Levothyroxine Treatment and Occurrence of Fracture of the Hip

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Background: Levothyroxine sodium is widely prescribed and has been implicated as a cause of reduction in bone mineral density and, therefore, suggested to be a major contributor to the risk of osteoporotic fractures.

Objective: To investigate whether levothyroxine use increases the risk of developing osteoporotic fractures.

Methods: We conducted a population-based, case-control analysis of the risk of a femur fracture in a large cohort of patients who had been prescribed levothyroxine. We used the United Kingdom General Practice (primary care) Research Database to identify 23,183 patients who had been prescribed long-term thyroid hormone therapy and to identify for each patient taking levothyroxine 4 controls matched for age, sex, primary care practice, and duration of registration on the database. The number of patients who had sustained a fracture of the proximal femur was ascertained for each group, together with drug therapies and medical diagnoses likely to affect fracture risk.

Results: Of the 23,183 patients prescribed thyroid hormone, a mean±SE of 1.61%±0.08% had sustained a fracture of the femur, compared with 1.44%±0.04% of 92,732 controls (P=.06). When analyzed according to sex, a significant difference in rate of fracture between patients taking levothyroxine and controls was found in males (P=.008). Compared with controls, patients taking levothyroxine had higher reported rates of medical diagnoses and therapies, potentially confounding the fracture risk. Independent predictors of the occurrence of fracture after adjustment for other factors were age (adjusted odds ratio [AOR], 1.11; 95% confidence interval [CI], 1.10-1.11; P<.001), medical diagnoses including rheumatoid arthritis (AOR in females, 1.69; 95% CI, 1.27-2.26; P<.001), excessive use of alcohol (AOR in females, 3.05; 95% CI, 1.94-4.76; P<.001), and prescription of drugs (eg, anticonvulsants; AOR in females, 2.49; 95% CI, 2.00-3.09; P<.001). Prescription of levothyroxine was an independent predictor of fracture occurrence in males (AOR, 1.69; 95% CI, 1.12-2.56; P=.01) but not females (AOR, 1.03; 95% CI, 0.92-1.16; P=.60).

Conclusions: The lack of association between fracture and levothyroxine prescription in the whole cohort is reassuring, although an independent association between levothyroxine prescription and fracture occurrence in male patients suggests that levothyroxine may contribute to fracture risk in this specific group.

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IT IS WELL ESTABLISHED that overt hyperthyroidism increases bone turnover and bone resorption, leading to decreased bone mineral density (BMD) and an increased risk of osteoporotic fractures. In a US population-based study of 95,16 women 65 years or older, a history of hyperthyroidism (present in 9.2% of the cohort) was shown to represent an independent risk factor for hip fracture (relative risk, 1.8; 95% confidence interval [CI], 1.2-2.6), even after adjusting for femoral neck BMD. In addition, in our United Kingdom population-based study of mortality in a cohort of 7,209 patients with a history of hyperthyroidism who had been treated with radioiodine, there was a significant excess of mortality due to fracture of the femur (standardized mortality ratio, 2.9; 95% CI, 2.0-3.9). Although the influence of overt hyperthyroidism on fracture risk appears clear, debate currently surrounds the question of whether more minor degrees of thyroid hormone excess, such as that often found in patients undergoing levothyroxine sodium therapy, are also associated with osteoporosis risk. Early studies reported significantly reduced bone mass in patients undergoing prolonged treatment with levothyroxine. As a result, much concern was generated about the potential risk of premature development of osteoporosis in patients receiving levothyroxine therapy. However, several well-
PATIENTS AND METHODS

SELECTION OF PATIENTS AND CONTROLS

Patients undergoing long-term thyroid hormone replacement (termed levothyroxine cases) and controls were identified from the GPRD. This database includes standardized sets of information collected from approximately 3.5 million patients in 300 primary care (general) practices in the United Kingdom (representative of the United Kingdom as a whole) and has been described in detail elsewhere.14-15 The baseline cohort was composed of all patients older than 15 years whose information was recorded on the GPRD. Those currently taking levothyroxine or triiodothyronine and who had been prescribed this therapy for at least 1 year were identified from computerized prescribing records, and details of dose and duration of therapy were retrieved. Four controls matched for age, sex, registration with the same primary care practice, and duration of registration with the database were selected for each patient who had been prescribed thyroid hormone. Potential cases and controls with any record in the database of hyperthyroidism or prescription of antithyroid medication were excluded, and no control had any history of prescription of levothyroxine or triiodothyronine.

IDENTIFICATION OF THE FEMUR FRACTURE AND CONFounding DIAGNOSES AND DRUG THERAPIES

The end point investigated was fracture of the proximal femur. Data on fracture occurrence and date of fracture were retrieved by searching computerized records using Oxford Medical Information System codes for fracture of the femur or hip. To investigate potential confounding factors, information was also retrieved for the levothyroxine group and controls regarding prescription of drugs known to affect bone metabolism and hence fracture risk (gonadal steroids, thiazide diuretics, glucocorticoids, calcitonin, tamoxifen citrate, calcium supplements, bisphosphonates, vitamin D or analogues, and anticonvulsants), as well as major medical diagnoses likely to affect risk of fracture of the femur. These medical diagnoses were chronic renal and liver disease, diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, hyperparathyroidism, osteomalacia, chronic pancreatitis, celiac disease, epilepsy, excessive alcohol use, and major cancers associated with metastasis to bone (breast, prostate, kidney, thyroid, multiple myeloma, lung, and colon).

STATISTICAL ANALYSIS

Quantitative variables were compared between groups using t tests and Mann-Whitney U tests. For categorical variables, individual associations were studied using \( \chi^2 \) tests and calculation of odds ratios and relative risks. Logistic regression was used to identify the combinations of factors that best predicted the probability of fracture of the femur for the levothyroxine group and the controls.

RESULTS

A total of 23 183 patients older than 15 years who had been prescribed thyroid hormone replacement for at least 1 year were identified, together with 4 controls matched to each patient prescribed thyroid hormone therapy (n=92 732 controls). Of those prescribed thyroid hormone replacement, 98.5% were receiving levothyroxine and 1.5% were prescribed triiodothyronine (those taking triiodothyronine were included with those taking levothyroxine for subsequent analysis of results). The mean dose of levothyroxine prescribed was 107 \( \mu g/d \), with a mean recorded duration of 3.1 years (recorded duration range, 1-22 years). Levothyroxine cases and control subjects were well matched for age and sex (mean ±SE age, 65.0±15.3 years vs 65.0±15.3 years; 88.3% female in both groups). The age distribution of levothyroxine cases and controls was as follows: age 16 to 19 years, 0.26%; 20 to 29 years, 1.56%; 30 to 39 years, 4.72%; 40 to 49 years, 10.30%; 50 to 59 years, 16.88%; 60 to 69 years, 22.94%; 70 to 79 years, 25.11%; 80 to 89 years, 15.37%; and 90 years or older, 2.86%.

Of the 23 183 patients prescribed levothyroxine, 373 (1.61%±0.08%) had sustained a fracture of the femur, compared with 1340 of 92 732 controls (1.44%±0.04%) \((P=.06, \chi^2 \) analysis). Findings in terms of comparison of fracture occurrence were similar when the levothyroxine cases and controls 60 years or older (which comprised 66.28% of the total) were considered alone (levothyroxine cases, fracture in 2.30%±0.11%; controls, fracture in 2.08%±0.05%; \( P=.09 \)). When patients in the study were divided into groups according to sex, a significant difference in fracture occurrence between levothyroxine cases and controls was evident only for the group conducted studies have since failed to demonstrate any detrimental effect on bone mass in levothyroxine-treated patients, even in those with thyroid hormone excess indicated by suppression of serum thyrotropin concentrations.8,9 Two recent meta-analyses10,11 of published literature have addressed this controversy and have concluded that thyroid hormone treatment, both in specific groups with suppressed serum thyrotropin and those with normal serum thyrotropin levels, is associated with reduction in BMD. These studies of BMD did not, however, address the question of whether levothyroxine therapy was a risk factor for fracture incidence or mortality. A study12 of 1100 patients undergoing levothyroxine replacement in Scotland found no significant differences in fracture rates in patients taking levothyroxine when compared with the general population, whereas another small study13 found no significant differences in fracture rates in 160 postmenopausal women with thyroid disease compared with 140 controls without.

In view of the prevalence of levothyroxine prescription in the general population and hence the potential importance for public health of an increased risk of osteoporotic fracture in levothyroxine users, we used the United Kingdom General Practice Research Database (GPRD) to investigate whether a diagnosis of fracture of the femur in a large cohort of patients receiving levothyroxine was more common in those taking thyroid hormone therapy than a matched control group.
of males prescribed levothyroxine (females: levothyroxine cases, 1.67% ± 0.08%, vs controls, 1.55% ± 0.04%, P = .22; males: levothyroxine cases, 1.17% ± 0.20%, vs controls, 0.68% ± 0.08%, P = .008). The mean dose of levothyroxine prescribed to female patients was significantly lower than that prescribed to male patients (105.7 ± 0.4 µg/d vs 120.6 ± 1.2 µg/d, P < .001), but for each sex, the levothyroxine dose prescribed to those who had sustained a fracture was not significantly different (P = .32) than that prescribed to those who had no history of fracture (females: 100.1 ± 2.8 µg/d vs 105.7 ± 0.4 µg/d; males: 114.1 ± 9.0 vs 120.6 ± 1.2 µg/d).

MEDICAL DIAGNOSES AND DRUG THERAPIES AND FRACTURE OCCURRENCE

Both female and male patients who had been prescribed levothyroxine had significantly higher reported rates of several medical diagnoses likely to be associated with increased risk of fracture of the femur (Table 1). In addition, a higher rate of prescription of thiazide diuretics, glucocorticoids, and anticonvulsants was evident in the levothyroxine groups compared with controls, whereas gonadal steroids, calcium supplements, and vitamin D were also prescribed more frequently (Table 1). The relevance of these major diagnoses and drug therapies to fracture risk was confirmed when levothyroxine and control groups were investigated separately. Significant associations between fracture occurrence and inflammatory bowel disease and diabetes mellitus were evident among females in both the levothyroxine and control groups (Table 2). Furthermore, prescriptions of glucocorticoids and anticonvulsants were associated with increased fracture likelihood in both the levothyroxine and control groups, as were prescriptions of calcium supplements and vitamin D among females, whereas prescription of estrogen replacement therapy was associated with reduced likelihood of fracture in females (Table 2).

INDEPENDENT ASSOCIATIONS OF FACTORS WITH OCCURRENCE OF FRACTURE

After allowing for associations of other factors with fracture, age, diagnoses of diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis, and excessive alcohol use were independently associated with fracture risk in females (Table 3). Anticonvulsant prescription and prescription of calcium supplements were also associated with fracture in females, but prescription of levothyroxine was not significantly (P = .60) associated with fracture occurrence in females (Table 3). In males, age, excessive alcohol use, and prescription of anticonvulsants were similarly independently associated with likelihood of fracture, as was levothyroxine prescription (P = .01) (Table 3). There was, however, no significant relationship among males prescribed levothyroxine between the dose of levothyroxine given and the likelihood of fracture (P = .97).

COMMENT

The data presented in this analysis of a very large United Kingdom population indicate that fracture occurrence is not more common in those prescribed levothyroxine than in a carefully matched cohort. The data nonetheless reveal that fracture of the femur is significantly associated with levothyroxine therapy in males, after correction for other confounding risk factors. Our observations have considerable implications for current practice given the prevalence of levothyroxine therapy among the general population and concern about levothyroxine use and fracture risk. A prevalence study performed in the West Midlands region of the United Kingdom revealed that 0.8% of a population of all ages received levothyroxine; this figure rose to 4.8% in the group older than 60 years. Other prevalence studies in the United Kingdom, Sweden, and the United States have provided similar find-
In the United Kingdom, levothyroxine is prescribed almost exclusively for well-established indications of primary or secondary thyroid failure, although in other countries thyroid hormone is sometimes prescribed for other indications, such as obesity or hyperlipidemia.19

The bone density data described5,8-11 suggest that patients undergoing long-term levothyroxine therapy may be at increased risk of osteoporotic fractures, especially postmenopausal women and those with subclinical hyperthyroidism (defined biochemically by suppression of serum thyrotropin concentrations). There is, however, a paucity of information about fracture risk in such subjects. The studies of fracture risk in subjects taking levothyroxine published so far12,13 have produced conflicting results. One of the most extensive studies addressing the risk of fracture was that of Cummings et al.3 Potential risk factors for hip fracture were assessed in 9516 white women with fractured femur in whom the odds of a small case-control study of 116 postmenopausal women and those with subclinical hyperthyroidism were excluded to remove the influence of this confounding factor observed in the study by Cummings et al and to allow investigation of any specific effect of levothyroxine therapy. The GPRD has been described in detail14 and used extensively for research and audit.15 A limitation of the present study was that information was not verified with patient primary care or hospital records because of the size of the cohorts retrieved. It is notable, however, that good agreement between GPRD prescribing data and national data from the Prescription Pricing Authority has been described, and, in addition, the sensitivity and positive predictive value of computerized information regarding major medical diagnoses have also been shown to exceed 90%,14,15 confirming earlier work by Jick and colleagues.21,22 It is likely, therefore, that patients prescribed levothyroxine and those sustaining fracture of the femur were correctly identified, but the duration of levothyroxine therapy is likely to be underreported since previous records may have been incompletely transferred to the database at the time of its introduction. This factor was taken into account by matching of patients and controls for duration of registration.

Table 2. Relative Risk (95% Confidence Interval) of Fracture of Femur Among Levothyroxine Cases and Controls Associated With Medical Diagnoses and Drug Therapies

<table>
<thead>
<tr>
<th>Diagnosis or Therapy</th>
<th>Females Thyroxine Cases</th>
<th>Females Controls</th>
<th>Males Thyroxine Cases</th>
<th>Males Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal disease</td>
<td>2.01 (0.88-4.56)</td>
<td>2.24 (1.26-4.00)</td>
<td>0.0 (4.57)</td>
<td>1.57 (0.22-11.39)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>1.74 (0.42-7.13)</td>
<td>1.93 (0.71-5.23)</td>
<td>0.0 (21.1)</td>
<td>0 (46.0)</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2.52 (1.33-4.79)*</td>
<td>1.74 (1.10-2.75)†</td>
<td>0 (7.27)</td>
<td>1.89 (0.26-13.8)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.63 (1.12-2.35)*</td>
<td>1.70 (1.34-2.16)†</td>
<td>1.05 (0.32-3.48)</td>
<td>1.45 (0.58-3.61)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.54 (0.86-2.77)</td>
<td>2.06 (1.50-2.84)‡</td>
<td>5.92 (1.35-25.9)‡</td>
<td>1.65 (0.23-12.0)</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>2.07 (0.65-6.57)</td>
<td>2.81 (0.88-8.95)</td>
<td>0 (0.28.9)</td>
<td>0 (0.511)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.82 (0.44-1.54)</td>
<td>1.60 (1.20-2.14)‡</td>
<td>0.67 (0.12-6.46)</td>
<td>2.92 (1.06-8.08)†</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>1.10 (0.79-1.53)</td>
<td>1.74 (1.49-2.04)‡</td>
<td>2.04 (0.71-5.89)</td>
<td>1.32 (0.53-3.29)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>2.33 (1.61-3.37)‡</td>
<td>1.97 (1.50-2.59)‡</td>
<td>3.27 (1.45-7.36)†</td>
<td>4.74 (2.03-11.1)†</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1.81 (1.12-2.92)‡</td>
<td>3.80 (3.00-4.81)‡</td>
<td>1.48 (0.35-6.27)</td>
<td>3.78 (1.51-74.6)‡</td>
</tr>
<tr>
<td>Gonadal steroids</td>
<td>0.23 (0.12-0.43)‡</td>
<td>0.19 (0.12-0.29)‡</td>
<td>3.84 (1.45-10.13)‡</td>
<td>0 (0.12)</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>2.42 (1.47-3.98)‡</td>
<td>4.12 (3.15-5.39)‡</td>
<td>0 (0-10.9)</td>
<td>0 (0-19.4)</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>3.46 (1.87-6.41)‡</td>
<td>3.77 (2.19-6.49)‡</td>
<td>3.74 (0.49-28.6)</td>
<td>0 (0-61.3)</td>
</tr>
</tbody>
</table>

* P < .01.
† P < .05.
‡ P < .001.

Table 3. Significance of Association of Variables With Fracture Occurrence After Adjusting for Other Associations

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Females Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
<th>Males Adjusted Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.11 (1.10-1.11)</td>
<td>&lt;.001</td>
<td>1.04 (1.02-1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>1.83 (1.25-2.69)</td>
<td>.002</td>
<td>3.98 (1.59-9.94)</td>
<td>.003</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.24 (1.01-1.52)</td>
<td>.04</td>
<td>2.38 (1.09-5.19)</td>
<td>.03</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.69 (1.27-2.76)</td>
<td>&lt;.001</td>
<td>1.69 (1.27-2.76)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol excess</td>
<td>3.05 (1.95-4.76)</td>
<td>&lt;.001</td>
<td>2.49 (1.90-3.18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>2.49 (2.03-3.09)</td>
<td>&lt;.001</td>
<td>2.49 (2.03-3.09)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1.63 (1.12-2.56)</td>
<td>.01</td>
<td>1.04 (1.02-1.05)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
on the GPRD. For this reason, we have not examined the relationship between fracture occurrence and date of commencement of levothyroxine therapy. In addition, data regarding serum thyrotropin concentrations were not available, so the current or previous prevalence of subclinical hyperthyroidism secondary to levothyroxine therapy in the present cohort can only be estimated from other cohorts investigated biochemically. Such studies have revealed that the prevalence of subclinical hyperthyroidism in those prescribed levothyroxine may be as high as 21%, although this figure is now likely to be lower because of concerns over BMD data during the past 10 years and a perceived trend toward prescription of lower doses.

In the present study, we found that the reported rate of fracture of the femur was not significantly greater among the cohort of 23,183 patients prescribed long-term levothyroxine therapy compared with a group of 92,732 control subjects. The same was true when comparison of the levothyroxine cases and controls was confined to those in the cohort 60 years or older in whom fracture is more likely to reflect osteoporosis and less likely to reflect major trauma. When findings in females and males were analyzed separately, however, it was evident that a significant difference in fracture occurrence between levothyroxine users and controls was evident in the male group. This sex difference may be explained by the higher levothyroxine dose prescribed to males than females (which may in turn reflect a higher mean weight of males), although the dose prescribed to those who had sustained a fracture was not different than those who had not sustained a fracture, arguing against a cause-and-effect relationship. The present findings in male patients are of interest, especially because few studies of levothyroxine therapy and BMD have included male patients. In fact, up to the time of a meta-analysis in 1996, BMD results in only 95 males in total had been published. The present data highlight the need for further investigation of the effects of levothyroxine therapy in males, since they may be at particular risk.

In addition to the lack of differences in likelihood of fracture between those prescribed levothyroxine and their controls, it was clear that although levothyroxine cases and controls were effectively matched for age, sex, primary care practice, and length of registration on the database, they were not matched in terms of potential confounding factors that affect fracture risk. Overrepresentation of diseases such as diabetes mellitus, rheumatoid arthritis, and chronic liver disease among those prescribed levothyroxine is likely to reflect association of autoimmune thyroid disease (the major cause of hypothyroidism in iodine-replete populations such as the United Kingdom) with other autoimmune disorders. In addition, chronic diseases such as liver and renal disorders often result in reduced circulating concentrations of levothyroxine and triiodothyronine and may, therefore, lead to prescription of levothyroxine. Anticonvulsants have a similar influence on tests of thyroid function, which may explain the significant difference in rate of prescription of this class of drug among levothyroxine users compared with controls. Increased rates of prescription of gonadal steroids, calcium supplements, and vitamin D may reflect concerns regarding osteoporosis risk among those taking levothyroxine or prescription of these agents in those who have already sustained a fracture. Increased frequencies of a second disease may also reflect the tendency for a second disease to be diagnosed more frequently in an individual already being followed up for another condition.

Examination of fracture occurrence associated with chronic disorders and drug therapies among either the levothyroxine group and controls confirmed the established influence of such factors as rheumatoid arthritis, diabetes mellitus, and chronic renal disease on risk of fracture in females; similar relationships were seen in males but were generally not significant because of group sizes. Similarly, a significant adverse influence of glucocorticoid and anticonvulsant therapy was seen in levothyroxine cases and controls of both sexes, an especially high prevalence of glucocorticoid therapy being observed in the male levothyroxine group. A protective effect of estrogen replacement therapy was also observed in females. An association between prescription of calcium supplements and vitamin D and increased fracture occurrence is likely to reflect prescription of these medications in those known to have osteoporosis or those who have already sustained a fracture. Multivariate analysis confirmed a marked independent influence of chronic diseases, such as rheumatoid arthritis, diabetes, and inflammatory bowel disease, on fracture risk and an adverse effect of various drugs (or the diseases for which they are prescribed, eg, epilepsy).

The finding of an independent influence of levothyroxine treatment on fracture risk in males comprising part of a large cohort of patients is of concern to those taking and prescribing levothyroxine, although the absence of independent effect in the large female majority of the cohort is reassuring. The present data in turn have important implications for public health in view of the prevalence of thyroid hormone therapy.

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