Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality

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Background: Subclinical hypothyroidism (SCH) has been associated with ischemic heart disease (IHD); however, it is unknown whether treatment of SCH with levothyroxine sodium will reduce the risk of IHD. The aim of this study was to investigate the association between levothyroxine treatment of SCH with IHD morbidity and mortality.

Methods: We used the United Kingdom General Practitioner Research Database to identify individuals with new SCH (serum thyrotropin levels of 5.01-10.0 mIU/L and normal free thyroxine levels) recorded during 2001 with outcomes analyzed until March 2009. All analyses were performed separately for younger (<40-70 years) and older (>70 years) individuals. Hazard ratios (HRs) for IHD events (fatal and nonfatal) were calculated after adjustment for conventional IHD risk factors, baseline serum thyrotropin levels, and initiation of levothyroxine treatment as a time-dependent covariate.

Results: Subclinical hypothyroidism was identified in 3093 younger and 1642 older individuals. For a median follow-up period of 7.6 years, 52.8% and 49.9% of younger and older patients with SCH were treated with levothyroxine, respectively. There were 68 incident IHD events in 1634 younger patients treated with levothyroxine (4.2%) vs 97 IHD events in 1459 untreated individuals (6.6%) (multivariate-adjusted HR, 0.61; 95% CI, 0.39-0.95). In contrast, in the older group there were 104 events in 819 treated patients (12.7%) vs 88 events in 823 untreated individuals (10.7%) (HR, 0.99; 95% CI, 0.59-1.33).

Conclusions: Treatment of SCH with levothyroxine was associated with fewer IHD events in younger individuals, but this was not evident in older people. An appropriately powered randomized controlled trial of levothyroxine in SCH examining vascular outcomes is now warranted.

roid state. Empirical observation of real-life outcome may provide information to guide future practice. We have examined the United Kingdom General Practitioner Research Database (GPRD), a large primary care database, which provided a unique opportunity to ascertain cardiovascular morbidity and mortality in patients with SCH stratified by subsequent levothyroxine treatment.

METHODS

GPRD DATABASE

We examined case records from the GPRD, which is the world’s largest primary care database, for which detailed characteristics have been described elsewhere. In brief, the GPRD is a database of anonymous longitudinal records containing medical information on a population of more than 10 million patients (approximately 16% of the UK population) who participate via contributing family physician practices. The GPRD population broadly reflects the demographics of the UK population. Information collected includes demographic characteristics, lifestyle factors, medical symptoms and diagnoses, laboratory test results, medication prescriptions with dose instructions, referrals to specialists, and hospital discharge reports. Quality control of data entry and consistency with medical records are checked regularly. The reliability of data concerning vascular events has previously been shown to be more than 90%.

STUDY DESIGN

We identified a group of patients with SCH within the GPRD cohort and analyzed outcomes according to subsequent treatment with levothyroxine. In calendar year 2001, serum thyrotropin was measured 322,291 times in patients from 314 GPRD-contributing practices. After exclusion of individuals treated with thyroid hormones (n = 2279) and antithyroid drugs (n = 165), individuals aged 40 years or older with first-ever increased serum thyrotropin levels of 5.01 to 10.00 mIU/L and normal serum free thyroxine (FT4) levels (0.7-1.9 ng/dL) were identified (n = 8351). We excluded individuals with a history of ischemic heart disease (n = 583) or cerebrovascular disease (n = 214) and those individuals who were registered with practices that did not fulfill at least 12 months of predefined data quality criteria leading up to their index elevated thyrotropin level (n = 1647). Poor-quality records as judged by lack of continuous follow-up or with incomplete or inaccurate data recording were excluded. In addition, individuals treated at any time before their index elevated serum thyrotropin level, smoking status, history of diabetes mellitus (present or absent), body mass index (BMI), blood pressure, total cholesterol level, socioeconomic deprivation score, total cholesterol level, index serum thyrotropin level, smoking status, history of diabetes mellitus, systolic and diastolic blood pressure, and use of levothyroxine therapy as a time-dependent covariate were included. Outcome hazard ratios (HRs) were calculated using Cox proportional analysis in the levothyroxine–treated groups. The result of the test for interaction between younger and older age groups and levothyroxine treatment status to confirm whether there was a significant difference in the primary outcome of fatal and nonfatal IHD events between the 2 age groups. The reliability of data concerning vascular events has previously been shown to be more than 90%.

OUTCOMES

A priori, the planned primary outcome was a composite of incident fatal and nonfatal first-recorded diagnosis of IHD identified by the relevant ICD-10 codes (120-125) or Read/Oxford Medical Information System (Read/OXMIS) codes (eAppendix 2) and all-cause and cause-specific mortality during the study period. New-onset atrial fibrillation was identified from the relevant Read/OXMIS codes (eAppendix 3). Levothyroxine use was identified through individual GPRD prescribing records.

STATISTICAL ANALYSIS

At the outset, the analyses were performed separately for individuals aged 40 to 70 years (younger group) and those older than 70 years (older group) at baseline based on cohort data showing that the upper limit of the serum thyrotropin reference range exceeds 5.00 mIU/L after the age of 70 years. To validate this a priori categorization, we performed a test for interaction using Cox proportional hazards between younger and older age groups and levothyroxine treatment status to confirm whether there was a significant difference in the primary outcome of fatal and nonfatal IHD events between the 2 age groups. The result of the test for interaction was positive (P = .004). Therefore, all analyses were performed separately for younger and older SCH individuals. Similarly, we also tested for the interaction between levothyroxine treatment and the primary outcome in men and women and found no significant difference (P for interaction = .66); hence, both sexes were analyzed together. Outcome hazard ratios (HRs) were calculated using Cox proportional analysis in the levothyroxine–treated vs the untreated groups, with the primary analysis adjusting for the following baseline cardiovascular risk factors: age, sex, BMI, socioeconomic deprivation score, total cholesterol level, index serum thyrotropin level, smoking status, history of diabetes mellitus, systolic and diastolic blood pressure, and use of levothyroxine therapy as a time-dependent covariate so that participants switched stratum when levothyroxine therapy was initiated. The assumption of proportional hazards was tested and met by plotting scaled Schoenfeld residuals against time for each covariate. A secondary analysis of HR was also performed adjusting for baseline age and sex alone because mild hypothyroidism may adversely influence some cardiovascular risk factors. For individuals in whom baseline cardiovascular risk factors were not available within 180 days of their index elevated serum thyrotropin level (21% of the total cohort), the last available reading was carried forward. Further analysis was performed to calculate HRs for the primary outcome using length of exposure to levothyroxine (in months) as a continuous variable (untreated individuals would have a value of zero) to detect any temporal effects of treatment of SCH. Data in relation to baseline characteristics and variables were compared using the t test or χ2 test for continuous and categorical data, respectively. Variables that were not normally dis-
Table 1. Baseline Characteristics of Individuals With Subclinical Hypothyroidism in 2001 Stratified by Younger (40-70 Years) and Older (>70 Years) Age Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Not Treated (n = 1459)</th>
<th>Treated (n = 1634)</th>
<th>P Value</th>
<th>Not Treated (n = 823)</th>
<th>Treated (n = 819)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger (40-70 y)</td>
<td>55.9 (8.34)</td>
<td>55.9 (8.4)</td>
<td>.75</td>
<td>79.89 (6.45)</td>
<td>79.37 (6.22)</td>
<td>.12</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>1204 (82.5)</td>
<td>1429 (87.4)</td>
<td>&lt;.0001</td>
<td>622 (75.6)</td>
<td>693 (84.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI mean (SD)</td>
<td>27.83 (5.94)</td>
<td>28.12 (6.24)</td>
<td>.20</td>
<td>25.35 (4.63)</td>
<td>26.33 (5.11)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>136.45 (20.9)</td>
<td>135.23 (19.28)</td>
<td>.09</td>
<td>149.37 (23.5)</td>
<td>149.37 (22.0)</td>
<td>.99</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>80.97 (11.28)</td>
<td>80.91 (10.91)</td>
<td>.88</td>
<td>81.1 (11.64)</td>
<td>81.56 (11.03)</td>
<td>.39</td>
</tr>
<tr>
<td>Thyrotropin level, mIU/L</td>
<td>6.32 (1.25)</td>
<td>6.74 (1.36)</td>
<td>&lt;.0001</td>
<td>6.32 (1.22)</td>
<td>6.77 (1.38)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FTS level, mean (SD), ng/dL</td>
<td>1.04 (0.34)</td>
<td>1.00 (0.23)</td>
<td>.001</td>
<td>1.13 (0.34)</td>
<td>1.08 (0.27)</td>
<td>.003</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td>226 (52)</td>
<td>225 (47)</td>
<td>.14</td>
<td>229 (53)</td>
<td>230 (48)</td>
<td>.79</td>
</tr>
<tr>
<td>Diabetes mellitus, No. (%)</td>
<td>263 (18.0)</td>
<td>295 (18.1)</td>
<td>.98</td>
<td>221 (26.9)</td>
<td>218 (26.6)</td>
<td>.91</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>262 (18.3)</td>
<td>288 (17.9)</td>
<td></td>
<td>85 (10.9)</td>
<td>76 (10.1)</td>
<td>.70</td>
</tr>
<tr>
<td>Former</td>
<td>286 (20)</td>
<td>341 (21.2)</td>
<td>.70</td>
<td>181 (23.1)</td>
<td>157 (20.8)</td>
<td>.42</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>882 (61.7)</td>
<td>977 (60.8)</td>
<td>.24</td>
<td>516 (66.0)</td>
<td>521 (69.1)</td>
<td>.10</td>
</tr>
<tr>
<td>Index of deprivationa</td>
<td>22.88 (17.5)</td>
<td>22.14 (16.75)</td>
<td>.24</td>
<td>21.36 (15.86)</td>
<td>22.66 (16.58)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the height in meters squared); BP, blood pressure; FTS, free thyroxine.
SI conversion factors: To convert FTS to picomoles per liter, multiply by 12.871; to convert total cholesterol to millimoles per liter, multiply by 0.0259.
*aIndex of deprivation is provided to give information on practice postcode–based socioeconomic status using the Index of Multiple Deprivation. This score is calculated differently for each of the 4 countries of the United Kingdom. A high score indicates the most deprived, whereas a low score indicates the least deprived on a scale of 1 to 80.

RESULTS

BASELINE FEATURES AND TREATMENT

Baseline characteristics of the younger (n = 3093) and older (n = 1642) groups with SCH are given in Table 1. Overall, during the follow-up period, 52.8% and 49.9% of individuals were treated with levothyroxine in the younger and older groups, respectively. The median levothyroxine sodium dosage was 75 µg/d (range, 12.5-175 µg/d). In the individuals with SCH who were not treated during the follow-up, 58.2% were still in an SCH state, 38.4% had reverted to euthyroidism, 2.5% were in the subclinical hyperthyroid state (thyrotropin level <0.4 mIU/L and normal FT4 levels), and 1.3% had progressed to overt hypothyroidism (thyrotropin level >10 mIU/L and/or FT4 level <0.7 ng/dL). In the levothyroxine–treated group with SCH, 12.2% began treatment after progression to overt hypothyroidism, and 6.4% of individuals had discontinued treatment during the follow-up period (Figure 1).

OUTCOME OF SCH IN THOSE 40 TO 70 YEARS OF AGE

During the follow-up period (median, 7.6 years; range, 0–8 years), IHD events (both fatal and nonfatal) occurred in 165 individuals (3.3%) from the younger group. After adjustment for baseline cardiovascular risk factors, age, sex, baseline serum thyrotropin levels, and levothyroxine use as a time-dependent covariate, the number of incident IHD events was lower in the levothyroxine–treated group (adjusted HR, 0.61; 95% CI, 0.39-0.95) (Table 2 and Figure 2). Adjustment only for baseline age and sex did not change the result (Table 2). All-cause mortality was lower in the levothyroxine–treated younger group (multivariate-adjusted HR, 0.36; 95% CI, 0.19-0.66), mostly because of a reduction in circulatory and cancer-related deaths (Table 2). Incident cerebrovascular disease events were unchanged (Table 2). In the temporal analysis, for each month of exposure to levothyroxine the adjusted HR for IHD events was 0.989 (95% CI, 0.986-0.993). Incident atrial fibrillation was not related to levothyroxine exposure (multivariate-adjusted
Table 2. Outcomes in Relation to Treatment of Subclinical Hypothyroidism by Age Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age 40-70 y (n = 3083)</th>
<th>HR (95% CI)</th>
<th>Age and Sex Adjusted</th>
<th>Age 70 y (n = 1642)</th>
<th>HR (95% CI)</th>
<th>Age and Sex Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>Treated</td>
<td>Multivariate Adjusted</td>
<td>Untreated</td>
<td>Treated</td>
<td>Multivariate Adjusted</td>
<td>Untreated</td>
</tr>
<tr>
<td>Fatal and nonfatal IHD events</td>
<td>(n = 1459)</td>
<td>(n = 1634)</td>
<td>(n = 823)</td>
<td>(n = 819)</td>
<td>(n = 823)</td>
<td>(n = 819)</td>
</tr>
<tr>
<td>Fatality and nonfatality IHD events</td>
<td>97 (6.6)</td>
<td>68 (4.2)</td>
<td>0.61 (0.39-0.95)</td>
<td>0.64 (0.41-0.99)</td>
<td>88 (10.7)</td>
<td>104 (12.7)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>94 (6.4)</td>
<td>55 (3.4)</td>
<td>0.36 (0.19-0.66)</td>
<td>0.43 (0.30-0.78)</td>
<td>333 (40.5)</td>
<td>288 (35.2)</td>
</tr>
<tr>
<td>Death due to circulatory diseases (I00-199)</td>
<td>38 (2.4)</td>
<td>23 (1.4)</td>
<td>0.54 (0.37-0.92)</td>
<td>0.61 (0.37-0.91)</td>
<td>118 (16.3)</td>
<td>134 (17.1)</td>
</tr>
<tr>
<td>Death due to IHD events (I20-I25)</td>
<td>27 (1.7)</td>
<td>17 (1.0)</td>
<td>0.43 (0.19-2.05)</td>
<td>0.55 (0.38-1.19)</td>
<td>70 (6.3)</td>
<td>56 (5.5)</td>
</tr>
<tr>
<td>Death due to malignant neoplasms (C00-C97)</td>
<td>35 (2.2)</td>
<td>21 (1.2)</td>
<td>0.59 (0.21-0.92)</td>
<td>0.81 (0.36-1.95)</td>
<td>73 (6.5)</td>
<td>49 (4.6)</td>
</tr>
<tr>
<td>Fatal and nonfatal CVA</td>
<td>44 (3.0)</td>
<td>55 (3.4)</td>
<td>1.03 (0.51-2.13)</td>
<td>1.09 (0.75-1.89)</td>
<td>147 (17.9)</td>
<td>145 (17.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>36 (2.3)</td>
<td>35 (2.0)</td>
<td>0.76 (0.26-1.73)</td>
<td>0.87 (0.59-1.44)</td>
<td>87 (7.7)</td>
<td>86 (8.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CVA, cerebrovascular disease; HR, hazard ratio; IHD, ischemic heart disease.

A Adjusted for age, sex, body mass index, socioeconomic deprivation score, total cholesterol level, index serum thyroidopin level, smoking status, history of diabetes mellitus, systolic and diastolic blood pressure, and levothyroxine use as a time-dependent covariate so that patients switched stratum at the time of treatment initiation.

B Circulatory events include IHD, CVA, and peripheral vascular disease. International Statistical Classification of Diseases, 10th Revision (ICD-10) codes are presented in parentheses.

Figure 2. Multivariate-adjusted cumulative event plots for levothyroxine sodium–treated and untreated individuals with subclinical hypothyroidism for fatal and nonfatal ischemic heart disease. A, Younger patients (P = .02). B, Older patients (P = .56). Multivariate analysis shown is adjusted for age, sex, body mass index, socioeconomic deprivation score, total cholesterol level, index serum thyroidopin level, smoking status, systolic and diastolic blood pressure, history of diabetes mellitus, and levothyroxine use as a time-dependent covariate.

OUTCOME OF SCH IN THOSE OLDER THAN 70 YEARS

During the follow-up period (median, 5.2 years; range, 0-8 years), IHD events occurred in 192 individuals (11.7%) in the older SCH group. After adjustment for baseline cardiovascular risk factors, age, sex, baseline serum thyrotopin levels, and levothyroxine use as a time-dependent covariate, incident IHD events were not different in the levothyroxine–treated group (adjusted HR, 0.99; 95% CI, 0.59-1.33) (Table 2 and Figure 2). Adjustment for only baseline age and sex did not change the result (Table 2). All-cause mortality was similar in the levothyroxine–treated older group (multivariate-adjusted HR, 0.71; 95% CI, 0.56-1.08). Cause-specific mortality and incident cerebrovascular events were also comparable in the treated older group (Table 2). For each month of exposure to levothyroxine, the risk of IHD events was unchanged (HR, 1.001; 95% CI, 0.998-1.004) after multivariate adjustment. Incident atrial fibrillation was not associated with exposure to levothyroxine (HR adjusted for each month of exposure, 1.00; 95% CI, 0.999-1.001).

SENSITIVITY ANALYSES

Use of cardioprotective medication, contact with health professionals, and medication prescription during the follow-up period in the cohort are given in Table 3. The multivariate-adjusted HRs for incident fatal and nonfatal IHD events in the treated vs untreated SCH individuals by age, in decades, are given in Table 4. Further analysis of the primary outcome performed after censoring individuals' follow-up on the date when they received levothyroxine therapy showed that during a median follow-up of 4.3 and 3.8 years, respectively, treated vs untreated younger and older individuals had similar risks of incident IHD events (HR, 0.87; 95% CI, 0.59-1.23; and
HR, 1.12; 95% CI, 0.90–1.46; respectively). The HRs for IHD events were also analyzed after excluding individuals who had an IHD event within 6 months of starting levothyroxine therapy (n = 16), and HRs for IHD events remained similar in both age groups (data not shown). Also, we investigated the primary outcome by only including individuals who had persistent SCH during the full follow-up period in the untreated group and by further excluding individuals who commenced treatment with levothyroxine after progression to overt hypothyroidism. This approach demonstrated that the HR for IHD events (99 events in 2367 individuals) was 0.63 (95% CI, 0.42–0.94) in the 40 to 70-year-old group and 1.06 (95% CI, 0.91–1.74) in the older than 70–years age group (n = 106 events in 1079 people). Finally, to look for a biologically plausible gradation of the levothyroxine effect, we analyzed outcomes in relation to median baseline serum thyrotropin levels (6.6 mIU/L). This approach revealed that, in the 40 to 70–years group, compared with untreated individuals with SCH (referent HR of 1.0), treatment with levothyroxine reduced the risk of IHD events (HR, 0.62; 95% CI, 0.39–0.96; in those with thyrotropin levels <0.6 mIU/L; and HR, 0.48; 95% CI, 0.26–0.88; in those with thyrotropin levels ≥0.6 mIU/L; P = .007 for trend). In comparison, in the group older than 70 years, treated individuals with SCH who had a thyrotropin level less than 0.6 mIU/L at baseline had an HR of 1.02 (95% CI, 0.66–1.82), and those with a thyrotropin level of 6.6 mIU/L or higher had an HR of 1.19 (95% CI, 0.74–1.8) (P for trend = .08).

Currently, the optimum management of SCH with serum thyrotropin levels of 5 to 10 mIU/L is unclear. The evidence for improvement of symptoms after levothyroxine treatment is equivocal, and the evidence for improvement in vascular outcomes is nonexistent. This analysis of a large cohort of individuals from the UK GPRD has shown that treatment of SCH with levothyroxine in a real-life situation is associated with better outcomes in younger (<70 years) people with respect to incident fatal and nonfatal IHD events and mortality. On the other hand, treatment of older people with SCH was not associated with similar benefits.

A number of cross-sectional and longitudinal epidemiologic studies have assessed the relationship between SCH and IHD, with conflicting results. A recent meta-analysis with individual data showed that the risk of incident IHD was increased in patients with SCH, particularly in those with a thyrotropin level above 10.0 mIU/L. In addition, other meta-analyses have shown that the risk of developing IHD was higher only in younger individuals with SCH. Furthermore, SCH was associated with better survival in a study of 85-year-olds. However, most cohort studies and the meta-analyses obtained thereof did not account for subsequent treatment with thyroid hormones; therefore, their results may have missed an important confounder.
The mechanisms that underlie the results of our study, particularly the important differences in IHD outcomes between younger and older individuals, require explanation. Randomized trials of levothyroxine treatment of SCH have generally shown a beneficial effect on surrogate cardiovascular risk factors, for instance, reduction in low-density lipoprotein cholesterol levels. In addition, improvement in endothelial function, carotid intima media thickness, and left ventricular diastolic function has been shown with treatment in some intervention studies. However, in the absence of randomized controlled trial data concerning improved clinical outcomes, current guidelines have not advocated treatment of SCH unless the serum thyrotropin level is greater than 10 mIU/L. In support of this, data are emerging to indicate that the serum thyrotropin reference range may extend upward in healthy older individuals as far as 7.0 mIU/L. Hence, treating older individuals with a high serum thyrotropin level as judged by a reference interval derived from younger individuals may not be expected to improve outcome. It also remains possible that the benefits of treatment of SCH in older persons may be offset by an increased risk of levothyroxine-precipitating adverse cardiovascular events, such as atrial fibrillation, although we provide data, for the first time to our knowledge, that suggest no excess of atrial fibrillation in this group. One unpredicted finding was of lower precipitating adverse cardiovascular events, such as atrial fibrillation.

In conclusion, treatment with levothyroxine was associated with fewer IHD events and reduced all-cause mortality during an 8-year period of observation in 40 to 70-year-old individuals with SCH but not in those who were older. A prospective randomized controlled trial is required to confirm these findings.

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