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LEVOTHYROXINE USE IN THE ELDERLY IS ASSOCIATED WITH AN INCREASED RISK OF FRACTURES

Turner MR, Camacho X, Fischer HD, Austin PC, Anderson GM, Rochon RA, Lipscombe LL. **Levothyroxine dose and risk of fractures in older adults: nested case-control study.** BMJ 2011;342:d2238.

SUMMARY

BACKGROUND

Clinical hyperthyroidism is thought to increase the risk of fractures, especially in the elderly and postmenopausal women (1). Prior studies have shown that excessive thyroxine therapy resulting in subclinical hyperthyroidism (thyrotropin [TSH] suppressed below the reference range, with a free thyroxine level within the normal range) is associated with a lower bone density and bone quality (2). Previous studies have not definitively determined an increased risk of fractures in subclinical hyperthyroidism, in part, because of the inclusion of lower-risk, younger subjects and relatively small sample sizes. This report is unique in the large number of levothyroxine users (>200,000) with outcomes that can be quantitated by the national health system, which recorded new fractures at every emergency room visit and hospital admission in this population.

METHODS AND RESULTS

This study is a population-based, retrospective cohort study with a nested case–control design using a large population health database for Ontario, Canada. During the 5-year period ending March 31, 2007, a cohort of 213,511 adults older than 70 years who received at least one prescription for levothyroxine were followed for fractures until March 31, 2008. Subjects with a prior or current history of hyperthyroidism, thyroid cancer, hemodialysis, or palliative care were excluded. Case subjects were cohort members admitted to the hospital for any fracture, matched to five age- and sex-matched members of the cohort without fracture (controls). Fractures were excluded if they were associated with seizure, trauma, bone malignancy, or multiple myeloma. Members of the control group could become a "case" if fracture subsequently occurred. During the evaluation period, 22,236 (10.4%) of the subjects experienced a fracture; 88% of the subjects with fracture were women. Current users of levothyroxine had a higher risk of fracture (adjusted odds ratio [OR], 1.88; 95% confidence interval, 1.71 to 2.05) than those who had used levothyroxine in the past (>180 days before the index date). Among current levothyroxine users, high doses (>93 µg per day; OR, 3.45) and medium doses (44 to 93 µg per day; OR, 2.62) were associated with a significantly increased risk of fracture as compared with low-dose (<44 µg per day) levothyroxine therapy. There was a dose-related increased risk for

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all fractures, including hip fractures: low dose (OR, 1), medium dose (OR, 2.54; P<0.001), and high dose (OR, 3.39; P<0.001). Interestingly, there were fewer risk factors for fracture, including previous fractures, stroke, arrhythmia, dementia, and use of certain drugs in the high-dose group

CONCLUSIONS

This population-based study found a significant association between current levothyroxine use and increased risk of fractures in older adults (>70 years). There was a strong association with dose and with hip fracture in both sexes. Interpretation of this data is limited because thyroid function of the cohort was not able to be ascertained, but a recent reduction in levothyroxine dose was associated with a slight risk of fracture, which the authors speculate may indicate prior thyrotoxicosis in this group of patients.

COMMENTARY

Hypothyroidism is common with aging, with one study showing that 21% of elderly woman have TSH values above the reference range (3). This correlated with the estimate that over 20% of older women in North America are taking levothyroxine therapy (4). This study suggests that levothyroxine treatment may increase the risk of fractures in older people. The risk rises incrementally with the dose of levothyroxine typically used, >44 µg per day. Additional studies of large populations of adults younger than 70 years of age is needed to determine whether thyroid hormone with or without iatrogenic thyrotoxicosis is associated with unhealthy bones. Further, this study raises the speculation that the TSH target for older adults needs to be modified and lowered (5), as National Health and Nutrition Examination Survey studies suggest that 70% of older patients with TSH >4.5 mIU/L were within their age-specific reference range. Perhaps overreplacement with levothyroxine to achieve a TSH in a hypothyroid elderly patient within the reference range—that is, 0.4 to 4.5 mIU/L—may result in a relative thyroid hormone excess and abnormal bone metabolism.

— Stephanie L. Lee, MD, PhD

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