even above 10mU/L), highlighting the importance of repeat thyroid function testing (unless clinically urgent) before commencing levothyroxine therapy.

Treatment

Whom to treat

The TSH threshold for index levothyroxine prescription remains contentious and excess levothyroxine therapy resulting in low or suppressed TSH concentrations is associated with adverse cardiovascular outcomes. However, overt hypothyroidism (concentrations of TSH above and FT4 below the respective reference ranges) should be treated, given it is usually symptomatic and associated with adverse health outcomes. Specific situations, such as resolving thyroiditis, should be managed expectantly. The most recent guidance from the European Thyroid Association, American Thyroid Association, and NICE recommends overt hypothyroidism should be treated with levothyroxine.^{107,142–144}

Subclinical hypothyroidism Guidance from the European Thyroid Association, American Thyroid Association, and NICE^{107,142–144} recommends levothyroxine can be considered for subclinical hypothyroidism at TSH levels of 10 mIU/L or higher on two separate occasions, 3 months apart. A TSH level of 10 mIU/L is chosen as levels above this are unlikely to return to the normal population reference range.¹⁴⁵

Age is also an important factor when considering whom to treat. The European Thyroid Association and NICE recommend considering a trial of levothyroxine treatment in individuals younger than 65 years with symptoms of hypothyroidism and normal FT4 concentrations if TSH levels are above the reference range (but lower than 10 mIU/L) on two separate occasions, 3 months apart. However, they recommend stopping treatment if symptoms persist despite normalisation of TSH. This difference in approach by age reflects the differences in reference ranges outlined above and a potentially differing response to treatment. American Thyroid Association guidance also considers levothyroxine treatment for patients who are at risk of cardiovascular comorbidities.^{143,144}

The health impact of subclinical hypothyroidism remains uncertain. No clear advantages of treating subclinical hypothyroidism in older individuals (>65 years) have been observed in terms of neurocognitive function and quality of life,^{146–148} and a meta-analysis from two clinical trials found no benefit to hypothyroid symptoms and fatigue.¹² A high TSH level within the normal range appears to be protective and has been shown to be associated with reduced mortality risk in older euthyroid individuals.¹⁴⁹ Furthermore, overtreatment in older individuals increases the

risk of atrial fibrillation and osteoporosis, complications that are very common in this age group.¹⁵⁰

Subclinical hypothyroidism is associated with increased risk of cardiovascular mortality in younger (<65 years) populations but not in older (≥65 years) individuals.^{151,152} Furthermore, treatment of subclinical hypothyroidism with levothyroxine in younger individuals was linked with fewer adverse cardiovascular outcomes in younger but not older individuals.^{151,152} At present, there is insufficient evidence that treatment of younger individuals (<65 years) with subclinical hypothyroidism improves symptoms or quality of life.⁵¹ We are still missing a definitive trial showing benefit of levothyroxine in subclinical hypothyroidism in younger individuals. Therefore, treatment might still be considered in these individuals, and current guidance reflects this. We outline a possible approach of when to initiate thyroid hormone replacement (figure 2). People who are planning pregnancy or undergoing in-vitro fertilisation should be treated differently as per local guidance.

What to treat with

Since the 1970s, levothyroxine monotherapy taken on an empty stomach remains the treatment of choice. The clinical experience with levothyroxine and data on its efficacy and safety are extensive. For most patients, a daily dose of levothyroxine transforms a debilitating and potentially fatal condition into one that is easily treatable. The optimal daily dose in overt hypothyroidism is 1.5–1.8 µg per kg of bodyweight,^{107,142,144} rounded to the nearest 25 µg. In younger patients with no substantial comorbidities, the full required dose can be given at the start of treatment. Clinicians should consider starting levothyroxine at a dose of 25–50 µg/day, with subsequent titration in adults aged 65 years and older and in those with a history of cardiovascular disease, as excessive doses of levothyroxine might result in worse cardiovascular outcomes, especially in older patients.¹⁰⁷

Levothyroxine absorption is enhanced during fasting and is reduced by many foods and beverages, particularly caffeine and milk. Patients should therefore be given clear advice that levothyroxine should ideally be taken on an empty stomach, with water, at least an hour before a meal.¹⁵³ Although this approach promotes levothyroxine absorption, it might be too inconvenient for some patients to maintain compliance. Alternative strategies include taking levothyroxine at bedtime or taking levothyroxine consistently 30 min before breakfast.

If patients do not meet the treatment targets mentioned in the next section, clinicians might need to consider several factors (panel 3) before contemplating alternatives to levothyroxine monotherapy. Careful patient selection is important when determining whether the patient is likely to benefit from a trial of combination thyroid hormone replacement. If a patient is inappropriately selected, it could put the patient at risk of adverse effects without any treatment benefit, or it could delay treatment for another treatable diagnosis.

Treatment targets Once started on levothyroxine monotherapy, treatment targets include normalisation of TSH concentrations and resolution of physical and mental symptoms, while avoiding undertreatment or overtreatment.¹⁴⁴ For adults who are taking levothyroxine for primary hypothyroidism, it is typically recommended that TSH concentrations are checked roughly every 3 months until stable (defined as two similar measurements within the reference range, 3 months apart), and then once a year thereafter.¹⁰⁷ During preconception and pregnancy, stricter levothyroxine treatment targets are used, which is typically a normal-range TSH level below 2.5 mIU/L.^{142,144}

Failure to reach treatment targets Failure to normalise thyroid function tests TSH normalisation was often not attained in patients 5 years post-levothyroxine in a large population dataset; 15% of patients had a TSH concentration below the reference range and 21% had a TSH concentration above the reference range.⁷

Several key factors might prevent patients from normalising thyroid hormone levels. These include inadequate intake of levothyroxine (either due to an insufficient dose prescribed or to low treatment adherence), interaction with other medication, or coexisting medical conditions (for example, low cortisol levels in Addison's disease resulting in a rise in TSH in some patients, that normalises with steroid treatment).¹⁵⁴ Levothyroxine absorption might be adversely affected by concomitant ingestion of medications, including calcium and iron compounds, antacids, and proton-pump inhibitors. Increased levothyroxine requirements have been reported in hypothyroid patients who start oestrogen replacement therapy or receive tyrosine kinase inhibitors.¹⁵⁵ We provide a summary of the most common causes of persistently elevated TSH levels despite apparently adequate levothyroxine replacement (panel 4).

Treatment adherence can be an issue for patients and clinicians. Low adherence might be suggested by a discordant thyroid hormone pattern (eg, high TSH and high FT4 concentrations, indicative of pretest medicating). A supervised levothyroxine absorption test to distinguish non-adherence from other reasons for undertreatment might be useful. Supervised oral therapy (once or twice a week) is one potential strategy to counteract non-adherence, although there have been few successful studies to date and the sample sizes have been small.^{156,157}

Gastrointestinal malabsorption of oral levothyroxine is an emerging cause of refractory hypothyroidism and, although rare, is likely to be more frequent than previously believed.¹⁵⁸ Case reports have shown that parenteral (mostly intravenous) levothyroxine therapy can be used in patients with uncharacterised malabsorption.¹⁵⁹ Additionally, both liquid and soft gel formulations of levothyroxine can be trialled in cases of (unknown causes of) malabsorption.¹⁵⁸

Patients might sometimes prefer to take more levothyroxine than their thyroid function tests indicate they require, which might result in a low or suppressed TSH concentration.¹¹ Suppressed TSH following levothyroxine is also more apparent if patients originally presented with depression, tiredness, or fatigue.⁷ Similarly to the diagnosis of hypothyroidism, the clinical implication of suppressed TSH is heavily influenced by age. In younger individuals, increased risks of adverse outcomes were observed in patients with TSH concentrations less than 0.1 mIU/L (but not 0.1–0.4 mIU/L), in terms of all-cause mortality,¹⁶⁰ atrial fibrillation, and stroke risk.¹⁶¹ Further studies are needed in this area, with longer follow-up. There is some evidence that in older individuals (median age 67 years), even slight levothyroxine over-replacement is associated with adverse outcomes with regard to cardiovascular mortality,¹⁶² potentially indicating a lower thyroid-status setpoint in these individuals.

Failure to resolve symptoms Symptoms of hypothyroidism and impaired quality of life might persist despite normalisation of TSH. Approximately 10–15% of patients express dissatisfaction on levothyroxine despite TSH normalisation, due to persistent, residual symptoms that might reflect ongoing hypothyroidism.^{10,11} Depression is one of the most common comorbidities, accounting for persistent symptoms of ill health despite treatment of hypothyroidism.⁷ The cause of ongoing symptoms and impaired quality of life are complex—even pre-diagnostic factors, such as pretreatment expectations and the number of visits to their general practitioner before diagnosis of hypothyroidism, might influence patients' treatment satisfaction.¹⁶³ Four potential themes of failed symptom resolution have been postulated: (1) low tissue T3

concentrations; (2) somatic symptoms and related disorders coexisting with treated hypothyroidism; (3) ongoing thyroid autoimmunity; and (4) other conditions and psychosocial factors related to a hypothyroidism diagnosis.

Patients on levothyroxine display ongoing substantial impairment of psychological wellbeing compared with controls of similar age and sex.¹⁶⁵ Typical persistent hypothyroid symptoms include lethargy, sleepiness, memory problems, depression, and weight gain.⁶ However, symptoms consistent with the presence of hypothyroidism are non-specific and cannot be reliably used to differentiate individuals with hypothyroidism from euthyroid controls.⁴

The management of patients who remain symptomatic is challenging and frequently frustrating for both clinicians and patients. An open, empathic, and patient-centred approach is essential. Patients' symptoms should be acknowledged rather than dismissed. Small dose adjustments that maintain TSH concentrations within the reference range are a potential initial strategy. The intraindividual variation in thyroid function tests is much narrower than the interindividual variation in healthy individuals, suggesting that every individual has a unique hypothalamic–pituitary–thyroid axis setpoint located somewhere within the broad population-based reference range. This broad range might explain why there is no benefit from targeting low-normal versus high-normal TSH concentrations when patients are analysed as a group, but individual patients might benefit.¹⁶⁶ The individual hypothalamic–pituitary–thyroid axis setpoint is predominantly determined by genetic factors.¹⁶⁷ Although large steps have been made in deciphering the responsible genetic variants for causing hypothyroidism and variation of TSH concentrations within the reference range, follow-up studies are needed to identify whether these can be used to guide treatment.

Other non-thyroidal causes of persistent symptoms should be seriously considered. In cases of autoimmune thyroid disease, further causes might include concomitant autoimmune disorders, such as rheumatoid arthritis, coeliac disease, and Addison's disease, as autoimmune disorders frequently cosegregate. Another potential explanation for symptoms not improving despite normalisation in TSH concentrations might be the inflammatory nature of autoimmune thyroiditis and persistently increased circulating cytokine levels. Selenium might have a role in reducing TPO-Ab concentrations,^{168,169} although results and potential benefits from selenium supplementation studies have been inconsistent.¹⁷⁰ A randomised controlled trial of 150 individuals with persistent symptoms of hypothyroidism and high TPO-Ab titres, despite restoration of euthyroidism, showed that thyroidectomy improved quality of life and reduced TPO-Ab titres.¹⁷¹ Benefits have been shown to persist for up to 5 years, although the complication rate was higher than postulated at the beginning of the study.¹⁷²

Alternative treatments to levothyroxine monotherapy
Combination thyroid hormone replacement
When considering alternatives to levothyroxine monotherapy, clinicians should be vigilant of other conditions or non-thyroidal factors that might explain a patient's ongoing symptoms (panel 3). Liothyronine is considered as an alternative treatment because the intact thyroid gland secretes some tri-iodothyronine (equivalent to approximately 20% of the total body production of triiodothyronine), with the majority arising from peripheral conversion of thyroxine.¹ Furthermore, patients treated with levothyroxine monotherapy tend to have serum triiodothyronine concentrations at the lower end of, or even below the reference range. Several studies have shown that serum tri-iodothyronine concentrations are significantly lower for the same concentration of TSH in patients on levothyroxine than in patients with euthyroidism,^{173,174} and to maintain tri-iodothyronine levels in the reference range, a high concentration of FT4 might be required. Additionally, preclinical studies of thyroidectomised rats treated with

levothyroxine indicate that plasma and tissue tri-iodothyronine are not normalised despite normalisation of serum TSH, whereas this was the case when treated with levothyroxine–liothyronine combination therapy in the physiological ratio for rats.¹⁷⁵ Levothyroxine-treated hypothyroidism is also associated with reduced tri-iodothyronine signalling in the liver and brain.¹⁷⁶ Additionally, a meta-analysis of 65 studies revealed that both total cholesterol and LDL cholesterol concentrations remain elevated, even after serum TSH has been normalised.¹⁷⁷ NHANES data show that patients on levothyroxine are 54% more likely to be on statins than controls matched for age, sex, and ethnic background.¹⁷⁸ Although a normal TSH concentration reflects euthyroidism in the pituitary gland, this might not necessarily reflect euthyroidism in all tissues,¹⁷⁹ due to tissue-specific differences in type 2 deiodinase activity and other factors involved in thyroid hormone regulation.

Combination levothyroxine–liothyronine therapy remains controversial and has not shown clear superiority over levothyroxine monotherapy in clinical trials. To date, there have been ¹⁸ randomised controlled trials comparing the efficacy of combination levothyroxine–liothyronine therapy versus levothyroxine monotherapy.¹³¹ Furthermore, four systematic reviews and meta-analyses^{12,13,180,181} of these trials found no clear benefit of combination levothyroxine–liothyronine therapy over levothyroxine monotherapy in terms of mood, health-related quality of life, or cognitive function. However, all these trials have one or more important limitations, such as small sample sizes and inadequate liothyronine dosing (once daily and supraphysiological doses). Furthermore, most studies did not specifically enrol patients with persistent complaints despite biochemical euthyroidism, which is the group of interest for whom a physician could consider combination therapy. Additionally, the trials did not use the latest thyroid-specific outcome measures, such as ThyPRO.¹⁸²

A few studies have attempted to identify genetic subgroups in which combination therapy could be more effective. For instance, individuals with genetic variants in DIO2 (rs225014)¹⁸³ and MCT10 (rs12885300)¹⁸⁴ have shown preference for combination levothyroxine–liothyronine therapy with a potential additive effect.¹⁸⁴ However, these studies had limitations due to multiple testing¹⁸³ and small sample size.¹⁸⁴ Although individual genetic variants might have poor discriminatory power in determining who might benefit from levothyroxine–liothyronine combination therapy, alternative strategies, such as a panel of genetic variants or the use of thyroid hormone metabolites or metabolomics, might provide better insight into tissue thyroid status.

A trial designed to take the aforementioned limitations into account is urgently needed to get a definitive answer on whether combination therapy is an effective strategy for levothyroxine monotherapy-treated patients with persistent symptoms despite biochemical euthyroidism. A UK study highlighted the current gaps in understanding, where there was a 49-fold variation in the number of liothyronine prescriptions per 1000 levothyroxine prescriptions by local prescribing region.¹⁸⁵ The high costs of liothyronine in the UK has undoubtedly contributed to this variation.¹⁸⁶ Other factors include regional factors such as the levels of deprivation and the extent of antidepressant prescribing by general practitioners.¹⁸⁷

While awaiting a definitive answer from clinical studies, society guidelines by the European Thyroid Association and the British Thyroid Association now recommend that a trial of combination therapy with levothyroxine and liothyronine might be considered in individuals who unambiguously do not respond to levothyroxine treatment alone.¹⁸⁸ Physician surveys across Europe suggest this guidance is broadly followed.¹⁸⁹ Strict specialist supervision with an

endocrinologist and clear communication of the uncertainty benefits of combination therapy are required, and treatment should be discontinued if there is no evidence of response.¹⁹⁰

When considering combination thyroid hormone replacement, several factors should be considered (panel 3). A few careful dosing considerations are needed when changing levothyroxine monotherapy to combination levothyroxine–liothyronine therapy. The European Thyroid Association and the British Thyroid Association have provided guidance for clinicians for calculating a levothyroxine–liothyronine combined dosing regimen.^{188,190}

Other thyroid hormone replacement regimens

Liothyronine monotherapy is not recommended, largely due to safety concerns associated with the presence of supraphysiological FT3 concentration. DTE was not endorsed in either the European or US guidelines.^{144,188} Nevertheless, interest in DTE from patient groups and alternative physicians has grown.¹⁹¹ A working knowledge of DTE is therefore useful for endocrinologists, as they might be involved in providing advice in the care of these patients. A key concern of DTE is the high risk for supraphysiological doses of tri-iodothyronine. Historically, there have also been concerns regarding the stability and dosing of DTE, but this might be less of an issue in the past decade. DTE is often prescribed in grains: one grain is typically around 60–65 mg of DTE and most commonly contains 38 µg of thyroxine and 9 µg of tri-iodothyronine. Further details on the equivalence of levothyroxine, levothyroxine–liothyronine, and DTE are available in previously published studies.¹⁹²

Randomised controlled trials have recently evaluated the effectiveness of DTE in hypothyroidism. In a randomised, double-blind, crossover trial, DTE did not significantly improve quality of life, although weight loss occurred on DTE, and almost half of patients preferred DTE to levothyroxine.¹⁹³ In a three-arm, double-blind study of levothyroxine, levothyroxine–liothyronine, and DTE, outcomes were similar for all three treatment groups, although the most symptomatic individuals on levothyroxine at baseline responded to levothyroxine–liothyronine and DTE therapy.¹⁹²

Deprescribing thyroid hormone replacement

Due to the falling TSH threshold for the initiation of levothyroxine,⁷ there has been an increasing interest in whether deprescribing levothyroxine should be considered in individuals for whom the treatment benefits might be marginal, especially in those who have been over-replaced. A systematic review highlighted that up to a third of patients remained euthyroid after levothyroxine discontinuation.¹⁹⁴ Deprescribing levothyroxine is most likely to benefit patients who were diagnosed with subclinical hypothyroidism based on a single TSH measurement and who have not shown clinical improvement.¹⁹⁵

Hypothyroidism in pregnancy

The importance of thyroid status in pregnancy has been extensively reviewed,⁷⁰ and the management of hypothyroidism during pregnancy is beyond the scope of this Seminar. Poor control of hypothyroidism in women with established hypothyroidism during pregnancy is associated with adverse obstetric outcomes, including fetal loss, premature birth, abnormal birthweight, and pre-eclampsia, as well as poor neurocognitive outcomes in the offspring.⁷⁰ Due to the early, increased demand for thyroid hormone during pregnancy, clinical guidelines recommend increasing the dose of levothyroxine as soon as pregnancy is confirmed and this can be done simply by taking an additional dose of levothyroxine twice a week,¹⁹⁶ with prompt

follow-up (within 4 weeks) in an antenatal clinic. Importantly, the American Thyroid Association thyroid pregnancy guidelines take into account TPO-Ab status and suggest differing TSH thresholds when considering starting levothyroxine treatment during pregnancy (>2.5 mIU/L in those who are TPO-Ab positive and >4.0 mIU/L in those who are TPO-Ab negative).¹⁹⁷ However, there is no apparent substantial benefit of treating TPO-Ab-positive individuals with TSH concentrations of 2.5 mIU/L or less.^{198–20}

Further research

Hypothyroidism is common, with well-established biochemical tests to confirm the diagnosis and the mainstay of treatment is safe and inexpensive. However, there are several important issues to address, which are crucial for maintaining optimal health in large numbers of individuals, as hypothyroidism and borderline thyroid function tests are so common. Clarity regarding the potential role of liothyronine in individuals who are dissatisfied with or remain symptomatic on levothyroxine is needed. Randomised controlled trials investigating the effects of combination therapy with liothyronine (ideally long-acting forms) and levothyroxine compared with levothyroxine monotherapy and placebo are needed. Standardised thyroid-related quality-of-life scores, such as ThyPRO, should be used and guidance from an international consensus panel should be followed when treating patients with non-standard levothyroxine therapy. Additionally, the value of treating subclinical hypothyroidism in individuals younger than 45 years needs to be clarified, by comparing levothyroxine replacement to normalise TSH concentrations with placebo, in such individuals, particularly focusing on cardiovascular and quality-of-life outcomes.

Greater clarity and more tailored guidance on treatment for hypothyroidism, particularly in special situations, such as those planning a pregnancy, are needed. In addition, older individuals who are already established on levothyroxine treatment might need a lower dose, given the observed changes in reference ranges and decreased mortality risk associated with a lower thyroid function in those older than 75 years. Identification of patients most likely to benefit from deprescribing thyroid hormone and how best to manage that process is of particular interest.

As in other fields in medicine, major advances in various –omics techniques, such as genomics and metabolomics, will probably inform future management of hypothyroidism. For example, our increased understanding of the genetic architecture of thyroid function and disease should be taken forward to individualise diagnosis and management of thyroid diseases based on genetic background. Given the profound impact of thyroid hormone on metabolism, metabolomics could be an attractive option for identifying markers that better reflect tissue thyroid status and predict patient dissatisfaction with levothyroxine monotherapy or responsiveness to combination thyroid hormone replacement.

Thyroid status and iodine status are closely linked. Mild to-moderate iodine deficiency is still prevalent in Europe and iodine deficiency remains an ongoing threat to global health, particularly to offspring neurological development. Increased focus on monitoring for iodine deficiency and managing the risks posed by endocrine-disrupting chemicals that can exacerbate iodine deficiency is needed.

Contributors

PNT and KB drafted the outline for this Seminar, which was further developed by PNT, MMM, AH-D, and KB. The literature search was done by PNT and MMM. PNT, MMM, AH-D, and KB selected studies from the literature search, drafted separate sections of the manuscript, and provided crucial input on all other sections of the manuscript. All authors have verified the underlying data from the literature review.

Declaration of interests

PNT has received funds from the British Thyroid Foundation and the Association of Physicians of GB & Ireland for studies on hypothyroidism, and from PassPACES as an examiner. He received a Leadership and Development Award from the Society for Endocrinology; is Chair of the Welsh Endocrine and Diabetes Society; a member of UK Iodine; and is a member of the British Thyroid Association executive committee. MMM has received financial support from ACE Pharmaceuticals (Zeewolde, the Netherlands) for a randomised controlled trial of levothyroxine–liothyronine replacement in patients with hypothyroidism. AH-D is Principal Investigator and member of the steering committee of the HORIZON 2020 EUTHyroid grant; coordinator and Primary Investigator of the GRAN-T-MTC (ERA-NET FP7) grant and the HORIZON 2020 TECANT grant; has received consulting fees and travel support for expert meeting attendance from Institut Biochimique (IBSA) and Recordati; has received speaker honoraria from IBSA, Ipsen, Novartis, Merck, Berlin Chemie—Menarini, and Pfizer; is President of the Polish Society of Endocrinology, Chairperson of the Polish Commission for the Control of Iodine Deficiency Disorders, and Team Leader for the Polish Society of Endocrinology guidelines for the diagnosis and treatment of thyroid diseases; and has participated in an advisory board for Ipsen. KB is President of the British Thyroid Association, Chair of the Clinical Committee and Council Member of the Society for Endocrinology, member of the European Thyroid Association executive committee, and member of the programme organising committee of the American Thyroid Association; she has received grant funding from the National Institute for Health and Care Research (NIHR), Research for Patient Benefit (NIHR200772) and NIHR Health Technology Assessment (NIHR135261); she has received consulting fees from Eli Lilly, Eisai, SERB, Egetis Pharmaceuticals, and the Medicines and Healthcare products Regulatory Agency; she has received speaker honoraria from the Emirates Diabetes and Endocrine Society and Eisai; she has received editor honoraria from Best Practice and Research Clinical Endocrinology and Metabolism, and honoraria from NICE as clinical lead for the Thyroid Diseases guidelines; she was the recipient of the Society for Endocrinology Outstanding Clinical Practitioner Award; she is Associate Editor for the Journal of the Endocrine Society for which she receives honoraria; and is on the international advisory board for The Lancet Diabetes & Endocrinology.

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A	
Pattern of thyroid function	Most likely causes
TSH↑ FT ₄ ↓	Overt hypothyroidism pattern Chronic autoimmune thyroiditis (most common) Iatrogenic (eg, amiodarone); post-treatment for thyrotoxicosis (eg, radioiodine and total or partial thyroidectomy) Drugs Post-thyroiditis Thyroid infiltration
TSH↑ FT ₄ →	Subclinical hypothyroidism pattern Chronic autoimmune thyroiditis (most common) Iatrogenic (eg, amiodarone); post-treatment for thyrotoxicosis (eg, radioiodine and partial thyroidectomy) Post-thyroiditis Non-thyroidal illness recovery phase TSH resistance Drugs (eg, amiodarone) Presence of macro-TSH Addison's disease
TSH↓→ FT ₄ ↓	Central hypothyroidism pattern Hypothalamic and pituitary dysfunction Non-thyroidal illness early phase Assay interference Isolated TSH deficiency
B	
Pattern of thyroid function	Most likely causes
TSH↓→ FT ₄ ↓	Levothyroxine under-replacement Poor absorption Poor treatment compliance Assay interference
TSH↓→ FT ₄ ↑	Poor treatment compliance (taking a substantial levothyroxine dose on day of test) Assay interference Non-thyroidal illness Drugs (eg, amiodarone and heparin) Resistance to thyroid hormone

Figure 1: Summary of the main patterns of thyroid function test results and their interpretation in patients with hypothyroidism
Before (A) and after (B) starting levothyroxine replacement therapy.
TSH=thyroid-stimulating hormone. FT₄=free thyroxine.

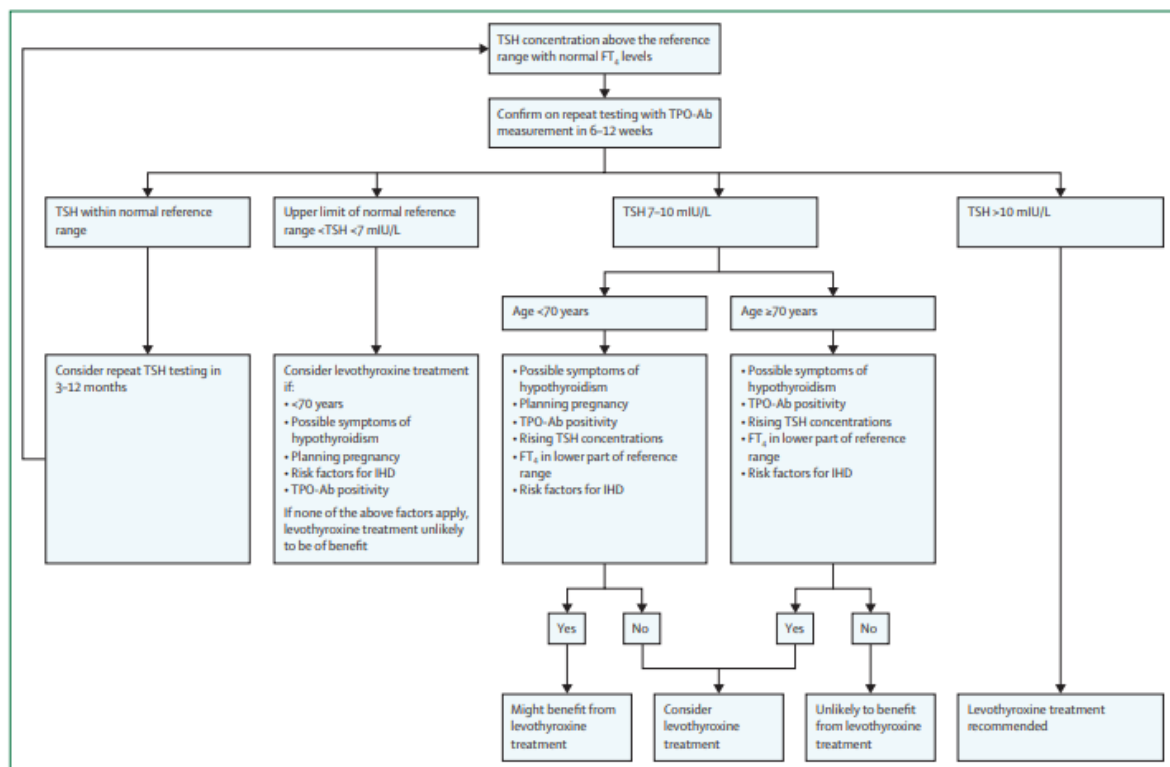


Figure 2: Considerations and treatment thresholds for starting thyroid hormone replacement in patients with subclinical hypothyroidism

Recommendations are based on guidelines from the American Thyroid Association,¹⁰⁹ European Thyroid Association,¹¹⁰ and the UK National Institute of Health and Care Excellence.¹⁰⁷ FT₄=free thyroxine. IHD=ischaemic heart disease. TPO-Ab=thyroid peroxidase antibodies. TSH=thyroid-stimulating hormone.