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Management of Primary Hypothyroidism: Statement by the British Thyroid Association Executive Committee

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Management of Primary Hypothyroidism

Statement by the British Thyroid Association Executive Committee

Endorsed by the Association for Clinical Biochemistry and Laboratory Medicine, British Thyroid Foundation, Royal College of Physicians and the Society for Endocrinology

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Background

Primary hypothyroidism is an insidious condition with a significant morbidity and often subtle and non-specific symptoms and clinical signs [1, 2]. The earliest biochemical abnormality is an increase in serum thyroid-stimulating hormone (thyrotrophin) (TSH) concentration associated with normal serum free thyroxine (T4) and triiodothyronine (T3) concentrations (subclinical hypothyroidism), followed by a decrease in serum free T4 concentration, at which stage most patients have symptoms and benefit from treatment (overt hypothyroidism) [1-3]. In the UK, the prevalence of spontaneous hypothyroidism is between 1% and 2%, and it is more common in older women and ten times more common in women than in men [4, 5]. The cause is either chronic autoimmune disease (atrophic autoimmune thyroiditis or goitrous autoimmune thyroiditis (Hashimoto's thyroiditis)) or destructive treatment for hyperthyroidism with either radioiodine or surgery which may account for up to one-third of cases of hypothyroidism in the community [6]. Less frequent causes include surgery and radioiodine ablation for benign nodular thyroid disease and thyroid cancer, external beam irradiation of malignant tumours of the head and neck and drugs including lithium, amiodarone and interferon [1]. Congenital hypothyroidism affects about one newborn in 3,500-4,000 births [7].

The term subclinical hypothyroidism describes the finding of a raised serum TSH but a normal free T4 [3, 8, 9]. It represents a compensated state in which increased TSH output is required to maintain normal circulating thyroid hormone levels. An elevated serum TSH is a sensitive indicator of some degree of thyroid failure and there is a clear inverse relationship with free T4 levels. The term implies that patients should be asymptomatic, although symptoms are difficult to assess, especially in patients in

whom thyroid function tests have been checked because of non-specific complaints such as tiredness. Subclinical hypothyroidism is common in studies of healthy people in the community and is found in 5-10% of the population, being more common in women and increasing with age [9]. It can progress to overt hypothyroidism, particularly if anti-thyroid antibody positive [10]. In the community, the most common aetiology is chronic autoimmune thyroiditis [6].

There has been a growing controversy about the upper limit of the reference range for serum TSH [11, 12]. Reference ranges are derived from a reference population that comprises a large group of subjects who do not have thyroid disease and are otherwise well. By convention, a reference range usually only comprises 95% of a reference population. Thus 2.5% of "normal" individuals will fall above the reference range and 2.5% will fall below the range. For serum TSH the reference population shows a log normal distribution and has a diurnal variation with the reference range in thyroid disease free individuals typically cited as between 0.4-4.0 mU/l [8]. The reference range varies in different ethnic communities, pregnancy and by age [13]. It has been reported that serum TSH distribution progressively shifts towards higher concentration with age [13]. Studies addressing the relationship between symptoms suggestive of thyroid hormone deficiency and the biochemical finding of subclinical hypothyroidism have produced conflicting results [3]. It is recognised that up to one quarter of the healthy normal population may have "hypothyroid" symptoms such as lethargy and weight gain [14]. The evidence for benefit in randomised controlled trials of thyroid hormone treatment in subclinical hypothyroidism is inconsistent and further studies are needed [3, 15]. Although epidemiological studies have shown an association between subclinical hypothyroidism and coronary heart disease in younger people (<65 years) [16] or those with high TSH (>10 mU/L) [17], recent

evidence suggests that in older people higher serum TSH and lower free T4 concentrations within the euthyroid range are associated with lower risk of multiple adverse events including mortality [18]. In neonates and children, pregnancy, or in women trying to conceive a mildly increased serum TSH should always be treated as mild thyroid failure which is associated with adverse outcomes for both mother and fetus [19].

In England, 3% of people are prescribed synthetic L-T4 [20] with the goal of therapy being to restore patient well-being and normalise serum TSH levels [21]. Most patients respond satisfactorily but a minority of treated individuals experience persistent symptoms despite adequate biochemical correction [22]. The care of such individuals is challenging and remains the subject of considerable public interest [23]. Although some non-mainstream practitioners advocate the use of alternative thyroid therapies including Liothyronine (L-T3) and thyroid extracts, combination therapy with L-T4 and L-T3 is also prescribed by accredited specialists. In the United States, 3.6% of endocrinologists report that they would give L-T3 to patients with hypothyroidism with persistent symptoms and normal biochemical thyroid status [24].

In 2008 the Royal College of Physicians (RCP) issued a position statement on the diagnosis and management of primary hypothyroidism endorsed by various professional bodies namely the British Thyroid Association (BTA), the British Thyroid Foundation (BTF), the Association for Clinical Biochemistry and Laboratory Medicine (ACB), the British Society of Paediatric Endocrinology and Diabetes (BSPED), the Society for Endocrinology (SFE), and the Royal College of General Practitioners (RCGP) [25]. This RCP statement, updated in 2011, did not support the use of thyroid extracts or L-T3 in the treatment of hypothyroidism and recommended that L-

T3 “should be reserved for use by accredited endocrinologists in individual patients” [25].

More recently, the European Thyroid Association (ETA) published guidelines on the use of L-T4/L-T3 combination therapy in primary hypothyroidism [26] and subsequently, the American Thyroid Association (ATA) [27] and the Latin America Thyroid Society (LATS) [28] have released their own separate hypothyroidism treatment guidelines. These international guidelines have generated further interest in the role of L-T3 in hypothyroidism and have been interpreted in some quarters as representing a departure from the earlier UK RCP position [29].

It is recognised that clinicians must be committed to delivering individualised patient-centred care and shared decision making in all patients with primary hypothyroidism. This report summarises the key points in the ETA and ATA guidelines and contains a statement on the management of primary hypothyroidism written by the BTA and endorsed by the ACB, BTF, RCP and SFE based on the current evidence and international guidelines.

Methods

The current statement serves to update the previous 2006 RCP joint position statement on the diagnosis and management of primary hypothyroidism. We have focused on patients with primary hypothyroidism and have not addressed in detail the care of subgroups such as pregnant women, patients treated for thyroid cancer, or secondary hypothyroidism. Excellent guidelines for the management of these other conditions are available elsewhere. The statement is intended to provide concise guidance for primary care practitioners, hospital physicians, clinical biochemists, and endocrinologists involved in caring for patients with hypothyroidism.

A plain English summary of the guidelines will be made available for patients and interested members of the public on the websites of the BTA and BTF.

The statement has been developed following consultation within the BTA and with relevant stakeholder groups. All authors are members of the BTA executive committee with expertise in thyroid disease management and research. An initial face to face meeting was held in December 2014 by committee members, during which the scope and remit of the proposed position statement was decided. Following this, individual reviewers undertook a primary review that addressed key clinical questions relating to the diagnosis, indications, monitoring, therapeutic choice, and treatment targets in the management of hypothyroidism. The primary reviewers examined the recent hypothyroidism guidelines of the ATA and ETA including original research informing these guidelines that was considered relevant to the remit of the current position statement. Furthermore a systematic search of PubMed was undertaken and additional references were sourced through references of individual articles. An initial draft was sent out to consultation by e-mail to executive and senior members of the BTA who revised the original draft. Consensus on recommendations was reached through discussions. Wider consultations were then held with representatives of the SFE, ACB, and RCP, as well as with the BTF, the patient support charity for thyroid disorders. The document was finalised following feedback from each of these bodies and agreement from all authors was reached on the final statement. No external funding was received, either by the BTA or by individual members, for the development of this statement, and all conflicts of interests are declared.

In addition to the statement we have summarised the relevant recommendations from the ATA and ETA guidelines relating to the diagnosis and management of

primary hypothyroidism. These recommendations are grouped into themes each addressing a specific clinical question. The strength of the recommendations and the quality of the evidence supporting these recommendations are included as judged by the authors of the original guidelines. Recommendations made in the BTA statement are also rated as strong (1) or weak recommendations (2) and the quality of evidence rated as high (+++), moderate (++0), low (+00), or insufficient (000) according to the GRADE system classification for clinical practice recommendations [30, 31].

Summary of ETA and ATA guidelines

The key recommendations are summarised in Tables 1-10 and each Table addresses a relevant question reviewed in either or both guidelines.

1. L-T4 is the treatment of choice in hypothyroidism. The goal of therapy is to restore physical and psychological well-being and normalise serum TSH (Table 1).

2. The adequacy of therapy should be determined both by clinical and biochemical assessment and under-treatment and over-treatment should be avoided due to their detrimental health effects (Table 2).

3. There is insufficient evidence to recommend monitoring serum T3 as a therapeutic target in hypothyroidism (Table 3).

4. A proportion of patients on L-T4 therapy have persistent symptoms despite normal serum TSH levels. Such symptoms should be acknowledged and alternative aetiologies sought (Table 4).

5. There is insufficient evidence that combination therapy with L-T4 and L-T3 therapy is superior to L-T4 monotherapy (Table 5).

6. L-T4/L-T3 therapy may be considered as an “experimental approach” in compliant LT4-treated hypothyroid patients who have persistent complaints despite reference range serum TSH values, provided they have received adequate chronic disease support and associated autoimmune diseases have been ruled out (ETA) (Table 5-6). There is currently insufficient evidence to support the routine use of such a trial of L-T4 and L-T3 outside a “formal clinical trial or N of 1 trial” (ATA) (Table 5).

7. Thyroid hormone therapy is not recommended in euthyroid individuals with (i) suggestive symptoms of hypothyroidism, (ii) obesity, (iii) depression or (iv) urticaria (Table 7).

8. The routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation, nutraceuticals and over the counter preparations are not recommended in the management of hypothyroidism (Table 8).

9. Genetic characterisation for deiodinase gene polymorphisms is not recommended as a guide to the use of combination L-T3 and L-T4 therapy in hypothyroidism (Table 9).

10. Clinicians treating patients with hypothyroidism have an ethical obligation to avoid potential harmful therapies without proven benefits. The balance of clinical evidence regarding the efficacy of monotherapy versus combination therapy calls for further well designed randomised controlled trials (Table 10).

Commentary

The ETA and ATA guidelines differ in scope although the key recommendations on the diagnosis and management of hypothyroidism are comparable. The ATA guidelines comprehensively address the management of hypothyroidism and include sections on in-hospital management, secondary hypothyroidism, the use of thyroid hormone analogues, and ethical considerations for clinicians and researchers. The ETA document on the other hand focuses specifically on the use of combination therapy and includes carefully considered suggestions for prescribing L-T3 in practice.

Both guidelines strongly recommend that L-T4 remain the therapy of choice in hypothyroidism and do not support the routine use of L-T4/L-T3 combination therapy due to insufficient evidence from controlled trials, lack of long-term L-T3 safety data, and unavailability of L-T3 formulations that mirror natural physiology.

A key feature of both guidelines is the acknowledgement of the subset of L-T4 treated patients who suffer persistent symptoms despite adequate biochemical thyroid status. However while both guidelines agree that a trial of L-T3 may occasionally be indicated in such patients there are significant differences between the guidelines in the implementation of such a trial.

The ETA would consider a carefully monitored experimental trial of L-T3 if symptoms persist after co-morbid conditions have been excluded. Such a trial should be conducted under specialist supervision, be reassessed after a period of three months and preferably include objective evaluations of response with standardised quality of life tools.

The ATA go further by insisting that any such trial must be rigorously implemented, either as part of a clinical trial, or N of 1 trial, with formal ethical and governance approvals. In addition the ATA highlight the ethical and legal obligations inherent on clinicians managing hypothyroidism including the responsibility to avoid potentially harmful therapies without proven advantage over existing therapies. The authors further assert that the balance of clinical evidence on the benefits of combination therapy over L-T4 monotherapy would demand that further randomised controlled trials are indicated.

The 2011 RCP statement concluded that L-T3 "should be reserved for use by accredited endocrinologists in individual patients" but did not specifically address management strategies for L-T4 treated patients with persistent symptoms after non-thyroid causes are excluded. Thus, the current ETA and ATA guidelines can be seen as an addition rather than a departure from this position.

Statement

Based on the current literature and following review of the published positions of the ETA and ATA, and in line with the best principles of good medical practice, the BTA, ACB, BTF, RCP and SFE have agreed the following statement:

1. It is important that high quality, unbiased, evidence based information about hypothyroidism is made available to patients and the public. We recognise the need to engage with patients and promote more research in hypothyroidism.

2. The diagnosis of primary hypothyroidism is based on clinical features of hypothyroidism supported by biochemical evidence i.e. elevated serum TSH together with low free T4 (overt hypothyroidism) or normal free T4 (subclinical

hypothyroidism). Primary hypothyroidism should not be diagnosed in individuals with normal serum TSH who otherwise have intact pituitary function (1/++0).

3. The evidence in favour of narrowing the serum TSH reference range is not convincing and cannot justify the large increase in the number of healthy people that would require investigation (1/++0).

4. A significant proportion of healthy subjects in the community have asymptomatic chronic autoimmune thyroiditis and a significant proportion have subclinical hypothyroidism. Spontaneous recovery has been described in subjects with subclinical hypothyroidism. It is more likely in those with negative anti-thyroid antibodies and serum TSH levels less than 10 mU/L, and within the first two years after diagnosis. The higher the serum TSH value, the greater the likelihood of development of overt hypothyroidism in subjects with chronic autoimmune thyroiditis.

5. Synthetic L-T4 remains the treatment of choice in hypothyroidism with the aim of therapy being to restore physical and psychological well-being while maintaining normal laboratory reference range serum TSH levels (1/++0). After initiation of therapy TSH should be monitored 6-8 weekly and the dose of L-T4 should be adjusted until a stable TSH is achieved, after which TSH can be checked 4-6 monthly, and then annually (1/+00).

6. It is acknowledged that a proportion of individuals on L-T4 are not satisfied with therapy and have persistent symptoms despite a normal serum TSH. Such symptoms should be given due consideration and patients should be thoroughly evaluated for other potentially modifiable conditions (Box 1). In some cases a retrospective review of the original diagnosis of hypothyroidism may be

necessary. Symptom and lifestyle management support should be provided and further dose adjustments may be required (1/+00).

7. Although fine tuning of serum TSH levels within the reference range may be indicated for individual patients, deliberate serum TSH suppression with high dose thyroid hormone replacement therapy (serum TSH <0.1 mU/L) should be avoided where possible as this carries a risk of adverse effects such as cardiac rhythm disorders including atrial fibrillation, strokes, osteoporosis and fracture (1/++0). As an exception, patients with a history of thyroid cancer may require deliberate suppression of serum TSH if there is a significant risk of recurrence.

8. For the vast majority of patients on L-T4, brand or named supplier prescribing is not considered necessary (2/+00). The Medicines and Healthcare Products Regulatory Agency (MHRA) have recently made recommendations to ensure the quality and consistency of L-T4 tablets that are on the UK market. Rarely patients may require a specific brand of L-T4 to be prescribed due to intolerance of generic preparations.

9. Serum T3 should not be used as a therapeutic target in the management of hypothyroidism as the value of this approach is unproven (1/+00).

10. L-T4/L-T3 combination therapy in patients with hypothyroidism should not be used routinely, as there is insufficient evidence to show that combination therapy is superior to L-T4 monotherapy (1/++0).

11. Clinicians have an ethical responsibility to adhere to the highest professional standards of good medical practice rooted in sound evidence. This includes not

prescribing potentially harmful therapies without proven advantages over existing treatments.

12. If a decision is made to embark on a trial of L-T4/L-T3 combination therapy in patients who have unambiguously not benefited from L-T4 then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences. Many clinicians may not agree that a trial of L-T4/L-T3 combination therapy is warranted in these circumstances and their clinical judgement must be recognised as being valid given the current understanding of the science and evidence of the treatments (2/+00).

13. The serum TSH reference range in pregnancy is 0.4-2.5 mU/L in the first trimester and 0.4-3.0 mU/L in the second and third trimesters or should be based on the trimester specific reference range for the population if available. These reference ranges should be achieved where possible with appropriate doses of L-T4 pre-conception and most importantly in the first trimester (1/++0). L-T4/L-T3 combination therapy is not recommended in pregnancy (1/+00).

14. There is no convincing evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism (1/+00).

Conclusions

This updated position statement reflects current best practice in the management of primary hypothyroidism. Levothyroxine therapy offers a safe, rational, and simplified approach to the correction of hypothyroidism, and for the vast majority of patients, treatment results in improved physical and psychological well-being. 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. Thus, future RCTs 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. The BTA hopes that this position statement along with other recently published scientific guidelines would support clinicians in implementing evidence based strategies in the management of hypothyroidism.

LIST OF ABBREVIATIONS

L-T4	Levothyroxine,
FT4,	Free thyroxine
FT3	Free triiodothyronine,
TSH	Thyroid Stimulating Hormone
L-T3	Liothyronine
ATA	American Thyroid Association
ETA	European Thyroid Association

STRENGTH OF RECOMMENDATIONS

1	Strong recommendation
2	Weak recommendation
SS	Summary statement where formal clinical recommendation is not feasible because of sparse evidence

QUALITY OF EVIDENCE

+++	High, grade A
++0	Moderate, grade B
+00	Low, grade C
000	Insufficient evidence

LIST OF TABLES

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TABLE 1: CHOICE OF THERAPY AND THERAPEUTIC TARGETS

Question	Guideline	Recommendation	Strength/ Evidence
Why is L-T4 monotherapy considered to be the standard of care for hypothyroidism?	ATA	L-T4 is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favourable side effect profile, ease of administration, good intestinal absorption, long serum half-life and low cost.	1/++0
What are the clinical and biochemical goals for L-T4 replacement in primary hypothyroidism?	ATA	L-T4 replacement therapy has three main goals. These are (i) to provide resolution of patients' symptoms and hypothyroid signs, including biological and physiologic markers of hypothyroidism, (ii) to achieve normalization of serum TSH with improvement in thyroid hormone concentrations, and (iii) to avoid overtreatment (iatrogenic thyrotoxicosis) especially in the elderly.	1/++0
Are clinical parameters such as cold sensitivity and dry skin useful by themselves for assessing adequacy of L-T4 replacement in primary hypothyroidism?	ATA	Although it may be helpful to follow changes in clinical symptoms longitudinally in patients treated for hypothyroidism, symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment. Therefore, symptoms should be followed, but considered in the context of serum TSH values, relevant co-morbidities, and other potential causes	1/+00
Are tissue markers of thyroid hormone action helpful in determining the adequacy of L-T4 replacement in primary hypothyroidism?	ATA	Tissue biomarkers of thyroid hormone action are not recommended for routine clinical use, outside of the research setting, since these parameters are not sensitive, specific, readily available, or standardized.	2/+00

TABLE 2: EFFECTS OF INADEQUATE OR EXCESS L-T4 THERAPY

Question	Guideline	Recommendation	Strength/ Evidence
What are the potential deleterious effects of excessive L-T4?	ATA	The deleterious health effects of iatrogenic thyrotoxicosis include atrial fibrillation and osteoporosis. Because of these effects we recommend avoiding thyroid hormone excess and subnormal serum TSH values, particularly serum TSH values below 0.1 mU/L, especially in older persons and post-menopausal women.	1/++0
What are the potential deleterious effects of inadequate L-T4?	ATA	The adverse effects of thyroid hormone deficiency include detrimental effects on the serum lipid profile and progression of cardiovascular disease. We recommend that patients with overt hypothyroidism be treated with doses of L-T4 that are adequate to normalize serum TSH, in order to reduce to eliminate these undesirable effects.	1/++0

TABLE 3: ROLE OF SERUM FREE T3 IN THE MANAGEMENT OF HYPOTHYROIDISM

Question	Guideline	Recommendation	Strength/ Evidence
Are variations in serum T3 concentrations within the reference range of physiologic or clinical significance? In addition, are mildly low serum T3 concentrations of clinical significance?	ATA	The significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown.	SS
Does L-T4 therapy that returns the serum TSH levels of hypothyroid patients to the reference range also result in normalization of their serum T3 levels?	ATA	Patients with hypothyroidism treated with L-T4 to achieve normal serum TSH values may have serum T3 concentrations that are at the lower end of the reference range, or even below the reference range. The clinical significance of this is unknown.	SS
Should L-T4 therapy for hypothyroidism, particularly in specific subgroups such as those with obesity, depression, dyslipidaemia, or who are athyreotic, be targeted to achieve high-normal serum free T3 levels or low-normal serum TSH levels?	ATA	There is insufficient evidence of benefit to recommend that treatment with L-T4 be targeted to achieve low-normal serum TSH values or high normal serum T3 values in patients with hypothyroidism, including those who are overweight, or those who have depression, dyslipidaemia, or who are athyreotic.	1/++0
Is there evidence of discordance between the thyroid hormone status of different tissues and the serum TSH concentration?	ATA	There are specific instances in which there appears to be discordance between the thyroid status of the pituitary gland, as reflected by the serum TSH, and the thyroid status of other tissues as indicated by various biomarkers. The clinical significance of this is not known.	SS

TABLE 4: PATIENT SATISFACTION WITH L-T4 THERAPY

Question	Guideline	Recommendation	Strength/ Evidence
Is there an unmet need in LT4-treated patients with hypothyroidism?	ETA	In LT4-treated hypothyroid patients with normal serum TSH values, psychological distress, impaired wellbeing and cognitive disturbances occur more often than in controls. Data suggest that 5–10% of L-T4 treated hypothyroid patients with normal serum TSH have persistent symptoms which can be related to the disease and L-T4 therapy.	1/+00 2/+00
Is there a biologic rationale for persistent complaints in L-T4 treated hypothyroid patients?	ETA	Suggested explanations for persistent symptoms in L-T4 treated hypothyroid patients despite normalisation of serum TSH, include: Awareness of a chronic disease, presence of associated autoimmune diseases, thyroid autoimmunity per se (independent of thyroid function), and inadequacy of L-T4 treatment to restore physiological T4 and T3 concentrations in serum and tissues.	2/+00
What approach should be taken in patients treated for hypothyroidism who have normal serum TSH values but still have unresolved symptoms?	ATA	A minority of patients with hypothyroidism, but normal serum TSH values, may perceive a suboptimal health status of unclear aetiology. Acknowledgement of the patients' symptoms and evaluation for alternative causes is recommended in such cases. Future research into whether there are sub-groups of the population being treated for hypothyroidism who might benefit from combination therapy should be encouraged.	2/+00
What tools may be useful in the clinical or research setting, to measure the impact of L-T4 replacement for primary hypothyroidism on patients' physical or psychological well-being, treatment satisfaction, or treatment preferences?	ATA	Of the established instruments used to measure hypothyroid symptoms, data are lacking regarding their sensitivity and specificity in the "everyday" clinical setting to recommend their routine clinical use. Further studies are needed to determine if and how to combine general psychological screening instruments, hypothyroidism-specific tools, and laboratory assessment of thyroid function to measure the impact of L-T4 replacement therapy on psychological well-being, treatment satisfaction, and preference in clinical practice. A combination of general instruments, combined with hypothyroidism-specific tools, may be the most effective way to examine psychological well-being in the L-T4 treated population in the research setting.	1/++0

TABLE 5: COMBINATION THERAPY WITH L-T4 AND L-T3

Question	Guideline	Recommendation	Strength/ Evidence
Is combination therapy with L-T4 and L-T3 superior to L-T4 monotherapy in the management of hypothyroidism?	ETA	Insufficient evidence that L-T4 + L-T3 combination therapy is superior to L-T4 monotherapy. L-T4 monotherapy remains the standard treatment of hypothyroidism.	1/++0 1/+++
	ATA	There is no consistently strong evidence of superiority of combination therapy over monotherapy with L-T4. Therefore, we recommend against the routine use of combination treatment with L-T4 and L-T3 as a form of thyroid replacement therapy in patients with primary hypothyroidism, based on conflicting results of benefits from randomised controlled trials comparing this therapy to L-T4 therapy alone and a paucity of long-term outcome data.	2/++0
Is there a place for combination therapy with L-T4 and L-T3 in patients who have persistent symptoms despite serum TSH values within the reference range?	ETA	Consider L-T4 and L-T3 as an experimental approach in compliant L-T4 treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously been given support to deal with the chronic nature of their disease and associated autoimmune diseases have been ruled out. L-T4 and L-T3 are not recommended in pregnancy and in patients with cardiac arrhythmias. Discontinue L-T4 and L-T3 if no improvement after three months.	2/+00 2/+00 2/++0
	ATA	For patients with primary hypothyroidism who feel unwell on L-T4 therapy alone (in the absence of an allergy to L-T4 constituents or an abnormal serum TSH), there is currently insufficient evidence to support the *routine* use of a trial of a combination of L-T4 and L-T3 therapy outside a formal clinical trial or N of 1 trial, due to uncertainty in long-term risk benefit ratio of the treatment and uncertainty as to the optimal definition of a successful trial to guide clinical decision-making.	000

TABLE 6: DOSE, ADMINISTRATION AND MONITORING OF L-T3 THERAPY

Question	Guideline	Recommendation	Strength/ Evidence
What is the appropriate dose of L-T4 and L-T3?	ETA	Start L-T4+L-T3 at L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight. L-T4 can be given once daily, the daily L-T3 dose should be divided (if possible) in two doses, one before breakfast and the largest one before bed.	2/+00 2/+00
Which preparations can be used in L-T4 and L-T3 combination therapy and how should their use be monitored?	ETA	Available LT4+LT3 combination preparations contain a LT4/LT3 dose ratio lower than 13:1, so it is recommended to use separate LT4 and LT3 tablets. L-T4+L-T3 should be monitored by thyroid function tests in blood samples taken before the morning dose, aiming at normal serum TSH, free T4 (FT4), free T3 (FT3), and FT4/FT3 ratio. If dose adjustment of L-T4+L-T3 combination therapy is necessary to achieve a normal serum TSH, free T4, free T3, and FT4/FT3 ratio, the dose of one component, preferably L-T3, should be changed,. L-T4 and L-T3 therapy should be supervised by accredited internists or endocrinologists	1/+00 1/++0 2/+00 2/++0

TABLE 7: USE OF THYROID HORMONE THERAPY IN EUTHYROID INDIVIDUALS

Question	Guideline	Recommendation	Strength/ Evidence
Is there a role for the use of L-T4 to treat biochemically euthyroid patients with symptoms that overlap with those of hypothyroidism?	ATA	Strongly recommend against the use of L-T4 treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use of L-T4 in this situation.	1/+++
Is there a role for the use of L-T4 or L-T3 to treat euthyroid patients with depression?	ATA	Recommend against the routine use of L-T4 for the treatment of euthyroid individuals with depression, due to a paucity of controlled data examining treatment efficacy in this setting. Although some uncontrolled and non-randomised data exist concerning successful use of L-T3 in euthyroid patients with depression, larger, prospective randomised placebo controlled studies are needed to more completely define the potential role of L-T3 in this condition, balancing the risks and benefits of therapy to measurable clinical outcomes.	2/+00 2/+00
Is there a role for the use of L-T4 or L-T3 to treat euthyroid patients with obesity?	ATA	Recommend against the treatment of obesity with L-T4 in euthyroid individuals, due to a lack of treatment efficacy for this condition. Recommend against the treatment of obesity with synthetic L-T3 due to a lack of controlled data proving treatment efficacy for this indication.	1/++0 1/+00
Is there a role for the use of L-T4 to treat euthyroid patients with urticaria?	ATA	Recommend against the treatment of urticaria with L-T4 in euthyroid individuals, due to a lack of treatment efficacy for this condition	1/++0

TABLE 8: ROLE OF OTHER THERAPIES IN HYPOTHYROIDISM

Question	Guideline	Recommendation	Strength/ Evidence
Is treatment with thyroid extracts superior to treatment with L-T4 alone?	ATA	Although there is preliminary evidence from a short-duration study that some patients may prefer treatment with extracts, high quality controlled long-term outcome data are lacking to document superiority of this treatment compared to L-T4 therapy. Furthermore, there are potential safety concerns related to the use of thyroid extracts, such as the presence of supraphysiological serum T3 levels and a paucity of long-term safety outcome data.	1/++0
Are there data regarding therapy with L-T3 alone, either as standard L-T3 or as sustained release L-T3, that support the use of L-T3 therapy alone for the treatment of hypothyroidism?	ATA	Although short-term outcome data in hypothyroid patients suggest that thrice daily synthetic L-T3 may be associated with beneficial effects on parameters such as weight and lipids, longer-term controlled clinical trials using a longer acting form of L-T3 are needed, before considering the endorsement of synthetic L-T3 therapy for routine clinical use.	1/++0
What is the recommendation regarding therapy with compounded thyroid hormones (either L-T4 or L-T3) for treatment of hypothyroidism based on current evidence?	ATA	Recommend against the routine use of compounded thyroid hormones due to concerns about safety and potency and due to the lack of data proving superiority to standard thyroid hormone preparations. However, in the case of suspected allergy to an excipient of standard thyroid hormone preparations that cannot be avoided with a change in brand or dose formulation, including a trial of L-T4 gel capsules, it may be reasonable to consider use of compounded products, although a controlled study of this approach has not been published.	1/+00
Is there a role for the use of dietary supplementation, nutraceuticals, and over the-counter products in either hypothyroid or euthyroid individuals?	ATA	Recommend against the use of dietary supplements, nutraceuticals, or other over the counter products either in euthyroid individuals or as a means of treating hypothyroidism. Particularly caution against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism in those with intact thyroid glands susceptible to becoming further dysregulated because of underlying thyroid pathology.	1/+00

TABLE 9: IMPACT OF GENETIC POLYMORPHISMS ON THE RESPONSE TO THERAPY

Question	Guideline	Recommendation	Strength/ Evidence
Could it be that trials comparing L-T4 and L-T3 combination therapy and L-T4 monotherapy have not targeted the right population?	ETA	Limited data suggest that psychological well-being and preference for L-T4 and L-T3 combination therapy may be influenced by polymorphisms in thyroid hormone pathway genes, specifically in thyroid hormone transporters and deiodinases.	2/+00
Should genetic characterization according to type 2 deiodinase gene polymorphism status be used to guide the use of combination synthetic L-T3 and L-T4 therapy in hypothyroidism, in order to optimise biochemical and clinical outcomes?	ATA	Currently, genetic testing is not recommended as a guide to selecting therapy for 3 reasons. i) Although there are data suggesting that specific polymorphisms of the type 2 deiodinase gene might be associated with therapeutic response to combination synthetic L-T3 and L-T4 therapy, controlled confirmatory studies are needed. ii) Currently genetic testing for these specific deiodinase polymorphisms is only available in the research setting. iii) The small effect of the type 2 deiodinase gene variants identified so far that do affect thyroid hormone concentrations suggests that other factors (e.g. yet unidentified genetic variants) may play a far greater role in determining an individual patient's thyroid hormone concentrations.	1/++0

TABLE 10: ETHICAL CONSIDERATIONS

Question	Guideline	Recommendation	Strength/ Evidence
What are the ethical obligations of clinicians in treating hypothyroidism?	ATA	Clinical ethical principles in L-T4 treatment for hypothyroidism revolve around two core ethical principles in medicine: the principles of beneficence and non-maleficence, which guide the risk/benefit analysis in clinical practice, and protect clinicians from deviating from practice to satisfy inappropriate patient demands. Additional ethical obligations revolve around the professional virtues of competence and intellectual honesty.	Ungraded
What are the research ethics issues involved in evaluating or designing clinical trials for the treatment of hypothyroidism?	ATA	There should be recognition that there are not enough data to resolve clinical disagreement amongst thyroid experts (called “clinical equipoise”) regarding treatment for hypothyroidism. Clinical equipoise is disturbed only by the results of well-designed randomised controlled trials that have the statistical power to settle the question of efficacy between monotherapy and combination therapy, or other forms of therapy.	Ungraded

Box 1: Some possible causes of persistent symptoms in euthyroid patients on L-T4

Endocrine/autoimmune
- Diabetes Mellitus
- Adrenal insufficiency
- Hypopituitarism
- Coeliac disease
- Pernicious anaemia

Haematological
- Anaemia
- Multiple myeloma

End-organ damage
- Chronic kidney disease
- Chronic liver disease
- Congestive cardiac failure

Nutritional
- Vitamin B12 deficiency
- Folate deficiency
- Vitamin D deficiency
- Iron deficiency

Metabolic
- Obesity
- Hypercalcaemia
- Electrolyte imbalance

Drugs
- Beta-blockers
- Statins
- Opiates

Lifestyle
- Stressful life events
- Poor sleep pattern
- Work related exhaustion
- Alcohol excess

Others
- Obstructive sleep apnoea
- Viral and post viral syndromes
- Chronic fatigue syndrome
- Carbon monoxide poisoning
- Depression and anxiety
- Polymyalgia rheumatica
- Fibromyalgia