



Drug Monitor

ONLINE EDITION

Looking for an *Antifracture* Dose of Levothyroxine

What's the best dose of levothyroxine for older patients with hypothyroidism? Doses commonly used in clinical practice, especially over 0.093 mg/day, may be too much for these patients. University of Toronto researchers, who followed 213,511 adults, aged between 70 and 105 years with at least 1 prescription for levothyroxine, say lower is better, having found a dose-related relationship between current levothyroxine use and risk of fracture. In fact, the increased risk remained even among patients who discontinued the drug within 6 months.

The primary outcome of the study was any fracture, excluding those due to seizure, trauma, cancer, or other disease. During the mean 3.8 years of follow-up, 22,236 (10.4%) people—mostly women (88%)—sustained at least 1 fracture. More than one-quarter died during follow-up.

Patients with fractures were more likely than controls to have a diagnosis of osteoporosis and to use bisphosphonates. Of the case patients, 20,514 were current users of levothyroxine.

Of those, 3,071 were low-dose users (mean daily dose, 0.046 mg); 10,907 were medium-dose users (mean daily dose, 0.076 mg); and 6,521 were high-dose users (mean daily dose, 0.122 mg).

Low-dose users were more likely to live in a long-term care facility, to have medical comorbidities affecting fracture risk, such as dementia or cardiac arrhythmia, and to have other risk factors for fracture, including treatment with selective serotonin reuptake inhibitors. Participants who were taking higher doses of levothyroxine were more likely to have diabetes and less likely to have osteoporosis.

Current and recent past use, within 180 days of index date, were both associated with a significantly increased risk of any fracture, but particularly hip fractures. Among current users, high cumulative doses of levothyroxine (> 0.093 mg/d) and medium cumulative doses (0.044-0.093 mg/d) were associated with a higher risk of fractures compared with low doses.

Because levothyroxine requirements decline with age, iatrogenic hyperthyroidism, which can reduce bone quality and bone mineral density, is more common in older people,

the researchers say. While the optimal levothyroxine dose for adults is 1.6 to 1.8 $\mu\text{g}/\text{kg}/\text{d}$, older people often require a much lower dose to achieve euthyroidism; most guidelines recommend a dose of 0.5 $\mu\text{g}/\text{kg}/\text{d}$. Despite this, however, studies show that levothyroxine dosage is often not adjusted as the patient ages, either because monitoring for thyroid dysfunction isn't carried out, or dose adjustments, identified by monitoring, aren't implemented.

Moreover, levothyroxine treatment may have deleterious effects on bone, even in people who are biochemically euthyroid, they note, citing recent research that shows the risk of vertebral fractures in older adults rises with serum thyroid-stimulating hormone use, even in the lower range of normal limits.

To minimize the risk of fracture, they conclude, research is needed to determine whether bone can be affected by "euthyroid" doses of levothyroxine, and whether treatment targets need to be adjusted in older people whose true "normal" thyroid-stimulating hormone levels may be higher than thought. ●

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