Thyroid hormone replacement: applying the Goldilocks principle

ANH TRAN, STEVE HYER, GABRIELLA BATHGATE AND ONYEBUCHI OKOSIEME

The Goldilocks principle, *i.e.* not too much or too little, but just right, is important when prescribing thyroid hormone replacement, especially in the elderly or women of reproductive age. The authors present the results of their multi-practice audit evaluating the monitoring of patients on thyroid hormone replacement in primary care.

In Goldilocks and the Three Bears, Goldilocks discovers that she can only eat porridge that is not too hot nor too cold, but ‘just right’, i.e. just the right temperature. This principle of ‘just the right amount’ (the Goldilocks principle) has been applied widely to medicine. In this article, we discuss the concept in relation to thyroid hormone prescribing and present relevant findings from a recent large multi-practice audit in the primary care setting, where the majority of patients with primary hypothyroidism are managed.

TSH targets, monitoring and QOF

Current guidelines recommend that target thyroid-stimulating hormone (TSH) concentrations for non-pregnant patients with primary hypothyroidism on levothyroxine replacement should be within the population reference range. Until 2014, the Quality and Outcomes Framework (QOF) included indicators for practices to maintain a register of patients with treated hypothyroidism (Thy001) and to monitor their thyroid function on at least a 12-monthly basis (Thy002). However, annual monitoring by itself has not been shown to be sufficient to ensure optimal hormone replacement in hypothyroid patients. Previous work suggests that while QOF indicators or equivalent electronic alerts improve the proportion of patients monitored, this alone does not ensure adequacy of replacement.

Risks of suboptimal thyroid hormone replacement

The adverse consequences of thyroid hormone over- or under-replacement have been the subject of many studies and are well described. Thyroid hormone over-replacement is associated with reduced bone mineral density and increased fracture risk, particularly in the elderly. Several epidemiological studies have also shown an association between low or suppressed TSH and atrial fibrillation, with the exception of the Framingham study; however, the evidence is not based on patients receiving levothyroxine.
Conversely, under-replacement in pregnant women, or those trying to conceive, may result in adverse pregnancy outcomes including miscarriage, preterm labour, stillbirth, postpartum haemorrhage and impaired foetal neuro-cognitive development. Current guidelines recommend aiming for TSH <2.5mU/L at conception and in the first trimester in women with primary hypothyroidism, and levothyroxine doses frequently need to be increased at confirmation of pregnancy.

The risks of under-replacement in the elderly are less certain as it appears that a slightly raised TSH may be associated with lower mortality rates in the very elderly. Furthermore, a recent multi-centre European intervention trial failed to show an advantage for thyroid hormone replacement in older patients with asymptomatic subclinical hypothyroidism. However, prolonged under-replacement is associated with an adverse lipid profile and deterioration in myocardial function.

A large Scottish observational cohort study demonstrated an increased risk of cardiovascular disease both in patients under-replaced with levothyroxine (TSH >4mU/L) as well as in those with suppressed TSH (<0.03mU/L), ie overtreated, across all age-groups. For this reason, it is recommended that TSH levels on thyroid hormone replacement should be maintained within the population reference range.

How common is suboptimal thyroid hormone replacement?

Using TSH concentration outside the local reference range to indicate suboptimal thyroid hormone replacement, UK-based community surveys and general practice audits have reported low TSH values (over-replacement) in 5–27% and high TSH values (under-replacement) in 11–30% of patient records. An earlier 2011 study reported comparable results, with suboptimal levothyroxine replacement in a total of 37% of hypothyroid patients identified through primary care practice records (20% were over-replaced and 17% under-replaced). More recently, we audited four practices in Surrey, and found a similar proportion of overtreated patients (21%), although with lower rates of under-replacement (9%).

Audit findings

During August 2018, we carried out a multi-practice audit across nine general practices in England with a combined registered population of 118,777 patients as part of a quality improvement project. Detailed electronic searches of primary care records were performed using EMIS Population Reporting Manager. Search rules were shared as an .xml file and data reports were returned by practices as .rtf files. Anonymised results were collated and analysed. Patient-identifiable data were not collected. Local lower and upper limits of TSH reference range varied between 0.3–0.55mU/L, and 4.2–5.6mU/L respectively.

A total of 3871 patients (excluding patients on anti-thyroid treatment as part of ‘block and replace’ treatment for hypothyroidism) were identified as currently receiving levothyroxine (L-T4) treatment (prevalence 3.3% of the total registered population).

Table 1 summarises the audit findings. In the 3871 patients receiving levothyroxine, the TSH was checked in the last 12 months in 3019 (78%) of patients, and TSH was both in the local reference range and checked within 12 months in 2208 (57%) of patients. Twenty patients had no TSH level on record.

A total of 585 patients (15%) were identified as being over-replaced (latest TSH below the lower limit of the local reference range). In the group with low TSH, 43% were aged over 65 years and 35% of low TSH values in the elderly group were <0.1mU/L.

By contrast, 375 patients (10%) were identified as being under-replaced (last TSH greater than the upper limit of the local reference range). Of the 1088 patients identified as being women of reproductive age (aged 15–55 years and not coded as menopausal or having had a hysterectomy), 143 (13%) had latest TSH above the upper limit of the local reference range, representing 38% of all undertreated patients. Among elderly patients aged over 65 years (1809 patients), 165 (9%) had TSH above the upper limit of the reference range, representing 44% of all undertreated patients.

A total of 63 patients were coded as either pregnant (59 patients) or trying to conceive (four patients) in the last 12 months. In 20 (32%) of these patients, the latest recorded TSH was more than 3mU/L.

In addition to the 3871 patients receiving levothyroxine, 18 patients were identified as receiving treatment with liothyronine (L-T3). Of these, 13 had their TSH checked in last 12 months. The numbers were otherwise too small for any other meaningful analyses. L-T3 therapy monitoring is complex and will not be discussed in this article.

Figure 1. Patient age distribution (in years), pooled across all practices in the audit

The majority of these patients (3581; 93%) were coded with primary hypothyroidism or subclinical hypothyroidism. Figure 1 shows the age distribution for pooled data across all practices; 82% of patients were female and 18% male. Patients coded with secondary hypothyroidism or hypopituitarisms (19 patients) were excluded from the main analyses, and patients coded with thyroid cancer (24 patients) were excluded from low TSH analyses.

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Improving the management of hypothyroidism in primary care

The importance of maintaining a register of patients with primary hypothyroidism and annual monitoring of thyroid function has long been recognised in the GP Contract and previously led to the removal of thyroid-stimulating hormone (TSH) monitoring from the Quality and Outcomes Framework (QOF) in 2014. However, in real-world practice, a proportion of individuals on thyroid hormone replacement will inevitably remain suboptimally treated. This raises concern about the potential risk of most harm from suboptimal replacement.

In this audit, we find that 22% of patients are not undergoing regular monitoring. Even in studies where regular TSH monitoring is up to 88%, suboptimal TSH values are found in more than a third of patients.

Management of suboptimal thyroid hormone replacement generally involves establishing and addressing the cause, adjusting levothyroxine dose if appropriate, followed by more frequent monitoring of thyroid function until TSH is normalised. Factors that can lead to under-replacement include poor compliance, memory impairment, age, interfering food or medications (eg coffee, dietary fibre, iron supplements, sucralfate, calcium carbonate, antacids, raloxifene, proton-pump inhibitors, bile acid sequestrants), malabsorption and lack of a recall system for patients suboptimally treated. Suboptimal treatment itself, both over- and under-replacement, may lead to memory impairment, which can compound the problem.

Patient education and increased professional awareness of the importance of optimising thyroid hormone replacement, and measures to improve detection and recall in primary care of levothyroxine-treated patients requiring treatment optimisation are needed. The British Thyroid Foundation has developed a range of useful resources for patients, including a thyroid and pregnancy guidance leaflet and alert card. These may be provided to women of reproductive age when levothyroxine is initiated or reissued, to raise awareness of the importance of optimising thyroid function particularly before conception and throughout pregnancy. Patient-held levothyroxine cards, analogous to warfarin record books, may be useful as a monitoring record, particularly for those with memory impairment. Supervised weekly administration of levothyroxine can be useful in selected patients with poor compliance, particularly elderly individuals with cognitive impairment.

Electronic system alerts, similar to QOF alerts, may be beneficial to help highlight patients with suboptimal TSH and those who require thyroid function monitoring. Dedicated alerts to remind healthcare professionals to offer written thyroid and pregnancy guidance leaflet and alert card. These may be provided to women of reproductive age when levothyroxine is initiated or reissued, to raise awareness of the importance of optimising thyroid function particularly before conception and throughout pregnancy. Patient-held levothyroxine cards, analogous to warfarin record books, may be useful as a monitoring record, particularly for those with memory impairment. Supervised weekly administration of levothyroxine can be useful in selected patients with poor compliance, particularly elderly individuals with cognitive impairment.

Table 1. Thyroid-stimulating hormone (TSH) monitoring of patients coded with hypothyroidism or subclinical hypothyroidism and taking levothyroxine, or currently taking levothyroxine for uncertain reasons (n=3871)

<table>
<thead>
<tr>
<th>Category</th>
<th>Pooled data (all practices)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Coded with primary/ subclinical hypothyroidism</td>
<td>3581</td>
<td>93</td>
</tr>
<tr>
<td>TSH check within last 12 months</td>
<td>3019</td>
<td>78</td>
</tr>
<tr>
<td>Last TSH within local reference range</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 12 months</td>
<td>2208</td>
<td>57</td>
</tr>
<tr>
<td>Within 15 months</td>
<td>2394</td>
<td>62</td>
</tr>
<tr>
<td>Last TSH &gt;0.1mU/L and ≤ULN within 15 months</td>
<td>2748</td>
<td>71</td>
</tr>
<tr>
<td>Last TSH out of local range</td>
<td>960</td>
<td>25</td>
</tr>
<tr>
<td>Undetreated*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last TSH &gt;ULN</td>
<td>375</td>
<td>10</td>
</tr>
<tr>
<td>Undertreated and women of reproductive age**</td>
<td>143</td>
<td>38% of all TSH &gt;ULN</td>
</tr>
<tr>
<td>Undertreated and aged &gt;65 years</td>
<td>165</td>
<td>44% of all TSH &gt;ULN</td>
</tr>
<tr>
<td>Last TSH ≥10mU/L</td>
<td>102</td>
<td>3</td>
</tr>
<tr>
<td>Overtreated*,†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last TSH &lt;LLN</td>
<td>585</td>
<td>15</td>
</tr>
<tr>
<td>Last TSH &lt;LLN, aged ≥65yrs</td>
<td>254</td>
<td>43% of all TSH &lt;LLN</td>
</tr>
<tr>
<td>Last TSH &lt;0.1mU/L</td>
<td>232</td>
<td>6</td>
</tr>
<tr>
<td>Last TSH &lt;0.1mU/L and aged ≥65 years</td>
<td>81</td>
<td>35% of all TSH &lt;0.1mU/L</td>
</tr>
<tr>
<td>Last TSH &lt;0.05mU/L</td>
<td>150</td>
<td>4</td>
</tr>
</tbody>
</table>

ULN = upper limit of normal, based on local reference range; LLN = lower limit of normal, based on local reference range; *Excludes diagnoses within past 6 months; **Females aged 15–55 years, not coded with menopause or hysterectomy; †Excludes thyroid cancer

Of particular concern are patients aged over 65 years who are at risk from over-replacement, and women of reproductive age, either currently pregnant or trying to conceive, who are at risk from under-replacement in pregnancy.

In the fairy tale, Goldilocks found her perfect porridge, but in real-world practice, a proportion of individuals on thyroid hormone replacement will inevitably remain suboptimally treated. However, case-finding to identify and prioritise therapeutic adjustment in patient groups who may suffer greater harm from suboptimal replacement is valuable. Of particular concern are patients aged over 65 years who are at risk from over-replacement, and women of reproductive age, either currently pregnant or trying to conceive.
The importance of accurate coding

A limitation of this and other similar studies is the reliance on accurate coding (eg of hypothyroidism, hypopituitarism, thyroid cancer) to identify patients with TSH out of range. Our study identified 290 levothyroxine-treated patients without a code for either hypothyroidism or hypopituitarism (which includes secondary hypothyroidism, ie TSH deficiency). Without individual record review, it was not possible to ascertain the indications for thyroid hormone replacement in this group. However, these patients were included in the analysis as, irrespective of the indication for levothyroxine treatment, it would still be expected that TSH be monitored and maintained within the reference range unless they have hypopituitarism or are receiving suppressive doses of levothyroxine following thyroid cancer treatment. While inaccuracies in coding, for example secondary hypothyroidism miscoded as primary hypothyroidism, could result in an overestimate of those labelled as ‘overtreated’, this is probably unlikely to be a major factor given the very low prevalence of these conditions.

Summary

Evidence from this and similar studies has consistently shown that a significant proportion of patients treated for hypothyroidism are not undergoing regular monitoring and are not achieving target TSH levels on treatment. The evidence is based on data collected from a large sample of electronic patient records. Greater awareness among patients and prescribers of the importance of optimal thyroid hormone replacement, and implementation of practical solutions to address the challenges of inadequate treatment in primary care, are needed. The incidence of miscoding, eg secondary hypothyroidism miscoded as primary hypothyroidism, and what impact this may have on the relevant studies, is not known but could be the subject of future studies.

References


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Declaration of interests

None to declare.

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