Management of Hypothyroidism

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BTA President and BTF Trust Board Member
BTF Milton Keynes
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The thyroid gland – part of the endocrine system, made up of glands that make and secrete hormones into the bloodstream to control physiological functions – regulates how quickly the body burns energy, makes proteins and how sensitive it is to other hormones.
William Ord 1878
First photo of a patient with myxedema

At aged 21: Before onset of symptoms, seven and four years later
Theodore Kocher
1883
Clinical picture after
total thyroidectomy
similar to cretinism
Victor Horsley
1885
“Myxoedema due to the arrest of the function of the thyroid gland”
Treatment of Mrs S (46 yrs) by hypodermic injections of extract of sheep thyroid gland
BROWN SEQUARD'S

METHOD.

EXTRACTS OF ANIMAL ORGANS.
Testicle Extract,
Grey Matter Extract,
Thyroid Gland Extract, &c., &c.

Concentrated Solutions at 30%.
These preparations, completely aseptic, are mailed to any distance on receipt of a money order. Directions sent with the fluids.

Price for 25 Injections, $2.50.
Syringe Specially Gauged, (3 cubic c.) $2.50.

Used in the Hospitals of Paris, New York, Boston, &c.
Circular Sent on Application.

New York Biological and Vaccinal Institute,
Laboratory of Bovine Vaccine and of Biological Products.
GEO. G. RAMBAUD, Chemist and Bacteriologist, Superintendent.
PASTEUR INSTITUTE BUILDING, NEW YORK CITY.
## The Chronological Sequence of Events during the Search for and the Discovery of Iodine-Containing Thyroid Hormones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1890</td>
<td>Hypothyroidism successfully treated with implant of sheep thyroid gland.</td>
</tr>
<tr>
<td>1891-1892</td>
<td>Hypothyroidism successfully treated with enteral and parenteral administration of thyroid glands and thyroid extracts.</td>
</tr>
<tr>
<td>1895</td>
<td>Bauman measured large amounts of thyroidal iodine in an organic form firmly held as a constituent of thyroidal proteins. He postulated that the active principle was an iodine-containing substance. He attempted unsuccessfully to hydrolyze thyroidal proteins in order to isolate the active principle.</td>
</tr>
<tr>
<td>Late 1890s</td>
<td>Thyroid extracts standardized to contain 0.2% iodine in order to maintain equal potency between different preparations.</td>
</tr>
<tr>
<td>1915</td>
<td>Kendall succeeded in hydrolyzing thyroid proteins into simpler constituents. Further purification yielded a biologically active iodine-containing substance which was crystallized into a pure form. Kendall called this crystallized product thyroxin. Unfortunately, Kendall assigned the wrong structure to this compound.</td>
</tr>
<tr>
<td>1926</td>
<td>Harrington confirmed Kendall’s findings. He assigned the correct structure: thyroxine with four atoms of iodine.</td>
</tr>
<tr>
<td>1927</td>
<td>Harrington synthesized thyroxine from iodinated thyrosine. The end product was a racemic mixture of D- and L-thyroxine. Since L-thyroxine is 10 times more potent than D-thyroxine, the racemic mixture possessed one-half the potency of L-thyroxine.</td>
</tr>
<tr>
<td>1949</td>
<td>Chalmer published a procedure for the synthesis of pure (non-racemic) L-thyroxine from iodinated L-thyrosine with a high yield of 26%.</td>
</tr>
<tr>
<td>1952</td>
<td>L-triiodothyronine (L-T₃), an intermediate in the synthesis of T₄ from diiodothyronine that is 3-4 times more potent than L-T₄ (based on bioassays and basal metabolic rate), is isolated. Synthesis of L-T₃ is also achieved.</td>
</tr>
</tbody>
</table>
Thyroid extract

SIR,—We write to suggest that thyroid extract (Thyroid, BP) be removed from the British Pharmacopoeia and that its manufacture be abolished.

We continue to see patients who have been diagnosed as having myxoedema and who are being treated with apparently adequate doses of thyroid extract but who are clinically and biochemically hypothyroid. They have subsequently responded to thyroxine.

Although it is never possible to be certain that drugs prescribed are being taken, there is good evidence that the potency of thyroid extract is variable and its shelf-life dated.¹ As both active constituents, thyroxine and triiodothyronine, have been available for many years we see no reason for the retention of thyroid extract, which we consider to be dangerous.

W. Van't Hoff
R. Hoffenberg
D. R. London
R. Hall

G. M. Besser
J. S. Staffurth
D. C. Anderson
J. Jenkins
R. L. Himsworth
Peter Sonksen

Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism

M P J Vanderpump, J A O Ahlquist, J A Franklyn, R N Clayton, on behalf of a working group of the Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology

Summary of good practice for purchasers

- Thyroid disorders are among the most prevalent of medical conditions and increase with age
- Screening the healthy adult population for thyroid dysfunction is unjustified
- The diagnosis of thyroid dysfunction must be confirmed biochemically
- Each district general hospital should have a specialist in thyroid disorders with access to an experienced thyroid surgeon and thyroid disease register
- Patients with hypothyroidism need referral only in certain circumstances
- Serum thyroid stimulating hormone concentration should be measured yearly to ensure compliance with the treatment of hypothyroidism
- All patients with hyperthyroidism should be referred to a specialist at diagnosis
- In Graves' disease carbimazole is the medical treatment of choice via either a titrating or block-replace regimen
- Radioiodine is indicated in most types of hyperthyroidism but must be given with caution in the presence of active Graves' ophthalmopathy
- Thyroid surgery by an experienced surgeon is an alternative method of treating hyperthyroid patients
- All patients treated with radioiodine or partial thyroidectomy should have a yearly check of thyroid function
The Diagnosis and Management of Primary Hypothyroidism

A statement made on behalf of

The Royal College of Physicians
in particular its Patient and Carer Network
and the Joint Specialty Committee
for Endocrinology & Diabetes

The Association for Clinical Biochemistry
The Society for Endocrinology
The British Thyroid Association
The British Thyroid Foundation Patient Support Group
The British Society of Paediatric Endocrinology
and Diabetes

Endorsed by
the Royal College of General Practitioners
Thyroid Hormone Axis

Hypothalamus

TRH

TSH

T3 + T4

However

- T3 is the major feedback regulator of TSH secretion
- If TSH is normal, brain T3 must be normal
TSH by age and gender

(Canaris et al, 2000)
Follow-up of initial TSH result
(Meyerovitch et al, 2007)
Why are patients on L-T4?

- TSH > 10 ± symptoms
- TSH 4-10 ± symptoms ± thyroid antibodies
- TSH 1-4 + symptoms ± thyroid antibodies
- TSH ≤ 2.5 pre-conception or pregnancy
- TSH 1-2.5 + thyroid antibodies pre-pregnancy
- Post thyroid surgery for benign nodular goitre or Graves’ disease
- Post radioiodine for Graves’ disease
- Post thyroidectomy ± I131 for thyroid cancer
Thyroid Madness Definition:

1. Treating hypothyroid patients solely with T4-only meds.
2. Dosing solely by the TSH and the total T4, or using the outdated "Thyroid Panel".
3. Prescribing anti-depressants in lieu of evaluating and treating the free T3.
4. Telling thyroid patients that desiccated natural thyroid is "unreliable", "inconsistent", "dangerous" or "outdated".
5. Making labwork more important than the hypo symptoms which scream their presence.
6. Failing to see the OBVIOUS symptoms of poorly treated thyroid, and instead, recommending a slew of other tests and diagnoses.
Thyroid Hormone Production

- T4: 101 ug/d
- T3: 6 ug/d
- T3: 26 ug/d
- T3: 20 ug/d

20% Secreted, 80% Converted from T4

The T3 Hypothesis

- T4 101 ug/d
- No T4
- No T3
- T3 20 ug/d
  100% Converted from T4
  “Tissue T3 Deficiency”
T3 in my hypothyroid treatment equals HAPPY!
# Combined LT4 / LT3 Therapy

## Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective Benefit</th>
<th>Subjective Benefit</th>
<th>T4/T3 Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bunevicious 1999</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Walsh 2003</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sawka 2003</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Clyde 2003</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Siegmund 2004</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Saravanan 2005</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Escobar-Morreale 2005</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Apelhof 2005</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rodriguez 2005</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Levitt 2005</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Regalbuto 2007</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Slawik 2007 (Central)</td>
<td>No</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>Escobar-Morreale 2005 Review</td>
<td>No benefit of T4/T3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grozinsky-Glasberg 2006 Meta-Analysis</td>
<td>No benefit of T4/T3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LT4/LT3 Therapy of Hypothyroidism

Serum T3 and T4 Levels

![Graph showing serum T3 and T4 levels over time.](image-url)
What is “Armour”? 

• Natural desiccated thyroid hormone
• Constituents are animal L-T4 and L-T3
• Usually extracted from pig thyroid glands
• Tablets or “grains” contain approximately 38mcg of L-T4 and 9mcg of L-T3
• Wide variety of strengths in “grains”
• Authorised by the FDA but not by MRHA in UK
• Can be imported if prescribed
Thyroid Hormone Production

- **T4**: 101 ug/d
- **T3**: 20 ug/d
- **T3**: 26 ug/d

Secretion Ratio: T4:T3 = 14:1

20% Secreted, 80% Converted from T4

<table>
<thead>
<tr>
<th>Dose</th>
<th>LT4 + LT3</th>
<th>T4:T3*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/4 grains</td>
<td>9.5 + 2.25</td>
<td>2.8:1</td>
</tr>
<tr>
<td>1/2 grains</td>
<td>19 + 4.50</td>
<td>2.8:1</td>
</tr>
<tr>
<td>1.0 grains</td>
<td>38 + 9.0</td>
<td>2.8:1</td>
</tr>
<tr>
<td>1.5 grains</td>
<td>57 + 13.5</td>
<td>2.8:1</td>
</tr>
<tr>
<td>2.0 grains</td>
<td>76 + 18.0</td>
<td>2.8:1</td>
</tr>
<tr>
<td>3.0 grains</td>
<td>114 + 27.0</td>
<td>2.8:1</td>
</tr>
<tr>
<td>Normal</td>
<td>100 + 6</td>
<td>14:1</td>
</tr>
</tbody>
</table>

*Assumes 80% absorption LT4 and 100% absorption LT3*
<table>
<thead>
<tr>
<th>Year</th>
<th>Organization</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>RCP/SFE</td>
<td>Hyperthyroidism &amp; hypothyroidism</td>
</tr>
<tr>
<td>2004</td>
<td>ATA/AACE/Endocrine Society</td>
<td>Subclinical thyroid disease</td>
</tr>
<tr>
<td>2006</td>
<td>ACB/BTA/BTF</td>
<td>Thyroid function test guidelines</td>
</tr>
<tr>
<td>2011</td>
<td>RCP/SFE/BTA/ACB/BTF/ABCD</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>2012</td>
<td>ATA/AACE</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>2012</td>
<td>ETA</td>
<td>L-T4 and L-T3 in hypothyroidism</td>
</tr>
<tr>
<td>2013</td>
<td>LATS</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>2014</td>
<td>ATA</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>2015</td>
<td>BTA</td>
<td>Management of Hypothyroidism</td>
</tr>
</tbody>
</table>
1. L-T4 is the treatment of choice in hypothyroidism. The goal of therapy is to restore physical and psychological wellbeing and normalise serum TSH.

2. Adequacy of therapy determined both by clinical and biochemical assessment. Under- and over-treatment should be avoided due to detrimental health effects.

3. Insufficient evidence to recommend monitoring serum T3 as a therapeutic target in hypothyroidism.

4. Some patients on L-T4 therapy have persistent symptoms despite normal serum TSH levels. This should be acknowledged and alternative aetiologies sought.
5. Insufficient evidence that combination therapy with L-T4 and L-T3 therapy is superior to L-T4 monotherapy

6. L-T4/L-T3 therapy is an ‘experimental approach’ in compliant L-T4-treated hypothyroid patients with persistent complaints despite reference range serum TSH, provided they have received adequate chronic disease support and associated autoimmune diseases have been ruled out

7. Thyroid hormone therapy is not recommended in euthyroid individuals with suggestive symptoms of hypothyroidism, obesity, depression or urticaria
ETA and ATA Guidelines

8. 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.

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

10. Clinicians treating patients with hypothyroidism have ethical obligation to avoid potential harmful therapies without proven benefits. The balance of clinical evidence regarding the efficacy of monotherapy vs combination therapy calls for further well-designed randomised controlled trials.
Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee

Onyebuchi Okosime*, Jackie Gilbert†, Prakash Abraham‡, Kristien Boelaert§, Colin Dayan¶, Mark Gurnell**, Graham Leese††, Christopher McCabe‡‡, Petros Perros§§, Vicki Smith‡‡, Graham Williams¶¶ and Mark Vanderpump***

Summary

The management of primary hypothyroidism with levothyroxine (L-T4) is simple, effective and safe, and most patients report improved well-being on initiation of treatment. However, a proportion of individuals continue to suffer with symptoms despite achieving adequate biochemical correction. The management of such individuals has been the subject of controversy and of considerable public interest. The American Thyroid Association (ATA) and the European Thyroid Association (ETA) have recently published guidelines on the diagnosis and management of hypothyroidism. These guidelines have been based on extensive reviews of the medical literature and include sections on the role of combination therapy with L-T4 and liothryronine (L-T3) in individuals who are persistently dissatisfied with L-T4 therapy. This position statement by the British Thyroid Association (BTA) summarises the key points in these guidelines and makes recommendations on the management of primary hypothyroidism based on the current literature, review of the published positions of the ETA and ATA, and in line with best principles of good medical practice. The statement is endorsed by the Association of Clinical Biochemistry, (ACB), British Thyroid Foundation, (BTF), Royal College of Physicians (RCP) and Society for Endocrinology (SFE).
1. 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. Diagnosis of primary hypothyroidism is based on clinical features of hypothyroidism supported by biochemical evidence that is 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.
3. 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.

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 2 years after diagnosis. The higher the serum TSH value, the greater the likelihood of development of overt hypothyroidism.
5. Synthetic L-T4 remains treatment of choice with the aim of therapy being to restore physical and psychological well-being while maintaining normal laboratory reference range serum TSH levels. After initiation of therapy, TSH should be monitored 6–8 weekly then 4–6 monthly, and then annually.

6. 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. 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.
Box 1. Some possible causes of persistent symptoms in euthyroid patients on L-T4

<table>
<thead>
<tr>
<th>Endocrine/autoimmune</th>
<th>Nutritional</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Vitamin B12 deficiency</td>
<td>Stressful life events</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Folate deficiency</td>
<td>Poor sleep pattern</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Vitamin D deficiency</td>
<td>Work-related exhaustion</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Iron deficiency</td>
<td>Alcohol excess</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>Metabolic</td>
<td>Others</td>
</tr>
<tr>
<td>Haematological</td>
<td>Obesity</td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Hypercalcaemia</td>
<td>Viral and postviral syndromes</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Electrolyte imbalance</td>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>End-organ damage</td>
<td>Drugs</td>
<td>Carbon monoxide poisoning</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Beta-blockers</td>
<td>Depression and anxiety</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Statins</td>
<td>Polymyalgia rheumatica</td>
</tr>
<tr>
<td>Congestive cardiac failure</td>
<td>Opiates</td>
<td>Fibromyalgia</td>
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</tbody>
</table>
BTA/BTF Statement 2015

7. 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 <01 mU/L) should be avoided (risk of adverse cardiac and bone effects). Exception is patients with a history of thyroid cancer

8. For the vast majority of patients on L-T4, brand or named supplier prescribing is not considered necessary. The 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

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

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/LT3 combination therapy is warranted in these circumstances and their clinical judgement must be recognized as being valid given the current understanding of the science and evidence of the treatments.
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 preconception and most importantly in the first trimester. L-T4/L-T3 combination therapy is not recommended in pregnancy.

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.
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

• The management of patients with a suboptimal clinical response remains challenging

• The benefits of combination therapy with L-T4 and L-T3 are still unproven, and the potential for harm exists with unregulated use of unapproved therapies
Conclusions 2

• 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, optimize drug delivery and standardize 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
• Clinicians must be committed to delivering individualised patient-centred care and shared decision making
Thyroid panacea

- Obesity
- Fatigue
- Ageing
- Depression
- Mood
- Cholesterol