Persistent hyperactivity of the parathyroid glands in treated hypothyroid patients

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Abstract. Twelve untreated hypothyroid patients were submitted to EDTA infusion and the parathyroid hormone response to the induced hypocalcemia was studied with an amino-terminal specific assay. Eight of these patients were retested 6 months after achieving clinical and laboratory euthyroidism. The PTH response in the pretreatment condition was significantly higher than that obtained in a group of 10 normal individuals; this increased response had not normalized after 6 months of euthyroidism. This persisting hyperresponsiveness can be a contributory factor to the bone hypersensitivity to thyroid hormone replacement seen in hypothyroid patients.

Thyroid hormone replacement may be associated with bone loss, even when the patient does not show any clinical or laboratory signs of thyroid hormone excess (1,2). The reasons are uncertain, but since thyroid hormones have a synergic action with parathyroid hormone in bone cells (3) and parathyroid glands were described to be hyperresponsive in hypothyroidism (4), PTH could be a contributing factor to this bone loss. The calcitonin deficiency demonstrated in the particular set of patients with primary hypothyroidism could turn them specially prone to an unopposed action of thyroid and parathyroid hormones (5). In this study we provide evidence that treated hypothyroid patients, even 6 months after achieving euthyroidism, still show a supranormal PTH response to EDTA-induced hypocalcemia.

Subjects and Methods

The study group consisted of 11 females and 1 male (age range 18-48 years) with untreated hypothyroidism characterized by clinical and laboratory data of elevated serum TSH and low serum thyroid hormone concentrations (Table 1). All women were premenopausal and none was taking any hormone or drug known to affect bone metabolism. Eleven patients had spontaneous primary hypothyroidism, with high titres of serum antithyroid antibodies, and the last one had been submitted to total thyroiectomy one year previously in another hospital. They were treated with oral thyroxine (T₄) at a daily dose of 2.5 μg/kg and 8 of them were retested after a minimum of 6 months of clinical and laboratory euthyroidism.

The control group consisted of 10 normal individuals, 7 females and 3 males (age range, 26-45 years); none was taking any hormone or drug known to affect bone metabolism, and none had any clinical or laboratory evidence of thyroid disease; all women were premenopausal. The study protocol was approved by the Ethical Committee for Clinical Research in "Anima Nobile" of the Escola Paulista de Medicina and informed consent was obtained from all participants.

Hypocalcemia was induced by an EDTA infusion of a total of 30 mg/kg in 2 h. Indwelling catheters were placed in each antecubital vein; one was used for collection of the blood samples and the other for the infusion; 200 ml of a 5% glucose solution containing EDTA and 2.7 mg/kg of lidocaine was infused using a Harvard Apparatus infu-
Sex, age, total T<sub>4</sub>, free T<sub>4</sub> and TSH in the 12 patients with hypothyroidism. Normal values within parentheses.

<table>
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<tr>
<th></th>
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<th>Total T&lt;sub&gt;4&lt;/sub&gt;</th>
<th>Free T&lt;sub&gt;4&lt;/sub&gt;</th>
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<td>F</td>
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<td>&lt;12</td>
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</tr>
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</table>

Table 1.

Basal calcium levels were not significantly different among the three groups (normal controls and hypothyroid patients before and after treatment with T<sub>4</sub>) (Table 2). EDTA infusion induced a decline in serum calcium levels in all three groups (Fig. 1). The fractional calcium decrement per min (λ) obtained were: normal controls −1.49·10<sup>-3</sup>±9.33·10<sup>-5</sup> (mean ± SEM); untreated hypothyroid patients −1.57·10<sup>-3</sup>±9.8·10<sup>-5</sup>; treated hypothyroid patients −1.32·10<sup>-3</sup>±7.9·10<sup>-5</sup>; these values were not significantly different between groups (p>0.05). In the hypothyroid patients the basal PTH values were significantly higher before and after treatment than in controls (p<0.05) (Table 2). EDTA infusion induced an increase in the PTH concentrations in normal controls, as well as in the patients, before and after treatment (Fig. 2), analysis of the maximal ΔPTH values (Q) showed significantly higher results for hypothyroid patients, before and after treatment (p<0.05) (Table 2). No statistically significant difference could be shown between PTH values (basal and Q) of the hypothyroid patients before and after treatment (Table 2).

Results

Basal calcium levels were not significantly different among the three groups (normal controls and hypothyroid patients before and after treatment with T<sub>4</sub>) (Table 2). EDTA infusion induced a decline in serum calcium levels in all three groups (Fig. 1). The fractional calcium decrement per min (λ) obtained were: normal controls −1.49·10<sup>-3</sup>±9.33·10<sup>-5</sup> (mean ± SEM); untreated hypothyroid patients −1.57·10<sup>-3</sup>±9.8·10<sup>-5</sup>; treated hypothyroid patients −1.32·10<sup>-3</sup>±7.9·10<sup>-5</sup>; these values were not significantly different between groups (p>0.05). In the hypothyroid patients the basal PTH values were significantly higher before and after treatment than in controls (p<0.05) (Table 2). EDTA infusion induced an increase in the PTH concentrations in normal controls, as well as in the patients, before and after treatment (Fig. 2), analysis of the maximal ΔPTH values (Q) showed significantly higher results for hypothyroid patients, before and after treatment (p<0.05) (Table 2). No statistically significant difference could be shown between PTH values (basal and Q) of the hypothyroid patients before and after treatment (Table 2).

Table 2.

<table>
<thead>
<tr>
<th>Basal calcium (nmol/l)</th>
<th>Basal PTH (pmol/l)</th>
<th>Q (pmol)</th>
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<tr>
<td>Controls</td>
<td>Hypothyroid</td>
<td>Before treatment</td>
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<tr>
<td>2.32±0.09</td>
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<td>2.20±0.12</td>
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Fig. 1. Mean (± sd) serum calcium concentration during EDTA infusion in normal controls (○) and hypothyroid patients before (▲) and after treatment (●).

Fig. 2. Mean (± sd) serum PTH levels during EDTA infusion in normal controls (○) and hypothyroid patients before (▲) and after treatment (●).

Discussion

Thyroid hormones have a direct effect on bone (10). In addition, it is well documented that states of thyroid hormone excess, either in spontaneous hyperthyroidism or in excessive hormone administration, lead to bone loss (1,2,11-13). Furthermore, Coindre et al. (1), studying hypothyroid patients on standard replacement therapy where no clinical or laboratory signs of thyrotoxicosis were detected, demonstrated accelerated bone loss as early as the first month of treatment. Since parathyroid glands have increased response to hypocalcemia in hypothyroidism (4), and PTH has a possible role in bone resorption, we decided to investigate, in hypothyroid patients, what happens to the hyperreactivity of parathyroid glands with the return to euthyroidism.

EDTA infusion tests are commonly employed for the study of PTH secretion (14-16); in association with the use of PTH assays that measure the circulating biologically active form of the hormone, they provide a very sensitive and specific way of measuring the glands responsiveness (8,17). The recently available immunoradiometric assays that with great sensitivity and specificity measure the intact PTH form (18,19) have, for most applications, outdated all other PTH measuring methods. In spite of not being as sensitive as the above-mentioned methods, amino-terminal specific assays have enough sensitivity for an adequate analysis of the gland responsiveness. Additionally, recent in vitro studies have shown similar responses of the parathyroid tissue to extracellular calcium variations when assessed with amino-terminal and intact PTH assays (20).

Our study clearly demonstrates the persistence of an abnormally high PTH response to hypocalcemia in the group of treated hypothyroid patients, even after six months of clinical and biochemical euthyroidism. This implies that these patients, for at least 6 months, remain in a state of mild hyperparathyroidism with normal thyroid hormone levels. If the state of hypothyroidism was protecting their bones against the resorptive action of PTH and probably inducing the state of parathyroid hyperreactivity, euthyroidism does not give this protection. The fact that hypothyroid patients have calcitonin deficiency (5), a condition that is not reversed by the thyroid hormone replacement therapy, makes their bones particularly prone to a deleterious associated effect of thyroid and parathyroid hormones. The indication for an associated bone-sparing therapy, especially in the case of patients with high risk of osteoporosis, deserves additional studies.

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References


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