Adequacy of thyroid hormone replacement in a general population

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Received 17 October 2010 and in revised form 24 October 2010

Summary

Background: Suboptimal thyroid hormone replacement may carry harmful health consequences.

Aims: Our objectives were to determine the prevalence and factors associated with inadequate replacement in patients receiving treatment with levothyroxine.

Design: Retrospective general practice audit.

Methods: We identified levothyroxine users through electronic searches of primary care records in all 11 practices within a county borough. The adequacy of thyroid hormone replacement was determined from the current serum, serum thyrotropin (TSH) as: (i) adequate replacement (normal TSH; 0.4–4.0 mU/l); (ii) over replacement (low TSH; <0.4 mU/l); and (iii) under replacement (high TSH; >4.0 mU/l).

Results: Out of a registered patient population of 58 567, we identified 1037 patients who were first included in the hypothyroidism disease register between January 2004 and December 2009 (mean age 62.4 ± 15.9 years; female 85.9%, male 14.1%). Inadequate replacement was seen in 385 patients (37.2%), comprising 205 patients (19.8%) with over replacement and 180 patients (17.4%) with under replacement. Step-wise logistic regression showed that the factors associated with under replacement were male gender [odds ratio (OR) 2.85, confidence interval (CI) 1.86–4.38; P < 0.001 and younger age (OR 0.88, CI 0.80–0.98; P=0.02 per 10 year increase in age) while longer duration of treatment was associated with over-treatment (OR 1.06, CI 1.01–1.10). A thyroid function test was performed in the preceding 12 months in 914 patients (88.1%) and appropriate dose adjustments had been made in 81.0% (312/385) of patients with abnormal results.

Conclusions: Despite frequent monitoring and dose adjustment activities, inadequate thyroid hormone replacement remained a problem in over a third of levothyroxine users in this population.

Introduction

Thyroid hormone replacement with synthetic levothyroxine is the treatment of choice for hypothyroidism.¹ Levothyroxine is effective, inexpensive and associated with few side effects. The therapeutic goal in hypothyroidism is to achieve patients’ well-being and restore serum thyrotropin (TSH) to levels within the reference range.¹ However, inadequate replacement is common in patients receiving levothyroxine. In a survey of thyroid disease

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prevalence in Colorado, USA, up to 40% of patients taking thyroid medications had TSH levels outside the normal reference range. \(^2\) Abnormal thyroid function tests were also detected in a third of patients who self-reported thyroid disease or use of thyroid medications in the National Health and Nutritional Examinations Survey (NHANES III). \(^3\) Furthermore, a study in older levothyroxine users showed that only 43% were biochemically euthyroid. \(^4\)

Suboptimal thyroid hormone replacement may carry harmful health consequences. Uncorrected hypothyroidism is associated with adverse effects on body weight, \(^5\) lipid profile \(^6\) and blood pressure \(^7\) while thyroid hormone excess has been shown to increase the risks of atrial fibrillation, \(^8,9\) osteoporosis \(^10,11\) and fractures. \(^9\) In a cohort of older adults including patients taking levothyroxine, Sawin et al. \(^8\) showed an increased risk of atrial fibrillation in individuals with a suppressed serum TSH (<0.1 mU/l) although this risk was not seen at low but detectable TSH concentrations (0.1–0.4 mU/l). A recent analysis of a large database of levothyroxine treated patients (n = 17,684) also showed an increased risk of arrhythmias, cardiovascular disease and fractures in patients with either a high TSH (≥4.0 mU/l) or a suppressed TSH (≤0.03 mU/l) but not in patients with low but detectable TSH concentrations (0.04–0.4 mU/l). \(^9\) These studies thus show detrimental outcomes in patients with thyroid hormone under- or over replacement although the adverse effects of over replacement were seen in patients with suppressed TSH concentrations as opposed to those with low but detectable TSH levels.

The reasons for inadequate thyroid hormone replacement are varied and include factors such as inappropriate dosage, poor patient compliance or concurrent use of medications which interfere with L-T4 absorption. \(^12\) In addition some patients remain incorrectly replaced even after identifiable factors have been addressed. \(^12\) Detailed clinical profiles of individuals who respond inadequately to thyroid hormone replacement are however limited since existing data has largely been sourced from population surveys with restricted patient specific information. \(^2,3\) In particular, there is sparse data on the relationship between the adequacy of thyroid hormone replacement and various clinical characteristics such as age, gender, body weight, levothyroxine dose, duration of treatment and the presence of co-morbid conditions. Insights into these factors will enable more efficient therapeutic and monitoring strategies in hypothyroidism.

Our objective in this study was thus to determine the prevalence of thyroid hormone under- or over replacement in a general practice population and to identify clinical and demographic factors associated with inadequate replacement in this setting.

**Methods**

**Patients**

We identified levothyroxine users through electronic searches of primary care records in the Merthyr Tydfil county borough, comprising 11 general practices with a registered patient population of 58,567. Detailed electronic clinical records have been available in all 11 practices since the year 2004. Of 2601 patients receiving levothyroxine (4.4% of the entire population), we selected all patients who were first registered as levothyroxine users from January 2004 to June 2009 and who had received levothyroxine for at least 6 months (n = 1064, median duration of levothyroxine use 72 months, range 6–276 months). We excluded patients receiving anti-thyroid medications in addition to levothyroxine as part of a ‘block and replace’ regimen for hyperthyroidism (n = 12), patients with hypothyroidism due to pituitary disease (n = 9), patients on amiodarone (n = 3), two patients with thyroid hormone resistance, and one patient on lithium, resulting in a final study population of 1037 patients. We obtained demographic and clinical data for each patient including age, gender, body weight, body mass index, duration of levothyroxine treatment and dose of levothyroxine. The presence of co-morbid conditions including hypertension, diabetes and coronary heart disease were recorded from chronic disease registers. Serial thyroid hormones (FT4 and TSH) and levothyroxine dose adjustments were also documented. Anonymity of all data was ensured in line with Caldicott principles and the study protocol was reviewed and approved by the audit office of the Cwm Taf Local Health Board.

**Thyroid hormone assays**

During the period studied, thyroid hormones were routinely analysed in the biochemistry laboratory at Prince Charles hospital, Merthyr Tydfil. FT4 and TSH were measured by an electrochemiluminescence assay and analysed on an automated immunoassay analyser, the modular analytics E170 analyser (Roche Diagnostics GmbH, Mannheim, Germany). Reference ranges were: FT4, 10.3–23 pmol/l and TSH, 0.4–4.0 mU/l. The intra- and inter-assay coefficients of variation (CV) for FT4 was 1.4 and 2.8%, respectively, while the intra- and inter-assay CV for TSH was 1.5 and 4.2%, respectively.
Definitions

The adequacy of thyroid hormone replacement was determined from the current serum TSH as follows: (i) adequate replacement (normal TSH; 0.4–4.0 mU/l); (ii) over replacement (low TSH; <0.4 mU/l); and (iii) under replacement (high TSH; >4.0 mU/l). Patients were further classified as: (i) euthyroid (normal TSH and FT4); (ii) overt hyperthyroidism (elevated FT4 and suppressed TSH); (iii) Sub-clinical hyperthyroidism (normal FT4 and suppressed TSH); (iv) overt hypothyroidism (decreased FT4 and elevated TSH); and (v) sub-clinical hypothyroidism normal FT4 and elevated TSH.

Statistical analysis

Values are presented as means (SD) except where otherwise stated. All statistical analysis was performed using SPSS for windows (version 16.0, SPSS Inc, Chicago, Illinois, USA). We compared variables in different patient categories using the chi-squared test for categorical data and the one-way analysis of variance (ANOVA) for continuous data. Non-parametric data was compared with the Mann–Whitney U-test. Step-wise logistic regression was used to determine the association of various clinical and demographic factors with thyroid hormone over- and undertreatment. The level of statistical significance at which the null hypothesis was rejected was chosen as 0.05.

Results

Clinical and biochemical characteristics of patients

The clinical characteristics of patients are shown in Table 1. The mean age of patients was 62.4 ± 15.9 years, age range 10–101 years. There was a preponderance of females (85.9%). The TSH level was within the reference range in 652 patients (62.9%). A TSH above the normal range was seen in 205 patients (19.8%) while 180 patients (17.4%) had a TSH below the normal range. Of the latter group with TSH below the reference range, 95 patients (52.8%) had a low but non-suppressed TSH concentration (0.1–0.4 mU/l) while 85 patients (47.2%) had a suppressed TSH concentration (<0.1 mU/l).

Patients were further classified according to both FT4 and TSH concentrations as shown in Table 2. Only 57.7% of patients were euthyroid while 42.3% of patients had some abnormality of thyroid status. Sub-clinical hypothyroidism was the most common abnormality, seen in 17.2% of patients. Overt and sub-clinical hyperthyroidism was present in 7.5 and 9.8% of patients, respectively. A small proportion of patients had elevated FT4 levels with normal or high TSH concentrations (4.9 and 0.9%, respectively), suggesting recent increase in levothyroxine ingestion prior to testing.

Factors affecting levothyroxine over- and under-treatment

The factors affecting levothyroxine over- or under-treatment are shown in Table 1. In univariate
analysis, younger age, male gender and higher body weight were associated with TSH above the reference range. Patients in both the low and high-TSH groups received higher doses of levothyroxine. A longer duration of treatment and an inverse association with diabetes mellitus was seen in the low-TSH group. Factors which attained a significance of $P < 0.1$ on the univariate analysis were fed into a step-wise logistic regression model and analysed for association with low or high TSH in comparison with the normal TSH group. The results of the multivariate analysis are shown in Table 3. The factors associated with high TSH after multivariate analyses were age, male gender and higher levothyroxine dose. Low TSH was associated with longer duration of treatment and higher levothyroxine dose. The presence of diabetes mellitus was inversely associated with low TSH (Table 3).

### Frequency of monitoring and levothyroxine dose adjustments

A thyroid function test had been performed in the preceding 12 months in 914 patients (88.1%). Out of 385 patients with thyroid dysfunction, levothyroxine dose adjustments had been made in 312 patients (81.0%). No differences were observed between the demographic characteristics of patients who underwent testing in the previous 12 months and those who did not or between patients who had dose adjustments and those who did not (data not shown). Thyroid function tests were available in 802 patients (77.3%) at the end of the first 12 months of treatment. The clinical characteristics of these patients in relation to their 12-month TSH are shown in Table 4. Inadequate replacement was seen in 44.4% of patients, 31.3% with high TSH and 13.3% with low TSH. In univariate analysis, male gender was associated with high TSH at 12 months while a higher levothyroxine dose was seen in patients with low TSH. In multivariate analysis, male gender was associated with high TSH (OR 1.08, CI 1.01–1.12; $P < 0.01$). Higher levothyroxine dose also remained significantly associated with low TSH (OR 1.23, CI 1.1–1.32; $P < 0.001$, per 25 mcg increase in levothyroxine dose).

### Comparison of thyroid status at 12 months and at current evaluation

A comparison of the adequacy of thyroid hormone replacement at the 12-month and at the most recent evaluation is presented in Figure 1. The median duration between both evaluations was 60 months (range 6–260 months). Overall, TSH status improved over time. The proportion of patients with high-TSH decreased from 31.3% at the 12-month evaluation to 18.8% at the current evaluation while patients with normal TSH increased from 55.6% to 65.1%. The majority of patients (72.9%) with normal TSH at 12-months maintained this status at the current evaluation. The improvement in TSH status was mostly due to normalization of TSH in 60.6% of patients (152/251) with high TSH at 12 months as well as in 42.9% of patients (45/105) with low TSH.

Among the 105 patients with low TSH levels at 12 months, 43 (41%) had a suppressed TSH (<0.1 mU/l) while 62 (59%) had a low but

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### Table 2 Distribution of patients according to current FT4 and TSH concentrations

<table>
<thead>
<tr>
<th>TSH</th>
<th>FT4 $&lt; 10.3$ pmol/l (%)</th>
<th>FT4 $10.3–23$ pmol/l (%)</th>
<th>FT4 $&gt; 23$ pmol/l (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;$ 0.4 mU/l</td>
<td>1 (0.1)</td>
<td>101 (9.8)</td>
<td>78 (7.5)</td>
<td>180 (17.4)</td>
</tr>
<tr>
<td>0.4–4.0 mU/l</td>
<td>3 (0.3)</td>
<td>598 (57.7)</td>
<td>51 (4.9)</td>
<td>652 (62.9)</td>
</tr>
<tr>
<td>$&gt;$ 4.0 mU/l</td>
<td>18 (1.7)</td>
<td>178 (17.2)</td>
<td>9 (0.9)</td>
<td>205 (19.8)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>22 (2.1)</td>
<td>873 (84.2)</td>
<td>138 (13.3)</td>
<td>1037 (100)</td>
</tr>
</tbody>
</table>

### Table 3 Factors associated with levothyroxine under- and over-treatment

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>CI</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High TSH (under-treatment)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age $^a$</td>
<td>0.88</td>
<td>0.80–0.98</td>
<td>0.02</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.85</td>
<td>1.86–4.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Levothyroxine dose $^b$</td>
<td>1.24</td>
<td>1.10–1.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Low TSH (over-treatment)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment $^c$</td>
<td>1.06</td>
<td>1.01–1.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Levothyroxine dose $^b$</td>
<td>1.73</td>
<td>1.49–2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.33</td>
<td>0.17–0.62</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$^a$Per 10 year increase in age.
$^b$Per 25 mcg increase in levothyroxine dose.
$^c$Per 12 month increase in duration of treatment.
non-suppressed TSH concentration (0.1–0.4 mU/l). Of the 43 patients with suppressed TSH, nine remained suppressed at the current evaluation, five had become low but non-suppressed, 20 had normalized and nine had become high. Of the 62 patients with low but non-suppressed TSH, 16 remained unchanged at the current evaluation, nine had become suppressed, 25 had normalized and 12 had become high.

### Discussion

The management of hypothyroidism is now mostly undertaken in primary care. Maintenance of a hypothyroidism disease register and periodic monitoring of treatment are requirements of the United Kingdom General Practice contract, effective since 2004.\(^{13}\) Studies pre-dating 2004 highlighted shortfalls in levothyroxine dose prescribing in various primary care settings.\(^{14,15}\) The impact of the existing contract on clinical outcomes is nonetheless uncertain since up to date evaluations of thyroid hormone replacement are lacking. Here, we have determined the adequacy of thyroid hormone replacement in a primary care setting and explored the factors associated with inadequate replacement in this population. We show that despite regular biochemical monitoring and dose adjustments in the majority of levothyroxine users, a significant proportion (37.2%) remain inadequately replaced.

In a previous study in a general practice in North Suffolk, UK, 78% of patients on thyroid hormone replacement had TSH levels checked within 12 months but appropriate dose adjustment was only made in 29% of those with abnormal results.\(^{14}\) In our study, thyroid function tests were performed within the previous 12 months in 88.1% of patients and dose adjustments undertaken in 81.0% of those with abnormal results. Thus, our findings suggest significant improvements in monitoring and dose adjustment activities. However, the benefits of these improvements on clinical outcomes appear modest. Studies in general practices in England in the 1990s showed abnormal TSH levels in approximately half of patients receiving levothyroxine.\(^{14,15}\)

In Tayside, Scotland, 38.4% of registered levothyroxine users treated between 1993 and 2001 had out of range TSH levels.\(^{9}\) Thus, compared to earlier data our findings suggest that clinical outcomes remain unchanged or at best marginally improved.

### Table 4

Clinical characteristics of patients according to TSH level after 12 months of treatment

<table>
<thead>
<tr>
<th>TSH level (mU/l)</th>
<th>Number of patients (%)</th>
<th>Mean ± SD</th>
<th>Minimum, maximum</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH &lt; 0.4 mU/l</td>
<td>105 (13.1)</td>
<td>62.59 ± 14.34</td>
<td>21, 93</td>
<td></td>
</tr>
<tr>
<td>TSH 0.4–4.0 mU/l</td>
<td>446 (55.6)</td>
<td>63.2 ± 15.52</td>
<td>10, 101</td>
<td>0.284</td>
</tr>
<tr>
<td>TSH &gt; 4.0 mU/l</td>
<td>251 (31.3)</td>
<td>66.1 ± 15.52</td>
<td>21, 92</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>802 (100)</td>
<td>66.2 ± 15.52</td>
<td>10, 101</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 1

Comparison of the adequacy of thyroid hormone replacement at the 12th month and at the current evaluation.
The main factors associated with inadequate thyroid hormone replacement in our study were younger age and male gender. In the Tayside study, Flynn et al. similarly observed under-treatment in male levothyroxine users but in contrast found higher TSH levels in older patients. An analysis of another Scottish database in Aberdeen also showed poorer outcomes in older levothyroxine users. The reason for under-treatment in our younger male patients is unclear. Inadequate monitoring and dose adjustments do not appear to have been a problem in our cohort. In fact, average levothyroxine dose in patients with high TSH was higher than in euthyroid patients suggesting that upward dose titrations had been undertaken in under-treated patients. As with other chronic disorders, compliance might have played a role but does not satisfactorily explain our results since younger individuals are traditionally shown to adhere better to treatment than older patients with multiple co-morbidities. While our data may reflect regional patterns in treatment adherence behaviour, our findings challenge the notion that younger patients require less intensive monitoring than the elderly.

An unexpected finding in our study was the inverse association between diabetes status and low TSH. The relationship between thyroid function and diabetes is complex and expressed through multiple cellular and metabolic pathways. The impact of diabetes on levothyroxine requirements in patients with hypothyroidism is however unclear. Somwaru et al. reported both over- and under-treatment in patients with diabetes but in keeping with our findings, Flynn et al. showed that diabetic patients were less likely to be over-treated. These observations do not necessarily imply a disturbance of levothyroxine pharmacokinetics in diabetic patients and alternatively may point to factors extrinsic to the patient. For instance, frequent clinical contact with primary and secondary care in diabetic patients could have provided additional opportunities to optimize treatment. The relationship between diabetes and levothyroxine requirements will nonetheless merit clarification in prospective studies.

Our study has limitations. Our data was dependent on electronic practice records which were generally robust but sometimes lacked additional useful information. For example, we were unable to analyse the aetiology of hypothyroidism as this information was occasionally missing. Thus, our cohort would have inadvertently included a small number of patients who were receiving levothyroxine following treatment of thyroid carcinoma. It is possible that the TSH levels in such patients were deliberately kept suppressed, in line with the prevailing wisdom at the time. The strength of our study is that it provides an up to date evaluation of thyroid hormone replacement under the current general practitioner contract. By systematically auditing all practices in an entire locality, we have eliminated potential bias from individual practices. Furthermore, we have taken into account the adequacy of replacement at different time points. Thus, unlike previous studies which have presented single snapshots of thyroid status we are able to show that thyroid hormone replacement improves with duration of treatment but entails the risk of overshooting into over replacement.

In Wales, >100,000 patients (i.e. 3.38% of the population) are on the hypothyroidism disease register. Our data suggests that a third of these individuals equivalent to 1% of the entire population will be inadequately replaced and will remain at risk of cardiovascular disease, arrhythmias, neurocognitive decline, osteoporosis and fractures. More effective management is therefore needed to curtail this disease burden in the population. In a hospital endocrinology clinic, it was shown that with appropriate management, adequate thyroid hormone replacement was achievable in 87.5% of patients. Thus clinicians should routinely address factors which contribute to sub-optimal response in individual patients such as compliance, drug interactions or malabsorption. In some patients, treatment response may be improved by switching the timing of levothyroxine administration from the usually recommended pre-breakfast to bedtime dosing. Finally, supervised weekly levothyroxine administration has been shown to be safe and effective and may be considered in the least compliant patients.

We conclude that despite regular biochemical monitoring thyroid hormone replacement remains sub-optimal in a significant proportion of the population we have studied. Clinicians should aim to restore serum thyrotropin to normal levels by routinely addressing factors which may affect levothyroxine availability.

Acknowledgements

We thank all participating Practices in the Merthyr Tydfil County Borough.

Conflict of interest: None declared.

References


