Longitudinal study of bone loss after thyroidectomy and suppressive thyroxine therapy in premenopausal women

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Suppressive doses of L-thyroxine, a common form of therapy after thyroidectomy for different thyroid diseases, prevent further growth of abnormal tissue. Patients taking suppressive doses of L-thyroxine frequently have elevated serum thyroxine and free thyroxine concentrations, but serum triiodothyronine levels are within the normal range (1). These patients do not usually show biological or clinical signs of hyperthyroidism, but controversy exists as to whether such patients might have adverse tissue effects (2, 3). Thyroid hormones have important effects on bone metabolism and hyperthyroidism alters the bone remodelling activity and increases mainly cortical bone porosity, even if trabecular volume and cortical width may also be reduced (4). Cross-sectional studies have shown a reduction in bone density after prolonged suppression of the pituitary-thyroid axis with L-thyroxine (5-7) and marked bone mineral changes have been observed also under replacement therapy in hypothyroidism (8, 9).

The bone effects of thyroid hormone therapy could be particularly important in thyriodectomized patients in whom a decrement of calcitonin secretion, a potentially protective factor for bone (10), occurs.

The aim of this longitudinal study was to assess the effects of suppressive doses of L-thyroxine on the appendicular and axial bone mineral content in premenopausal thyroidectomized women.

Materials and methods

The subjects for the study were chosen from all the premenopausal women consecutively admitted during the course of one year for thyroidectomy and were candidates for suppressive therapy. Criteria for exclusion were the presence of other medical disorders, the use of drugs known to interfere with bone and mineral metabolism or previous treatment with thyroid hormones.

Fourteen premenopausal women (age: 43±6.8 years) undergoing thyroidectomy for goiter (N=6) and carcinoma (N=8) were recruited. All the patients were euthyroid at the time of the study. Each subject gave written informed consent to the study.

Ten patients underwent near-total thyroidectomy and four subtotal thyroidectomy. All were normally menstruating before and throughout the study. After surgery the women began a suppressive therapy with L-thyroxine. The initial dose was 150 µg/day (3 µg·kg⁻¹·day⁻¹) followed by monthly changes, depending on incomplete suppression of TSH (increase of the dose) or excessive levels of serum T₄ (decrease of the dose). The final dose, generally reached within four months, was maintained throughout the study.

All the patients were evaluated at six-month intervals. Radial bone mineral density was measured by single-photon absorptiometry at the distal third of the radius using a Gambio densitometer equipped with a ³¹¹Am source. The in vivo cv of the method is 3.2%. Lumbar spine (L₂-L₄) bone mineral density was measured by dual-photon absorptiometry using a Norland densitometer equipped with a ¹⁵³Gd source. The in vivo cv of the method is 3.5%. The bone mineral density for both measurements was expressed as g/cm².

Serum T₄ and T₃ were measured by radioimmunoassay and serum TSH was assessed by a sensitive immunoradiometric assay with a detection limit of 0.2 µU/l (TSH MAIAclone, Serono Diagnostics, Milan, Italy).

An iv calcium stimulation test (3 mg/kg) (11) was carried out 6 to 15 months after thyroidectomy in all the
patients to evaluate the residual calcitonin reserve. Calcitonin was determined at 10, 20 and 30 min after injection by a radioimmunoassay kit (Nichols Inst., S. Juan Capistrano, CA) with a sensitivity of 0.6 pmol/l, a within-assay cv of 6% and a between-assay cv of 8%.

A group of 24 healthy, premenopausal age-matched women who had bone density determinations during the period of the study served as control subjects. These women were clinically and biochemically normal and participated in a concurrent longitudinal study designed to evaluate the physiologic age-related bone loss and including annual biochemical and densitometric tests. At the end of the observation period, 13 out of 24 had a three-year follow-up and 11 a two-year follow-up. All of them were still regularly menstruating.

Because of variable follow-up in thyroidecomy women (see Results), the individual rate of change of the bone mass was expressed as the slope of linear regression of bone density on time (g·cm$^{-2}$·month$^{-1}$). The number of scans used for calculation of the regression in each patient ranged from three to seven. Since trend analysis showed no significant deviation from linearity of the bone mineral density changes, this summary measure seems to give a valid description of the data. The comparisons between groups were made with the Mann-Whitney test. Correlations were performed with the Spearman test. The significance of serum calcitonin increments after iv calcium and the difference from zero of the mean slope were evaluated by one-sample Student's $t$-test. Results are given as mean ± sd.

Results

Thyroidecomy and control group data are given in Table 1. The clinical parameters shown are not significantly different between the two groups.

Of the 14 women who entered the study, all completed one year of follow-up and nine were monitored for three years. This was due to the fact that the patients lived in several regions of Italy: some who were followed at other institutions refused to return for further examinations.

Exogenous thyroxine therapy was individualized for each patient to suppress TSH secretion. The mean final dose was 147 ± 12 µg daily. T3 levels remained in the normal range (1.1–2.8 nmol/l), T4 was to the upper limit of the normal range (148 ± 33 nmol/l, normal range: 50–154) and TSH levels were below the detection limit of the assay. The patients with thyroid cancer had no evidence of recurrent tumour.

Radial bone mineral density showed no significant change during the study period in either group (Fig. 1), whereas vertebral bone mineral density decreased linearly in the thyroidecomy group (Fig. 2). Individual changes in vertebral bone mineral density are shown in Fig. 3. The mean slope of vertebral bone mineral density change was significantly different from zero ($p<0.01$) in the thyroidecomy group ($-0.0025±0.002$ g·cm$^{-2}$·months$^{-1}$) and was not significantly changed in the control group ($-0.0001±0.001$ g·cm$^{-2}$·months$^{-1}$) (Fig. 4). The mean annual percent decrease from baseline values (derived from the calculated slopes and intercepts) was $2.6±1.9\%$ (mean ± sd) in thyroidecomy subjects and $0.2±1.2\%$ in control women. The difference between the two groups was highly significant ($p<0.001$). On the contrary, the mean slope of the radial bone mineral density was not significantly different from zero within both groups, nor was there any difference between groups (Fig. 5).

Though the number of subtotal thyroidecomy was small, and a formal statistical analysis was not performed, we found no difference in the vertebral bone mineral density decrease according to the type of operation (Figs. 4–5).

After iv calcium, peak CT concentrations were generally reached 10 min after the injection. The maximum increments over baseline averaged $0.15±0.15$ pmol/l in the subjects who had a total thyroidecomy (p = NS) and $0.64±0.39$ pmol/l in those who had a subtotal thyroidecomy (p < 0.05). In contrast, the minimum increment observed in normal subjects in our laboratory is always greater than $2.3$ pmol/l (range: 2.3–29.3 pmol/l).

No correlation was found between either basal levels or increments of CT and bone mineral density changes. Furthermore, no correlation was observed between the L-thyroxine dose and bone mineral density variations.

Discussion

Our study shows that appropriate suppressive doses of L-thyroxine in premenopausal thyroidecomy women induce a marked spinal bone loss even without overt biochemical and clinical signs of hyperthyroidism, except for a mild increase in T4 levels to the upper limit of the normal range. The spinal bone mineral content of these patients decreased at a rate of 2.6% per year. As found in other studies (12), we also observed a wide interindividual variation in the rate of bone loss, mainly because of two subjects who showed a very high bone mineral density decrease. However, even after excluding these two patients, the difference from the control group was still significant. The radial cortical bone showed, on the contrary, only a slight, non-significant reduction.

Table 1. Clinical parameters of thyroidecomy patients (TX) and controls at the beginning of the study. Data are mean ± sd.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TX (N = 14)</th>
<th>Controls (N = 24)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>41±6.8</td>
<td>39±9.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58±8.2</td>
<td>56±7.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162±6.8</td>
<td>160±5.1</td>
</tr>
<tr>
<td>Radial bone mineral density (g/cm$^2$)</td>
<td>0.78±0.076</td>
<td>0.757±0.070</td>
</tr>
<tr>
<td>Vertebral bone mineral density (g/cm$^2$)</td>
<td>1.166±0.210</td>
<td>1.016±0.131</td>
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and no difference compared with the control group. The radial measurements were not corrected for fat; a thyroxine-induced decrease of fat tissue might have masked minor degrees of bone mineral density reduction (13). However, the effect on the lumbar spine seems greater than that on the radius.

Both spontaneous thyrotoxicosis (14) and exogenous hyperthyroidism due to therapy with excessive doses of thyroid hormone (15) have been reported to induce diffuse skeletal demineralization and multiple fractures.

Few cross-sectional studies have examined the effects on bone of L-thyroxine given in either suppressive or replacement doses. In a group of premenopausal women treated with thyroxine for a minimum of five years, Paul et al. (6) found no reduction in bone density at the lumbar spine but a 13% reduction at the femoral neck and a 10% reduction at the femoral trochanter. Ross et al. (5) and Taelman et al. (7) reported, respectively, a 9% and 5% reduction in radial bone density in premenopausal women who had been taking L-thyroxine for more than 10 years.

Longitudinal studies are few and far between and have been performed so far only in hypothyroid subjects given replacement therapy with thyroid hormones. Stall et al. (16) found an accelerated rate of bone loss only in women who had low TSH levels, whereas Toh and Brown (17) observed no significant loss of cortical bone mineral in hypothyroid males replaced to euthyroid
Bone loss in T₄-suppressed thyroidectomized women

Our longitudinal study differs from the others since we examined euthyroid subjects receiving suppressive doses of L-thyroxine. In agreement with other studies, we have shown that this drug treatment induces a decrease in

state. On the contrary, Ribot et al. found that even appropriate thyroid replacement therapy could lead to a significant reduction in vertebral and femoral bone mineral density during the first year of treatment (12).

Fig. 3. Individual measurements of vertebral bone mineral density (BMD) of thyroidectomized subjects.

Fig. 4. Individual slopes of vertebral bone mineral density. Filled triangles represent subjects with subtotal thyroidectomy. See text for statistical evaluation.

Fig. 5. Individual slopes of radial bone mineral density. Filled triangles represent subjects with subtotal thyroidectomy. See text for statistical evaluation.
bone mass, even though there are some discrepancies in the skeletal site preferentially affected. We have no definite explanation for these discrepancies, but it is conceivable that the different experimental designs—longitudinal instead of cross-sectional—and, perhaps, the different subject selection—euthyroid instead of hypothyroid—may at least in part explain the difference between previous reports and our study.

Even if we did not find any correlation with the administered doses, the importance of the amount of the drug cannot be excluded since the sample size was small and, moreover, we have no data on the serum levels of free T3 and T4, which should reflect more closely the tissue exposure to the biologically active hormones.

The results of the iv calcium test clearly show that thyroidectomized subjects had a markedly impaired or absent calcitonin response. At least in theory, the accelerated bone loss observed in thyroidectomized patients could be related to the deficiency of calcitonin. In addition to suppressive L-thyroxine therapy, McDermott et al. (10) suggested that calcitonin deficiency in thyroidectomized patients might be a causative factor in the development of osteoporosis. However, more recent studies (18, 19) have not confirmed this hypothesis. We found no correlation between calcitonin level or decreased calcitonin response to a provocative stimulus and bone mass. However, our study does not permit evaluating the relative importance of calcitonin deficiency because of the small number of patients with significant increases of calcitonin to calcium infusion.

In conclusion, our findings indicate that when a suppressive therapy with L-thyroxine is necessary the bone loss rate should be monitored at regular intervals to evaluate the evolution of bone loss and the need for preventive treatment when these women pass their menopause. Although the optimal site for the early detection of bone loss is not established, our data suggest, in agreement with others (16), that the lumbar spine is more sensitive than the radial shaft. Longer studies are needed to evaluate the impact of this effect of thyroxine therapy on the postmenopausal bone loss and on the risk of fractures.

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References
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