Levothyroxine and Bone

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Thyroid hormones play an important role in the development of the skeleton in children, and in maintaining bone mineral content in adults. Hyperthyroidism is associated with loss of bone mineral content, with increased risk of fractures. This has raised concerns that treatment (especially over treatment) with levothyroxine (LT4) might mimic these adverse effects on the skeleton. Clinical data on the effects of LT4 administration on bone are conflicting. In general, the use of LT4 to maintain euthyroid levels of thyroid hormones in patients with hypothyroidism, or even the use of thyrotropin-suppressive therapy following removal of thyroid tumours, does not appear to carry a substantial risk of osteoporosis or fractures. Nevertheless, a cautious approach to avoid over treatment is recommended, especially in patients with or at risk of developing osteoporosis.

1 Overview of the Effects of Thyroid Hormones on the Skeleton

Thyroid hormones (principally triiodothyronine, derived from naturally produced thyroxine or exogenously administered levothyroxine [LT4]) are essential for the normal development of the skeleton [1, 2]. Untreated congenital hypothyroidism, where there is a profound lack of thyroid function from birth, is associated with delayed development of the skeleton, impaired development of epiphyseal growth plates, short stature (dwarfism), reduced mineralisation of bones, scoliosis and congenital hip displacement, among other complications [1, 2]. Reduced bone turnover

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in adults with hypothyroidism may result in increased bone mineralisation and mass, but such changes are slow to develop and this phenomenon has not been well studied clinically [2]. Hypothyroidism is not strongly associated with fractures [3, 4] although one meta-analysis described such a relationship that was apparently independently of changes in bone mineral density (BMD).

Hyperthyroidism increases the rate of turnover of bone, with a net loss of bone mineralisation; accordingly, suboptimally managed hyperthyroidism can be a cause of osteoporosis and increased fracture risk [1, 2]. Restoration of euthyroid status reverses the loss of bone mineral content and also ameliorates the excess fracture risk in patients with hyperthyroidism [5]. Meta-analyses of cohort studies have revealed an excess risk of fractures in people with subclinical hyperthyroidism [3, 4, 6], and even in populations with high-normal free thyroxine (FT4) and low-normal thyrotropin (thyroid-stimulating hormone, TSH), according to current reference ranges [7].

The association of even mild severities of hyperthyroidism with bone loss and increased fracture risk raises a question over the possibility of an adverse effect on the skeleton of either over treatment with LT4, or during receipt of the TSH-suppressive doses of LT4 administered following the surgical removal of thyroid tumours. This chapter reviews clinical studies of bone health in people receiving treatment with LT4 in these settings.

2 Bone Health in Patients Receiving Treatment with Levothyroxine

2.1 Patients with Congenital Hypothyroidism

Early and continuous treatment with LT4 has been shown to promote normal growth [8, 9] and BMD or other indices of bone health [10–12] in children with congenital hypothyroidism, relative to their euthyroid peers (Fig. 1), and normal BMD in adults [13]. Maintenance of a healthy weight and calcium intake appears to be an important determinant of bone health in these children, as in other populations [11].

2.2 Adult Patients with Hypothyroidism

2.2.1 Subclinical Hypothyroidism

Administration of LT4 to women with subclinical hypothyroidism increased the rate of bone turnover although whether this effect of LT4 *per se*, or a reversal of a previous hypothyroid-induced reduction in bone turnover was unclear [14]. A meta-analysis of studies in populations with subclinical hypothyroidism found no clinically significant reduction in bone loss during LT4 treatment in pre-menopausal women (2.7% after 8.5 years of treatment), but there was more significant bone loss in post-menopausal women (9.0% after 9.9 years of treatment) [15]. In contrast, a randomised, controlled trial found no effect of 14 months of LT4

Fig. 1 Mean height and z-scores for bone mineral density and bone quality in adolescent/early adult subjects with congenital hypothyroidism treated early and continuously from birth with levothyroxine. ^aAd-SoS is “amplitude-dependent speed of sound” in bone, a measure of bone quality. Measurements were made in 12 males and 25 females (mean age 18 ± 1 year). (Drawn from data presented in Ref. [9])

vs. no treatment on BMD in 17 women with subclinical hypothyroidism [16]. Observational data over 3 years showed that the bone-preserving effect of hormone replacement therapy for post-menopausal women was blunted during administration of LT4 for subclinical hypothyroidism [17]. Finally, BMD in adolescent girls treated with LT4 for subclinical hypothyroidism for 2–5 years had similar BMD to a control group [18].

2.2.2 Overt Hypothyroidism

LT4 dosage >150 mg/day, vs. lower doses, was associated with increased risk of fractures in women aged ≥65 years with hypothyroidism and a prior history of osteoporosis (Fig. 2) [19]. There was no significant effect in women without prior osteoporosis in this study. Another cross-sectional, observational study in post-menopausal women found reduced BMD associated with a longer duration of LT4 treatment, with no significant relationship between LT4 dosage and BMD in these women [20]. Another observational study in post-menopausal women found no association between LT4 treatment and bone loss, irrespective of the degree of suppression of TSH [21].

Fig. 2 Risk of fractures associated with different daily doses of levothyroxine in a large database population stratified by osteoporosis status at baseline. ^aNo prior diagnosis of osteoporosis and no prescriptions for bisphosphonates; ^bprior diagnosis of osteoporosis regardless of treatment; ^cprior diagnosis of osteoporosis without prescription of bisphosphonate or raloxifene; ^dprior diagnosis of osteoporosis with prescription of bisphosphonate or raloxifene; ^efor age, comorbidities, co-medications, Charlson comorbidity score, health service usage. (Drawn from data presented in Ref. [19])

Fig. 3 Risk of a composite outcome of osteoporotic fractures or death, according to the prevailing level of thyrotropin (TSH), in a population-based database study of individuals receiving treatment with levothyroxine from the UK. ^aAdjusted for age, gender, history of hyperthyroidism, history of osteoporotic fracture, presence or absence of diabetes. (Drawn from data presented in Ref. [22])

Large database studies have also evaluated the effect of LT4 treatment on bone in general populations of patients with hypothyroidism. In one study, patients receiving LT4 therapy were at increased risk of fractures if they had either a high TSH level (>4 mIU/L) or a suppressed TSH level (≤ 0.03 mIU/L), compared with patients with TSH within the reference range (Fig. 3) [22]. Patients with TSH 0.4–4.0 mIU/L were not at increased risk of fractures in this study. Another large database study of 162,369 people with hypothyroidism, of whom 97% received LT4 during follow-up, found increased fracture risk among those with TSH >10 mIU/L, compared with those well controlled to within the euthyroid range (HR 1.15 (95%CI 1.01–1.31, $p = 0.03$) [23]. These studies demonstrated the importance of optimisation of LT4 treatment, rather than LT4 treatment *per se*, for maintaining bone health.

A case-control study from Denmark, where all 124,655 patients with a fracture served as cases and 373,962 randomly selected age- and gender-matched people without fractures served as controls, found no association between LT4 treatment and risk of fracture [24]. An analysis of 23,183 LT4 users from the UK General Practice Research Database (i.e. managed in the primary care setting) also found no significant association between LT4 use and fracture risk overall although there was an apparent increased risk in males [25]. Other observational data also did not identify a significant effect of LT4 treatment on bone health [26].

The recent SORTED 1 trial found no difference in effects on bone health measured using circulating levels of C-terminal telopeptide (CTx) levels in very elderly patients (≥ 80 years) with hypothyroidism randomised to control of TSH in the standard reference range (0.4–4.0 mIU/L), or to a higher target range (4.1–8.0 mIU/L) [27]; see chapter, “Levothyroxine in the Older Patient” for a fuller account of this trial. CTx correlates inversely with TSH, including during treatment with LT4, and may provide a useful marker for following effects of LT4 on bone metabolism [28].

2.3 *Effects of Thyrotropin-Suppressive Doses of Levothyroxine*

Long-term treatment with high doses of LT4 may be administered to suppress the activity of residual thyroid tumour cells after total thyroidectomy for well-differentiated thyroid carcinoma (see chapter, “Levothyroxine and Cancer”). This setting has been likened to a state of “subclinical hyperthyroidism” by some authors [29].

The application of TSH-suppressive doses of LT4 has raised concern over its effects on bone health, given the known association between hyperthyroidism, osteoporosis and increased risk of fractures, as described above. Indeed, many clinical studies have applied various measures of bone mineral density or other markers of skeletal function to post-surgical, athyroid patients receiving TSH-suppressive therapy. Conflicting results of the effects of TSH suppression were reported in pre-menopausal women (adverse effect [30–41], or no clear adverse effect [42–47]), or post-menopausal women (adverse effect [40, 48, 49] or no clear adverse effect [31, 45, 47, 50–53]). Clear adverse safety signals for osteoporosis during TSH suppression did not emerge from several studies in populations that included female populations of mixed pre-/post-menopausal status [54–60], men [31, 45, 61–63] or a mixture of either gender [37, 64–67] (one small study in a mixed population demonstrated increased bone loss with TSH suppression in patients with thyroid cancer [68]). Trabecular bone score may be a more sensitive measure than bone mineral density of the effects of treatment with LT4 on bone structure this parameter has been used in patients who have [31, 32], or have not [69], received thyroidectomy and TSH suppression for thyroid cancer, although changes in this measure did not correlate with changes in BMD in LT4-treated patients in another study [70]. An absence of marked effects on bone health was also observed in studies in which pre-menopausal women [71–74], post-menopausal women [71, 74, 75] or mixed populations [76, 77] received less intensive TSH-suppressive therapy for benign thyroid nodules, or for goitre.

Several studies evaluated fracture risk. One study found that the 10-year fracture risk (assessed using FRAX, an online risk assessment tool) in women (mean age 52 years) did not correlate significantly with LT4 dose, the duration of LT4 therapy or FT4 [42]. Others found no marked increase in the risk of fractures associated with TSH-suppressive therapy [65, 78, 79]. One study found associations between the intensity of TSH suppression and fracture risk: the incidence of vertebral fractures was 45% for patients with TSH <0.5 mIU/L, compared with 24% for TSH 0.5–1.0 mIU/L and 4% for TSH >1.0 mIU/L [80]. Similarly, the risk of osteoporosis was increased in patients receiving a cumulative LT4 dose over time of >395 mg, but not in patients receiving a lower dose, among 9398 patients with new-onset thyroid cancer followed for an average of 6.6 years [81].

Determinants of bone health in patients receiving TSH-suppressive therapy appear to be complex and multifactorial. A family history of osteoporosis and oestrogen deficiency have been identified as risk factors for adverse effects on bone in this population [57, 58, 82]. TSH-suppressive therapy itself was shown not to affect

levels of sex hormone-binding globulin [83]. More data on the relationship of TSH-suppressive therapy and bone health are required, relating to older subjects, and men, in particular, however [84].

3 Clinical Perspectives

Clinical data on the effects of LT4 administration on bone are conflicting. The many studies reviewed above differed importantly in design, their populations, their durations and the indices of bone health measured, especially with regard to important clinical outcomes, such as fractures. In general, the use of LT4 to maintain euthyroid levels of thyroid hormones in patients with hypothyroidism, or even the use of TSH-suppressive therapy following removal of thyroid tumours, does not appear to carry a substantial risk of osteoporosis or fractures. Nevertheless, the associations between LT4 administration and loss of bone mineralisation or increased fracture risk in some studies suggests the use of a cautious approach to avoid over treatment, especially in patients with or at risk of developing osteoporosis, such as postmenopausal women, or the elderly.

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