In response to an enquiry from the Scottish Parliament Public Petition Committee
Number 22 February 2014

In the context of hypothyroidism, what is the evidence for the effectiveness of diagnostic tests and thyroid hormone replacement therapies?

What is a scoping report
Scoping reports ascertain the quantity and quality of the published clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They also serve to clarify definitions related to the research question(s) on that topic. They are intended to provide an overview of the evidence base, including gaps and uncertainties, and inform decisions on the feasibility of producing an evidence review product on the topic. Scoping reports are undertaken in an approximately 1-month period. They are based upon a high-level literature search and selection of the best evidence that Healthcare Improvement Scotland could identify within the time available. The reports are subject to peer review. Scoping reports do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produce an Advice Statement to accompany all evidence reviews. Further information on scoping reports is available at www.healthcareimprovementscotland.org

Key definitions

Hypothyroidism: The clinical consequence of deficient secretion by the thyroid gland.

Overt hypothyroidism: A serum thyroid-stimulating hormone (TSH) concentration above the normal reference range (the TSH concentration is almost always >10 mU/L in overt hypothyroidism) and a serum free thyroxine (FT4) concentration below the reference range. Clinical features of hypothyroidism may be absent or present.

Subclinical hypothyroidism: A serum TSH concentration above the normal reference range with an FT4 concentration within the reference range, confirmed on repeat testing after at least 3 months. Clinical features of hypothyroidism are usually absent.

Background
In the United Kingdom (UK), hypothyroidism is most often due to autoimmune hypothyroidism or thyroid damage following surgery or radioactive iodine therapy. Primary hypothyroidism is around ten times more common in women than in men. Clinical symptoms of hypothyroidism are non-specific and include dry skin, weight gain, cold intolerance, pain, fatigue, depression and memory problems. Diagnosis requires abnormal thyroid function test results. Although thyroid hormone replacement with levothyroxine (L-T4) provides resolution of symptoms for the majority of patients, around 5-10% of patients report impaired wellbeing and cognitive disturbances related to the disease and L-T4 therapy, despite thyroid function tests being restored to within the reference range.

The overall prevalence of subclinical hypothyroidism in the UK is around 8% in women and around 3% in men and may be around double this rate in people over 60. There is uncertainty as to the potential benefits and risks of screening for and treatment of subclinical hypothyroidism.

A recent review reported an association between variations in TSH and thyroid hormone levels and adverse health outcomes in individuals with test values within the reference range.

In the year 2012-13, 224,972 patients in Scotland had prescriptions for L-T4 dispensed in the community (C Young, Senior Information Analyst, ISD Scotland. Personal Communication, 9 October 2013).

This scoping report was developed following a request from the Public Petitions Committee of the Scottish Parliament in response to public petition PE01463 on Thyroid and Adrenal Testing and Treatment. http://www.scottish.parliament.uk/GettingInvolved/Petitions/PE01463
The following questions were scoped:

1. In patients with symptoms suggestive of hypothyroidism, what is the evidence on the clinical and cost effectiveness of adding tests for serum total tri-iodothyronine (TT3), serum free T3 (FT3) and serum reverse T3 (rT3) to routine hypothyroid testing (TSH + T4)?

2. What is the evidence on the clinical and cost effectiveness of adding adrenal testing or the adrenal stress index test to routine hypothyroid testing (TSH + T4)?

3. In patients diagnosed with hypothyroidism what is the evidence on the clinical and cost effectiveness of combined L-T4 + liothyronine (L-T3) therapy?

4. In patients diagnosed with hypothyroidism what is the clinical and cost effectiveness of treatment with natural desiccated thyroid extract?

5. What is the evidence on the clinical and cost effectiveness of treatment of subclinical hypothyroidism?

6. What is the evidence on the clinical and cost effectiveness of a trial of L-T4 in patients with symptoms suggestive of hypothyroidism but where thyroid function tests do not indicate hypothyroidism?

Literature search
A systematic search of the secondary literature was carried out between 5-11 September 2013 to identify systematic reviews, meta-analyses, health technology assessments and other evidence based reports.

Key websites were searched for guidelines, policy documents, clinical summaries, and economic studies.

Concepts used in all searches included: thyroid function tests, tri-iodothyronine, reverse tri-iodothyronine, adrenocorticotropic hormone, thyroxine, and thyroid. A full list of resources searched and terms used are available on request.

For questions 2, 4 and 6 no secondary evidence was identified. A systematic search of the primary literature was therefore conducted between 7-15 October 2013 on adrenal stress index/adrenal stress profile, natural desiccated thyroid extract and any treatment with thyroid hormones in a population with thyroid tests within the reference range.

Evidence base

<table>
<thead>
<tr>
<th>Publication type</th>
<th>Number of publications</th>
<th>References</th>
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<tr>
<td>Meta-analysis</td>
<td>2</td>
<td>5, 7</td>
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<tr>
<td>Evidence-based guideline</td>
<td>4</td>
<td>2, 4, 8, 9</td>
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<tr>
<td>Randomised controlled trial (RCT)</td>
<td>2</td>
<td>10, 11</td>
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</table>

Findings

1. Tests for TT3, FT3 and rT3
No systematic reviews were identified which assessed the clinical or cost effectiveness of adding tests for TT3, FT3 or rT3 to routine thyroid testing strategies in the context of hypothyroidism.

UK guidelines for the use of thyroid function tests published in 2006 were based on a non-systematic review of generally poor quality evidence from the United States (US) National Academy of Clinical Biochemistry (now archived). The review reported that serum T3 measurement has little specificity or sensitivity for diagnosing primary hypothyroidism, since enhanced T4 to T3 conversion maintains T3 concentrations until hypothyroidism becomes severe. A subsequent paper on thyroid function testing strategies based on the same literature recommended only one indication for adjunct T3 testing in the context of primary hypothyroidism. This was for the monitoring of T3 in patients on T4 replacement therapy where, for clinical reasons, it has been decided to keep TSH at <0.1mU/L.

The American Association of Clinical Endocrinologists (AACE) 2012 Guidelines for Hypothyroidism in Adults recommend that serum total T3 or assessment of serum FT3 should not be done to diagnose hypothyroidism.

Alterations in levels of rT3 are associated with acute non-thyroidal illness typically in hospitalised patients. No systematic review evidence was identified on the role of testing for rT3 in the context of hypothyroid symptoms.
2. Adrenal function tests

Chronic primary adrenal insufficiency is a rare disease with an estimated prevalence of 93-140 per million, based on studies conducted in European populations. It is suggested in editorial reviews that less than 1% of patients with autoimmune thyroid disease will develop adrenal insufficiency but the source of these data is unclear. In a cross-sectional study of 495 individuals with diagnosed hypothyroidism (Hashimoto’s thyroiditis) in specialist thyroid clinics in the UK there were seven cases of co-existing adrenal insufficiency (Addison’s disease), a prevalence of 1.41%. The low prevalence of adrenal insufficiency contraindicates routine testing.

No systematic reviews were identified assessing the clinical or cost effectiveness of routine adrenal function testing in the context of primary hypothyroidism.

The 2006 UK guideline on the use of thyroid function tests in the context of diagnosis of secondary hypothyroidism notes that referral to an endocrinologist for additional pituitary function tests (prolactin (PRL), follicle stimulating hormone (FSH), luteinising hormone (LH), adrenocorticotropic hormone (ACTH)/cortisol) may be required to make a diagnosis. It also states that tests of adrenal function are mandatory in patients with a high index of suspicion of hypopituitarism. The guideline development group recommended as good practice that secondary hypothyroidism can be distinguished from non-thyroidal illness on the basis of clinical history, measurement of FT3 and tests of other anterior pituitary hormones.

No studies were identified on the diagnostic validity or clinical utility of the adrenal stress index test/adrenal stress profile based on salivary cortisol measurements throughout the day and salivary dehydroepiandrosterone (DHEA).

3. Combined L-T4+L-T3 therapy

A well-conducted meta-analysis of RCTs (n=1,216) compared L-T3+L-T4 combination therapy with L-T4 monotherapy in patients with overt hypothyroidism. Five parallel trials and six crossover trials were included. Primary outcomes were quality of life, bodily pain, fatigue, anxiety, depression and insomnia. Treatment periods ranged from 5 weeks to 9 months. Continuous outcome data from a range of symptom measurement questionnaires were combined. Findings are outlined in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Number of studies</th>
<th>Estimate of standardised mean difference (SMD)</th>
<th>95% confidence interval (CI)</th>
<th>$I^2$ (heterogeneity)</th>
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<tbody>
<tr>
<td>Quality of life</td>
<td>7</td>
<td>0.03</td>
<td>-0.09 to 0.15</td>
<td>0%</td>
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<tr>
<td>Bodily pain</td>
<td>4</td>
<td>0.00</td>
<td>-0.34 to 0.35</td>
<td>73.5%</td>
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<tr>
<td>Fatigue</td>
<td>6</td>
<td>-0.12</td>
<td>-0.33 to 0.09</td>
<td>39.8%</td>
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<tr>
<td>Anxiety</td>
<td>7</td>
<td>0.00</td>
<td>-0.12 to 0.11</td>
<td>45.2%</td>
</tr>
<tr>
<td>Depression</td>
<td>11</td>
<td>0.07</td>
<td>-0.20 to 0.34</td>
<td>76.3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Insufficient data</td>
<td></td>
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Table 2 Results of meta-analysis comparing L-T3+L-T4 combination therapy with L-T4 monotherapy in patients with overt hypothyroidism.
No statistically significant differences were reported in the effectiveness of combined therapy compared with L-T4 monotherapy with respect to symptom improvement (Table 2).

The relative risk of adverse events when combination therapy was compared with monotherapy across nine studies was 1.19 (95% CI 0.63 to 2.24).

Evidence-based guidelines from the European Thyroid Association identified 13 randomised studies and described the heterogeneity across the evidence base arising from variations in the cause of hypothyroidism in the participants, L-T3 dose, the wide range of outcome measures and the variable duration of the studies. Patient preferences were examined. Based on five crossover trials (n=228), 48% of participants preferred combined therapy compared with the remaining 52%, who either preferred monotherapy (27%) or had no preference (25%)4. The guideline concludes that there is insufficient evidence that combination therapy serves the hypothyroid patient better than monotherapy and, based on high quality evidence of its effectiveness and safety, recommends that monotherapy remains the standard treatment of hypothyroidism.

Based on preference data and preliminary studies on deiodinase polymorphisms which had inconsistent results, the guideline goes on to recommend, based on low quality evidence, that psychological wellbeing and preference for combination therapy may be influenced by polymorphisms (natural genetic variations) in thyroid hormone pathway genes, specifically in thyroid hormone transporters and deiodinases. The guideline further recommends, based on low quality evidence, that combination therapy might be considered 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. Due to the potential for increased levels of serum T3 associated with combination therapy to provoke cardiac arrhythmias in susceptible patients, combination therapy is not recommended in pregnant women and in patients with cardiac arrhythmias. It is suggested that combination therapy is discontinued if no improvement is experienced after 3 months.

AACE 2012 Guidelines for Hypothyroidism in Adults recommend that the evidence does not support using L-T3+L-T4 combinations to treat hypothyroidism9.

In the year 2012, 1,060 patients in Scotland had prescriptions for L-T3 dispensed in the community. Of these patients, 217 had either a recent or historical diagnosis of thyroid cancer by the Scottish Cancer Registry and therefore had a specific indication for the use of L-T3 rather than levothyroxine as thyroid hormone replacement. (S Hecht, Information Analyst, ISD Scotland. Personal Communication, 15 May, 2014).

4. Treatment with desiccated thyroid extract

There are several brands of desiccated thyroid extract (DTE) preparation available. None is licensed in the UK. Armour® Thyroid (desiccated porcine thyroid glands) contains standard amounts of L-T4 and L-T3 according to United States Pharmacopoeia (USP) standards and specifications. It can be prescribed on a National Health Service (NHS) prescription as a specials product18. No community prescriptions for DTE were dispensed in the year 2012-13 and unlicensed products are not recorded in the Hospital Medicines Utilisation Database (J Vize, Senior Information Analyst, ISD Scotland. Personal Communication, 22 October 2013).

One small (n=78) randomised, double blind, controlled crossover trial comparing once daily Armour® Thyroid with once daily L-T4 was identified11. Participants were diagnosed with primary hypothyroidism and stable on L-T4 for 6 months. Following randomisation there were two 16-week treatment periods, with no washout period. There was a 10% dropout rate with 70 patients completing the study.

There were no statistically significant differences between treatment periods for the primary outcome measures; symptoms, general wellbeing and cognitive function as measured by questionnaires and neuropsychological tests. There were differences between the treatments in a range of biochemical outcomes: in the L-T4 period T3 resin uptake, rT3, total T4 and free T4
were higher, whilst for the DTE period there were higher levels of total T3 and lower high-density lipoprotein (HDL) cholesterol level. No adverse effects were reported during the study. The authors highlighted the potential for longer term adverse effects associated with increased serum T3 and HDL lowering in patients with or at risk of coronary heart disease.

At the end of the study 49% of patients preferred DTE, 19% preferred L-T4 and 33% had no preference. This difference was statistically significant. This difference in preference was not mediated by over-treatment since, although both values were within the reference range, TSH was higher when patients were receiving DTE. The mean weight of patients following the DTE treatment period was 2.86 lbs lower than following the L-T4 treatment period but weight loss was not a factor identified as a significant predictor of preference on logistic regression analysis.

5. Treatment of subclinical hypothyroidism
A well-conducted systematic review identified 11 RCTs, published up to May 2006 where L-T4 was compared with placebo in patients with subclinical hypothyroidism, and one study where the comparison was with no treatment. Studies were small with typically fewer than 50 participants. Study duration ranged from 6-14 months. Study quality was assessed using the Jadad scale and all studies were designated as high quality.

Nine studies (n=335) reported TSH levels. These were significantly reduced in the L-T4 treatment group (weighted mean difference -4.31 mU/L; 95% CI -4.73 to -3.88). I² for the analysis was 75.7%, indicating a high level of heterogeneity.

Seven studies examined parameters of symptom improvement, neuropsychological function or quality of life. Opportunity for meta-analysis was limited by the wide range of outcome measures used across the studies. Meta-analysis of four studies (n=155), found no evidence of benefit for L-T4 on symptom score improvement, (SMD -0.3; 95% CI -0.62 to 0.02). None of the studies reported statistically significant differences between groups in quality of life. One study (n=66) reported a statistically significant improvement in cognitive function in the L-T4 treatment group, as measured by a composite of the results of seven scoring tests. The validity of the measure is not clear and the authors of the primary study do not highlight this finding.

Lipid profiles were examined as secondary outcomes in seven studies. Meta-analysis of six of the studies (n=248) found that there were no significant differences between treatment groups in total cholesterol levels expressed as change from baseline, (mean difference -5.28; 95% CI -12.50 to 1.94).

Secondary outcomes also included a wide range of cardiac function tests. Small but statistically significant treatment-related improvements were identified in isovolumic relaxation time, index of myocardial performance and ratio of the pre-ejection period to the left ventricular ejection time. Meta-analysis of 2 studies (n=79) found reduced left ventricular ejection time in the L-T4 treated group (-8.47 ms; 95% CI -15.83 to -1.12). The clinical significance of these treatment differences is unclear.

None of the included studies examined cardiovascular mortality or morbidity, and in most of the studies adverse effects were not adequately examined.

The review authors conclude that treatment of subclinical hypothyroidism should be based on clinical judgment and patient preference.

UK guidelines recommend that if the serum FT4 concentration is normal and the TSH is elevated but <10mU/L then thyroxine therapy is not recommended as a routine therapy. However, thyroxine may be indicated in non-pregnant patients with goitre and in patients who are seeking pregnancy.

A large, multicentre, randomised, placebo-controlled trial led from NHS Greater Glasgow and Clyde is underway to assess the impact of thyroxine replacement in 3,000 adults aged ≥65 years who have persisting subclinical hypothyroidism. The estimated study completion date is June 2016 (NCT01660126).

6. L-T4 therapy in patients with symptoms consistent with hypothyroidism where thyroid function tests do not indicate hypothyroidism

One small, randomised, placebo-controlled crossover trial was identified examining the effects of L-T4 (100µg) treatment in patients with symptoms consistent with hypothyroidism.
Technologies scoping report

... (which were present for longer than 6 months), but with thyroid function tests within the reference range\(^\text{10}\). Twenty-two patients completed two 12-week treatment periods and a 6-week wash out period. Outcomes included cognitive function tests and assessments of psychological functioning and physical wellbeing. Across the wide range of tests, the only statistically significant difference found between the L-T4 treatment period and placebo period was an improvement on the visual reproduction score which assesses memory for non-verbal visual stimuli. There was no improvement in a similar memory test for visual stimuli with delay which would have been expected to record similar capacity. There was no mention of adverse effects in the study report.

Summary

An American non-systematic literature review reported that serum T3 measurement has little specificity or sensitivity for diagnosing primary hypothyroidism, since enhanced T4 to T3 conversion maintains T3 concentrations until hypothyroidism becomes severe.

No systematic reviews were identified assessing the clinical or cost effectiveness of routine adrenal function testing in the context of primary hypothyroidism. UK guidelines state that tests of adrenal function are mandatory in patients with a high index of suspicion of hypopituitarism. No studies were identified on the diagnostic validity or clinical utility of the adrenal stress index test/adrenal stress profile.

A meta-analysis found no statistically significant differences between the clinical effectiveness of combined LT-4+L-T3 therapy and L-T4 monotherapy. In an analysis of patient preference based on five crossover trials, 48% of study participants preferred combined therapy, compared with 27% who preferred L-T4 monotherapy.

Only one small trial comparing effectiveness of DTE with L-T4 was identified. There was no evidence of a difference between study periods on symptoms, general wellbeing and cognitive function.

A meta-analysis of studies of L-T4 treatment in patients with subclinical hypothyroidism reported no benefit to symptom scores or quality of life. Some small improvements in cardiac function tests were identified although the clinical significance of these is unclear. There was significant heterogeneity across studies and the study authors concluded that treatment should be based on clinical judgment and patient preference.

One small trial of L-T4 treatment in patients with symptoms consistent with hypothyroidism but with thyroid function tests within the reference range was identified. Across a battery of tests, clinical benefit of treatment was identified only in a test which assesses memory for non-verbal visual stimuli.

Further work for Healthcare Improvement Scotland

No further work is anticipated for Healthcare Improvement Scotland.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation. As a scoping report summarises information and does not provide recommendations a full equality impact assessment is not deemed necessary.

The scoping report process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org
Acknowledgements

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Healthcare Improvement Scotland invited the following individuals and organisations to peer review the draft technologies scoping report:

Dr Kristien Boelaert, Consultant Endocrinologist, on behalf of the British Thyroid Association, Independent clinical expert

Dr Johannes W Dietrich, Consultant Endocrinologist, on behalf of Thyroid UK, Independent clinical expert

Professor Rudolf Hoërmann, Endocrinologist, on behalf of Thyroid UK, Independent clinical advisor

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Dr Colin Perry, Consultant Endocrinologist, NHS Greater Glasgow & Clyde, Independent clinical advisor

Professor Rebecca Reynolds, Professor of Metabolic Medicine, University of Edinburgh/British Heart Foundation Centre for Cardiovascular Science, Independent clinical advisor

Karen Smith, Consultant Clinical Scientist, NHS Greater Glasgow & Clyde, Independent clinical advisor

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Dr Anthony Toft CBE, Consultant Physician and Endocrinologist, NHS Lothian, Independent clinical advisor

And also Laura McIver, Chief Pharmaceutical Advisor, Healthcare Improvement Scotland

Declarations of interest were sought from the clinical advisor and all peer reviewers. All contributions from peer reviewers were considered by the group. However the peer reviewers had no role in authorship or editorial control and the views expressed are those of Healthcare Improvement Scotland.

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NICE has accredited the process used by Healthcare Improvement Scotland to produce its evidence review products. Accreditation is valid for 5 years from January 2013. More information on accreditation can be viewed at www.nice.org.uk/accreditation
References


18. UK Medicines Information. What is the rationale for using a combination of levothyroxine and liothyronine (such as Armour® Thyroid) to treat hypothyroidism? 2011 Nov [cited 2013 Oct 01]; Available from: http://www.medicinesresources.nhs.uk/upload/NHSE_Armour_Thyroid_56_5final%5b1%5d.doc.