



LONG-TERM THYROXINE TREATMENT AND BONE MINERAL DENSITY

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Studies of the effect of thyroxine replacement therapy on bone mineral density have given conflicting results; the reductions in bone mass reported by some have prompted recommendations that prescribed doses of thyroxine should be reduced. We have examined the effect of long-term thyroxine treatment in a large homogeneous group of patients; all had undergone thyroidectomy for differentiated thyroid cancer but had no history of other thyroid disorders.

The 49 patients were matched with controls for age, sex, menopausal status, body mass index, smoking history, and calcium intake score; in all subjects bone mineral density at several femoral and vertebral sites was measured by dual-energy X-ray absorptiometry. Despite long-term thyroxine therapy (mean duration 7-9 [range 1-19] years) at doses (mean 191 [SD 50] $\mu\text{g}/\text{day}$) that resulted in higher serum thyroxine and lower serum thyrotropin concentrations than in the controls, the patients showed no evidence of lower bone mineral density than the controls at any site. Nor was bone mineral density correlated with dose, duration of therapy, or cumulative intake, or with tests of thyroid function. There was a decrease in bone density with age in both groups.

We suggest that thyroxine alone does not have a significant effect on bone mineral density and hence on risk of osteoporotic fractures.

Introduction

The relation between thyroid disease and osteoporosis was first recognised 100 years ago. Although effective antithyroid treatment means that the association of overt thyrotoxicosis and osteoporotic fractures is now rare, lately much attention has focused on the potential effect of mild to moderate hyperthyroidism on bone mineral density.

Increasing sophistication of tests of thyroid function, especially assays for serum thyrotropin that can distinguish low from normal values, has led to growing recognition that slight abnormalities of thyroid function are common. Many patients taking conventional doses of thyroxine (100-200 $\mu\text{g}/\text{day}$) have high concentrations of serum total and free thyroxine, and serum thyrotropin is frequently undetectable in such subjects; some argue that these findings indicate overtreatment and hyperthyroidism. Since thyroxine replacement therapy is needed by many people, especially those over 60 years old, any association between hyperthyroidism secondary to thyroxine therapy and a reduction in bone density could be an important clinical problem.

Several studies have used single or dual photon absorptiometry to define the influence of thyroxine treatment on bone mineral density. Most of these studies examined small numbers of patients, not grouped for age, sex, or menopausal status, and with varied histories of thyroid disease and doses of thyroxine administered. Two studies in the USA suggested that thyroxine therapy resulted in a reduction in bone mineral density. Despite the lack of evidence of an increased risk of osteoporotic fractures in patients taking thyroxine, these studies have had a strong influence on clinical practice, especially in the USA; the American Thyroid Association has recommended that prescribed doses of thyroxine should be reduced until serum concentrations of thyroxine and thyrotropin are returned to the normal range. Such a change in prescribing practice would increase the cost of biochemical monitoring and inconvenience to patients, and might lead to undertreatment of hypothyroidism.

In view of the conflicting results of previous studies on thyroxine treatment and bone density, we have examined the effect of long-term thyroxine treatment in a group of patients who had all undergone subtotal thyroidectomy for differentiated (papillary or follicular) thyroid cancer but had no history of thyrotoxicosis by comparing their femoral and vertebral bone densities with those of carefully matched controls.

Patients and Methods

49 patients (18 premenopausal women, 26 postmenopausal women, 5 men) took part in the study (table 1). No patient had evidence of recurrent or metastatic disease (all had persistently undetectable serum thyroglobulin; all radioisotope scans done were negative). Subjects with hypoparathyroidism were excluded. Each patient had received a constant dose of thyroxine since thyroidectomy; in most the dose was sufficient to suppress thyrotropin concentrations to below normal. The mean thyroxine dose was similar in women and men (premenopausal women 217 [range 10-300] μ /day; postmenopausal women 175 [100-200] μ /day; men 180 [100-200] μ /day), as was the duration of treatment (7.7 [1-19], 8.1 [1-19], and 7.9 [2-15] years, respectively). 17 patients had received iodine-131 ablation postoperatively.

Healthy controls were individually matched to patients for age, sex, menopausal status, and body mass index. Subjects with a history of thyroid disease were excluded and all controls had concentrations of serum free thyroxine, free triiodothyronine (T3), and thyrotropin within the normal ranges. The controls were selected by an alphabetical search of the register of a single general practice. 42% of those identified by age and sex satisfied our other inclusion criteria. 50% of eligible controls agreed to take part. The exclusion rate for thyroxine-treated thyroid cancer patients was similar (54%) and 68% of those approached agreed to take part. Exclusion criteria for both patients and controls included present or previous therapy with oestrogens, thiazide diuretics, calcium, vitamin D, or tamoxifen. No patient or control had a history of osteoporotic fracture, rheumatoid arthritis, diabetes mellitus, any other serious medical disorder, alcohol abuse, chronic amenorrhoea (>3 months in women aged less than 45 years), late menarche, early menopause, or oophorectomy. Patients and controls completed a questionnaire on dietary calcium intake, smoking history, and physical activity.

Venous blood samples were collected from patients and controls and serum was stored at -70°C until tests of thyroid function and measurements of calcium, inorganic phosphate, alkaline phosphatase, and parathyroid hormone were done. Serum free thyroxine and free T3 were measured by Amerlex M radioimmunoassay (Amersham International, UK; normal ranges 9-24 pmol/l and 2.0-9.0 pmol/l, respectively) and thyrotropin by immunoradiometric assay (IDS Gamma-BCT, Boldon, UK; detection limit 0.05 mU/l, reference range 0.4-4.5 Mu/l). Between-assay coefficients of variation for free thyroxine, free T3, and thyrotropin were less than 7% over a wide range of concentrations. Serum calcium, phosphate, and alkaline phosphatase were measured by routine laboratory methods and serum parathyroid hormone by immunoradiometric assay (N-tact Incstar, Wokingham, UK; between-assay coefficient of variation 8%).

The density of the femoral neck, Ward's triangle, and trochanter and of the lumbar spine (anterior-posterior and lateral) was measured by dual-energy X-ray absorptiometry with a dual-photon X-ray system (Lunar DPX-L, Lunar Corporation, Wisconsin, USA). The in-vivo precision was 1.6% for measurements of femoral neck, 3.2% for Ward's triangle, 2.2% for femoral trochanter, and 0.8% (anterior-posterior) and 3.6% (lateral) for lumbar spine. A Z score was calculated for each bone density measurement from the mean (SD) for the relevant control group ($Z \text{ score} = [\text{patient's value} - \text{group mean}] \div \text{group SD}$).

Results

There were no significant differences between patients and control in male and premenstrual female subgroups in smoking history, physical activity score, and dietary calcium intake, apart from the number of smoking years in the male subgroup (table 1). For the whole group, there were no differences between patients and controls apart from a small difference in physical activity score ($p < 0.05$).

In subgroup analysis there were no significant differences between patients and controls in inorganic phosphate, alkaline phosphatase, or parathyroid hormone (table II). For the whole group and for the male subgroup, serum calcium was significantly lower in patients than in controls, presumably as a result of previous thyroid surgery and radioiodine ablation, although there were no differences in serum parathyroid hormone or alkaline phosphatase (table II). For the whole group and for the male subgroup, serum calcium was significantly lower in patients than in controls, presumably as a result of previous thyroid surgery and radioiodine ablation, although there were no differences in serum parathyroid hormone or alkaline phosphatase (table II). Serum free thyroxine and free T3 concentrations were, however, higher in patients than in controls, and serum thyrotropin was lower, as a result of thyroxine treatment. There was greater variability in free thyroxine concentrations in patients than in controls, reflecting the differing doses of thyroxine. Serum thyrotropin was below the limit of assay detection ($< 0.05 \text{ Mu/l}$) in 13 premenopausal female patients, 20 postmenopausal women, and 2 men. Thyrotropin was below the normal range but detectable in 5 of the remaining 14 patients and within the normal range in 9.

There was no significant difference in bone mineral density between patients and control in any subgroup for any of the femoral and lumbar spine sites measured (table III). Analysis of data from the whole group of patients and controls again showed no difference in bone density. A plot of patient-control differences in bone mineral density showed scatter around zero at each site (fig 1). Calculation of patient Z scores confirmed the absence of any significant difference from the controls; mean (SE) patient Z scores were -0.032 (0.104) for femoral neck (fig 2A), -0.20 (0.090) for femoral trochanter, -0.167 (0.110) for Ward's triangle, 0.019 (0.110) for lumbar spine (anterior-posterior), and 0.023 (0.205) for lumbar spine (lateral). Bone mineral density at any site was not significantly correlated with duration of thyroxine therapy (fig 2B), thyroxine dose, cumulative thyroxine intake, or serum concentrations of free thyroxine or thyrotropin. There was, however, as expected, a significant negative relation both in patients and in controls between bone mineral density at each site and age ($p < 0.0005$ for each site).

There were no differences in bone mineral density or biochemical results between patients who received iodine-131 ablation in addition to thyroidectomy and those who did not, or between patients with undetectable thyrotropin concentrations and those with detectable low/normal concentrations. Exclusion of patients with detectable serum thyrotropin failed to reveal any difference in bone density between patients and controls.

Discussion

Our findings suggest that thyroxine alone does not have a significant effect on bone mineral density and hence on risk of osteoporotic features. The reasons for the discrepancy between the negative findings of this and other studies, and reports of reduced bone mineral density in thyroxine-treated patients are not clear. Our patient group was larger than those in previous studies, but the thyroxine doses and durations of treatment were similar to those described previously and patients were matched with controls more thoroughly for factors known to affect bone density. Most other studies have included patients with preceding thyrotoxicosis or long-standing goitre (and hence in many suppression of thyrotropin). Greenspan et al found that exclusion of patients with previously treated Graves' disease abolished differences in hip bone density between their postmenopausal thyroxine-treated patients and controls.

One other study examined the effect of thyroxine treatment in patients with previous thyroid cancer; reductions in femoral and lumbar spine bone mineral density among 10 postmenopausal women were reported. Again it is unclear why those findings do not accord with those of the larger study. Kung et al reported that thyroxine-treated patients with primary hypothyroidism (and no history of thyrotoxicosis) have lower femoral and radial bone densities than controls, although a lack of correlation between bone densities and dose or duration of thyroxine treatment of thyroid function test results in that study argues against a causal role for thyroxine.

The conflicting findings on the effect of thyroxine treatment on bone density are interpreted differently. Krolner et al suggested that minor differences in bone density are clinically insignificant in view of the lack of evidence for any increase in osteoporotic fractures and hence in morbidity or mortality. By contrast, Taelman et al believe that at least half their postmenopausal patients receiving thyroxine are at risk of such fractures.

Although the controversy persists, thyroxine doses prescribed in the USA have changed substantially and the recommendations of the American Thyroid association that thyroxine doses be reduced are supported by some physicians in the UK. Our large negative study adds weight to the argument that thyroxine therapy alone is without significant effect on bone mineral density; indeed it is possible that preceding thyrotoxicosis or goitre are more important risk factors for osteoporosis than thyroxine treatment itself. It is important that such negative findings are considered along with previous positive findings in view of the important consequences of changes in clinical practice. These consequences include cost implications resulting from repeated biochemical monitoring of patients, clinic visits, and dose adjustments, patient inconvenience, and potential risks of undertreatment of hypothyroidism.

Lancet 1992;340:9-13

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