Bone mass in totally thyroidectomized patients.  
Role of calcitonin deficiency and exogenous thyroid treatment

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Abstract. Calcitonin has an uncertain role in the preservation of bone mass. Since surgical thyroidectomy abolishes the calcitonin secretion in response to calcium, the bone mineral density at the radius shaft and lumbar spine was measured in 60 patients (5 men, 16 premenopausal, 34 postmenopausal euparathyroid and 5 postmenopausal hypoparathyroid women) who had undergone near total thyroidectomy for thyroid cancer 8.4±0.7 years before the study. All patients were maintained on suppressive doses of thyroid hormones. Bone mineral density values of the radius shaft (expressed as Z-score) of 34 postmenopausal euparathyroid women was significantly below the normal average (mean ± sem = −0.59±0.2; p=0.01). Bone mineral density of the lumbar spine was also below the normal average although the difference only approached statistical significance (−0.36±0.2; 0.05 <p<0.1). The bone mineral density of neither the radius nor the spine differed from normal levels in the premenopausal women and the postmenopausal hypoparathyroid women. Unexpectedly, the bone mineral density of the spine was significantly increased in the 5 thyroidectomized men. The results indicate that thyroidectomized women have a diminished bone mass after the menopause only if parathyroid function is normal. Since the patients were receiving thyroid hormone at suppressive doses, the present study is not able to separate the relative contributions of calcitonin deficit and exogenous thyroid on bone mass loss.

The physiological role of endogenous calcitonin secretion on the preservation of bone mass is not known. Since thyroidectomy abolishes the calcitonin secretion in response to calcium (1) thyroidectomized patients apparently provide a model to assess calcitonin influence on the axial and appendicular skeleton.

However, the results of previous studies have not been uniform. Some authors have found a reduced (2,3) and others a normal (4,5) bone mineral density compared with age-matched controls. In one study the results suggested that the bone mineral density was diminished in postmenopausal thyroidectomized patients (6).

The majority of thyroidectomized patients receive exogenous thyroid hormone in order to suppress TSH secretion and thyroid stimulation. The role of thyroid therapy on bone mass is a source of uncertainty. Thyroid replacement diminishes the bone mineral density of hypothyroid patients (7-10), but its effect on euthyroid subjects is controversial (8,11-13). Furthermore concomitant surgical hypoparathyroidism would reduce or abolish the increased rate of bone loss (14,15).

The present study have evaluated the bone mineral density in a large population of premenopausal and postmenopausal thyroidectomized women and a small number of men. The results indicate that the bone mineral density of thyroidectomized men and premenopausal women is not different from that of sex- and age-matched controls, but a diminution was observed in euparathyroid postmenopausal women.
Patients and Methods

Fifty-five women and 5 men who had undergone near total thyroidectomy for thyroid cancer were studied. Thirteen postmenopausal and 7 premenopausal women were studied in Sao Paulo and the remaining 40 patients in Buenos Aires. Surgery was performed 8.4±0.7 years (mean ±SEM) (range 2 to 24) before the study. In 37 patients surgery was followed by 3.8±0.6 therapeutic doses of 131I (range 1 to 22).

The age of the 55 women was 53.1±1.9 years (range 22 to 77) and that of the 5 men 33.4±1.6 (range 28 to 38). Sixteen of the 55 women were premenopausal and 39 were postmenopausal. Five of the postmenopausal patients had postsurgical hypoparathyroidism (two cases were diagnosed during our study and three patients were receiving oral calcium and vitamin D owing to the chronic deficit of PTH secretion).

All patients were maintained on suppressive doses of thyroid hormones. Fifty patients were receiving thyroxine. The dose of T4 was 222±8 μg/day (range 150 to 400). Ten patients were receiving T3 at an average dose of 78±6.2 μg/day (range 40 to 100). None of the patients were taking estrogens, corticosteroids or other medications that affect bone metabolism.

Biochemical measurements

Blood was drawn in the fasting state to determine the serum levels of calcium (16) phosphate (17), serum T4 and T3. The hormone concentrations were measured by radioimmunoassay.

Bone measurements

The bone mineral density of the spine was determined in both centres with the same type of dual photon densitometer (Lunar DP3, Madison WI) employing 155Gd (1 Ci) as the radioactive source. The results obtained in normal women were similar in both centres (18,19) and not different from the results obtained in other Caucasian populations (20,21). Since the average bone mineral density of the lumbar spine in normals was not different in both centres, the results obtained in Sao Paulo and Buenos Aires were analysed together.

The bone mineral density of the radius shaft was determined only in the patients studied in Buenos Aires, using a prototype forearm scanner equipment built at the University of Wisconsin, with 241Am as radioactive source. The bone mineral density was determined at one third of the forearm length proximal to distal ulna condyle. Technical details and normative data have been published (22).

The precision of both single and dual photon absorptiometry measurement on normal women were about 2%.

Statistical methods

The data were analysed by unpaired two tailed Student's t-test and simple correlation.

Because normal values for bone mineral density decline with age and vary between the sexes, the results were normalized by converting them to z-scores with the following formula:

\[
\text{Bone mineral density patient} - \text{Bone mineral density normal average})/\text{Standard deviation normal average}.
\]

Results

Table 1 shows the clinical and biochemical data of the patients studied. Average levels of serum calcium, phosphate, T4 and T3 were within the normal range, with the exception of serum calcium in postmenopausal hypoparathyroid women that was below normal levels. The years after thyroidectomy and the average daily dose of oral T4 did
Table 2.
Bone mineral density in the different groups of thyroidectomized patients (Z-score, mean ± SEM).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th></th>
<th></th>
<th>Postmenopausal hypoparathyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Premenopausal</td>
<td>Postmenopausal</td>
<td>Postmenopausal</td>
<td></td>
</tr>
<tr>
<td>L2-L4 (g/cm²)</td>
<td>+0.91±0.20 a</td>
<td>+0.20±0.20</td>
<td>-0.36±0.21</td>
<td>+1.0±0.80</td>
<td></td>
</tr>
<tr>
<td>(g/cm²)</td>
<td>(5)</td>
<td>(15)</td>
<td>(34)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Radius shaft</td>
<td>+0.13±0.80</td>
<td>+0.67±0.31</td>
<td>-0.59±0.21 b</td>
<td>+0.08±0.60</td>
<td></td>
</tr>
<tr>
<td>(g/cm²)</td>
<td>(5)</td>
<td>(9)</td>
<td>(21)</td>
<td>(5)</td>
<td></td>
</tr>
</tbody>
</table>

a) p<0.02 compared with normal controls.
b) p= 0.01 compared with normal controls.
Figures in parentheses denote numbers of subjects.

not differ among premenopausal and postmenopausal women.

Table 2 shows the results of bone mass assessment. The bone mineral density of postmenopausal euparathyroid women was significantly below the normal average in the radius shaft (Z score: -0.59±0.21; p=0.01). It was also below the normal average in the lumbar spine although the difference only approached statistical significance (Z score: -0.36±0.21; 0.05<p<0.1). The bone mineral density of the radius shaft and lumbar spine were not different from normal levels in premenopausal women and the levels in postmenopausal hypoparathyroid women. Unexpectedly, the bone mineral density of the spine was significantly increased in the 5 thyroidectomized men.

Fig. 1.
Bone mineral density (BMD) of the radius shaft versus age in 30 thyroidectomized euparathyroid women (r=-0.42, p<0.05).
A significant negative correlation was observed between age and bone mineral density of the radius shaft expressed as Z-score in euparathyroid women (Fig. 1), but not between bone mineral density of the spine and age. Furthermore, the length of time after thyroidectomy was not correlated with the bone mineral density of the radius shaft nor with the bone mineral density of the spine in postmenopausal women.

The axial and appendicular bone mass in postmenopausal women did not differ in the 6 receiving T₃ compared with those treated with T₄.

Discussion

The results of the present study indicate that the bone mineral density of the peripheral cortical bone in thyroidectomized postmenopausal women was significantly lower than the values observed in controls or in thyroidectomized premenopausal women. A diminution was also observed in the bone mineral density of the lumbar spine, but in this case the difference from controls or thyroidectomized premenopausal patients only approached statistical significance. On the other hand, the axial and peripheral bone mineral density of thyroidectomized premenopausal women or thyroidectomized hypoparathyroid patients was within the normal range.

The difference of bone mineral density between premenopausal and postmenopausal women in the present study is significant, since these two groups of patients did not differ in number of years after thyroidectomy, number of ¹³¹I doses, serum levels of calcium, T₄, T₃, and suppressive dose of T₄. Therefore, the deficit of calcitonin secretion and/or the exogenous administration of thyroid hormones to suppress TSH secretion seem to affect the skeleton differently depending upon the levels of endogenous estrogen secretion.

Previous studies on bone mass after thyroidectomy have not separately analysed the bone mineral density of premenopausal and postmenopausal women (2-5) nor did they state whether patients with deficient PTH secretion were excluded from the study. Since hypoparathyroidism is associated with an increased bone mass in axial and peripheral skeleton (14,15), the exclusion of patients with deficient PTH secretion is mandatory to analyse the effect of calcitonin deficiency on bone. Nevertheless the bone mineral density of the spine was found to be normal in one study (4) and diminished in a preliminary report (3). The peripheral bone mass was found to be normal by Hurley et al. (4) and Lowery et al. (6). However, the latter report found a tendency in postmenopausal thyroidectomized women towards a lower bone mineral density than in age-matched controls.

Hyperthyroidism causes bone loss (10,23,24) and administration of exogenous thyroid hormones to hypothyroid patients provokes a diminution of bone mass (7-10). There is, however, some controversy on the effect of suppressive doses of thyroxine on the appendicular skeleton: in premenopausal women, some authors found a significative loss (12) and others a normal peripheral bone mineral density (13). In postmenopausal women Georgitis et al. (11) found no significant decrease, but Taelman et al. (13) observed a diminution of the appendicular bone mineral density. The bone mineral density of the axial skeleton was found to be normal in both groups of women (8,11).

Our results indicate that thyroidectomized women have a diminished bone mass after the menopause only if PTH function is normal. Most likely an increased rate of bone turnover as a consequence of calcitonin deficit and exogenous thyroid administration augments the rate of bone loss caused by estrogen deficit after the menopause. The same increment of bone turnover would not be able to produce any effect in the premenopause when the skeleton is not in a negative balance owing to the protective role of estrogens. However, the present study is not able to separate the relative contribution of calcitonin deficit and exogenous thyroid administration on the reduced bone mass found in postmenopausal thyroidectomized women.

From a pathophysiological point of view further studies should be done in postmenopausal patients with deficit of calcitonin not receiving suppressive doses of thyroxine, to elucidate the role of calcitonin deficiency on the skeleton. However, from a clinical point of view thyroidectomized postmenopausal women receiving suppressive thyroid treatment have a lower bone mass than controls. Since this phenomenon was not observed in premenopausal women, administration of estrogens after the menopause should be beneficial in this group of patients to prevent bone loss and subsequent skeletal fractures.
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References


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