0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 6
Printed in U.S.A.

Antiresorptive Therapy in Hyperthyroid Patients: Longitudinal Changes in Bone and Mineral Metabolism

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ABSTRACT

The effect of antiresorptive therapy with nasal calcitonin (CT) in recently diagnosed hyperthyroid patients on conventional medical therapy as well as the evolution of bone metabolism were assessed. Forty-five patients with recent-onset hyperthyroidism (<12 weeks) were sex and menopause stratified and randomly allocated to treatment with carbimazole (Neotomizol), carbimazole plus low dose CT (Calsynar; 100 IU/day, 2 days/week), or carbimazole plus high dose CT (Calsynar; 100 IU/day, 14 days/month). Bone mineral density was measured by dual x-ray absorptiometry in lumbar spine, femoral neck, and Ward's triangle at 0, 9, and 18 months of treatment. We also determined free T_4, free T_3, TSH, osteocalcin, total and bone alkaline phosphatases, tartrate-resistant acid phosphatase, type I collagen C telopeptide, and urinary hydroxyproline every 3 months of follow-up. No significant difference was observed among treatments. A euthyroid state was attained at 3 months. Bone mass increased significantly at the 9 month evaluation ($P < 0.05$), with a 5–10% net gain during follow-up. Nevertheless, final bone mass was 4–8% smaller than expected. Bone formation markers were increased at 0 and 3 months, with reductions at 6–9 months; resorption bone markers showed a significant reduction at the 3 month evaluation.

These results indicate that the euthyroid state partially reduces hyperthyroidism-associated osteopenia, with a bone mass recovery period during the 6–9 early months of effective treatment. This recovery phase is characterized by raised bone formation markers and reduced bone resorption markers. The treatment with nasal CT at the doses assayed has no additional effect over that of attainment of the euthyroid state. (*J Clin Endocrinol Metab* **82:** 1989–1994, 1997)

PREVIOUS hyperthyroidism is a risk factor for osteoporosis (1, 2), a major public health problem. In histomorphometric studies, reconstruction of the remodeling sequence in patients with hyperthyroidism discloses a marked shortening of both the resorptive and formative phases of the remodeling cycle, with a negative balance of 9–10 μm/remodeling cycle (3). Osteoclastic and osteoblastic activities are enhanced, with a predominance of bone resorption resulting in increased levels of bone turnover markers (4) and in decreased bone mass, as determined by single photon absorptiometry (5), dual photon absorptiometry (6), and dual x-ray absorptiometry (7, 8), which is the most rapid, accurate, and reproducible method to evaluate bone mineral density (BMD) (9, 10).

Serum bone alkaline phosphatase determined by immunoradiometric assay (IRMA) and serum type I collagen C-terminal telopeptide (ICTP) determined by RIA have been introduced recently as formation and resorption bone turnover markers, respectively (11). These precise bone markers could clarify, in a prospective study, the existence of a bone mass recovery period after attainment of euthyroidism that has been suggested in patients treated with radioiodine (12). Moreover, recent reports have suggested the reversibility of thyrotoxic bone disease after more than 4 (13), 5 (14), or even 1 yr of euthyroidism (15).

Nevertheless, prospective studies to determine the potential benefits of bone antiresorptive therapy in patients with TSH-suppressive L-T_4 therapy have been proposed (16–18). Calcitonin (CT) is a potent inhibitor of osteoclast activity. Normal or low basal serum CT levels have been reported in hyperthyroid patients (19); however, the effect of exogenous CT in hyperthyroid patients is greater than that in normal controls (20).

This is the first prospective study designed to evaluate the evolution of axial BMD, bone turnover markers, and the potential effects of bone antiresorptive therapy with nasal salmon CT in hyperthyroid patients receiving standard medical treatment.

Subjects and Methods

Patients

Forty-five Spanish patients with recent onset (<12 weeks) of endogenous hyperthyroidism were enrolled from the out-patient clinic at the University Hospital of Granada (Granada, Spain). All patients were Caucasian. No patient was taking oral contraceptives, calcium supplements, vitamin D preparations, or other medications that might affect bone density. None had a history of hepatic or renal disorders, alcoholism, early menopause, or any other major medical condition. All subjects gave informed consent, and the study protocol was approved by the hospital's ethical committee.

Study design

The eligible patients were classified into three strata according to sex and menopause (stratum 1, men; stratum 2, premenopausal women; stratum 3, menopausal women). In each stratum, the patients were randomly assigned to receive carbimazole (CMZ; Gruppo Ferrer, Barcelona, Spain; Neotomizol; 45 mg/day initially with later adjustment to

Received December 30, 1996. Revision received March 3, 1997. Accepted March 11, 1997.

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normalize serum free T_4 and TSH; group A), CMZ plus low dose nasal salmon CT (Calsynar; Rhône-Poulenc-Rorer, S.A., Madrid, Spain; 100 IU/day, 2 days/week; group B), or CMZ plus high dose nasal salmon CT (Calsynar; 100 IU/day, 14 days/month; group C). The follow-up period was 18 months, with visits at 3-month intervals by the same investigator (E.J.).

Assessments

The study protocol included assessment of BMD by dual energy x-ray absortiometry (Hologic QDR1000, Hologic, Waltham, MA) at 9-month intervals in lumbar spine (LS; L2–L4), femoral neck (FN), and Ward's triangle (WT). The *in vivo* precision (coefficient of variation) was better than 2% at lumbar and femoral sites of measurement. Two thousand five hundred and fifty-two healthy normal subjects (1331 females and 1221 males) served to establish the mean BMD in the healthy Spanish population and to calculate the z-score for each BMD measurement (number of SDs of the patient's value from the mean of the control population in a 5-yr age band). The characteristics of this reference population have been described previously (21). Vertebral fractures and calcifications were excluded by x-ray study.

Morning samples of venous blood were taken from patients at 3-month intervals. Serum was assayed for TSH [RIA-gnost hTSH, Gif-Sur-Yvette, France; reference values (RV), 0.5–5 μU/mL], free T_4 (RIA-mat FT_4, Byk-Sangtec Diagnostica, Dietzenbach, Germany; RV, 0.9–2.0 ng/dL), free T_3 (RIA-coat FT_3, Byk-Sangtec Diagnostica, Dietzenbach, Germany; RV, 3.8–8.3 pg/mL). Serum total alkaline phosphatase (TOTALALP; Hitachi 704 autoanalyzer, Boehringer Mannheim, Mannheim, Germany; RV, 100–280 IU/L), bone alkaline phosphatase (BONEALP; Tandem-T, Ostase ImmunoRadioMetric Assay, Hybritech Europe, Liege, Belgium; RV: males, 12.4 ± 4.36 μg/L; females, 11.6 ± 4.11 μg/mL), osteocalcin (BGP; Osteocalcin ^{125}I RIA, Incstar Corp., Stillwater, MN; RV, 1.8–6.6 ng/mL), tartrate-resistant acid phosphatase (Hitachi 704 autoanalyzer, Boehringer Mannheim; RV, ≤7 IU/L), ICTP (Telopeptide ICTP[^{125}I] RIA, Orion Diagnostica, Espoo, Finland; RV, 1.8–5.0 μg/L), and fasting urine hydroxyproline/creatinine ratio (OHP/Cr; hydroxyproline, Organon Teknika, Boxtel, Holland; RV, <0.03) were also determined every 3 months as bone turnover markers. The initial determinations were made before CT and/or CMZ treatment were begun. Forty-three healthy volunteers from the staff and the students of our hospital served as homogeneous controls for the bone turnover makers in Fig. 5. Calcium intake was estimated by a food frequency questionnaire (22), and physical activity was estimated by self reports.

Compliance and adverse events

Compliance and adverse events were assessed by systematic questionnaire at every visit of follow-up. The lack of adherence for 14 days or more was considered exclusion criteria. There were no dropouts, but two patients (one from group B and one from group C) were excluded because of noncompliance.

Statistical analysis

The analysis of a nested design was carried out with three factors included: group, time, and patient. Fixed effect factor were groups and time (crossed), and random effect factor was patient, which was nested in group. This study has a power of 75% to identify a 30% difference in variances. When any factor or interaction between them was significant, pairwise comparisons were carried out using the Bonferroni method (because of unequal sample sizes). A covariance analysis was used with this nested design to control different variables by FT_4. The mean ± SD are shown for the different variables in tables, and the mean ± SEM are shown in figures. $P < 0.05$ was posed as the significance level. All analysis were carried out using BMDP software (BMDP Statistical Software, Los Angeles, CA).

Results

The baseline characteristics of patients who were included in the three groups were similar (Table 1). Hyperthyroid patients showed a significant reduction in basal BMD, with values approximately 10% lower than expected for age- and

TABLE 1. Characteristics of the patients at the baseline

	Group A (n = 15)	Group B (n = 14)	Group C (n = 14)	*P*
Age (yr)	32 ± 11	39 ± 12	38 ± 14	NS[a]
Sex				
Male	3/15 (20.0)	3/14 (21.4)	2/14 (14.3)	
Premenopausal female	11/15 (73.3)	10/14 (71.4)	11/14 (78.6)	NS[b]
Postmenopausal female	1/15 (6.7)	1/14 (7.1)	1/14 (7.1)	
Yr postmenopause	11	10	13	
BMI (kg/m^2)	22.5 ± 4.0	25.8 ± 5.4	24.0 ± 5.3	NS[a]
Calcium intake				
Low	6/15 (40.0)	6/14 (42.8)	7/14 (50.0)	
Medium	4/15 (26.7)	6/14 (42.8)	5/14 (35.7)	NS[b]
High	5/15 (33.3)	2/14 (14.4)	2/14 (14.3)	
Tobacco use				
No use	8/15 (53.3)	10/14 (71.4)	8/14 (57.1)	
<20 cigarettes/day	5/15 (33.3)	3/14 (21.4)	5/14 (35.7)	NS[b]
≥20 cigarettes/day	2/15 (13.4)	1/14 (7.2)	1/14 (7.2)	
Exercise				
Little activity	7/15 (46.7)	7/14 (50.0)	7/14 (50.0)	
Moderate activity	6/15 (40.0)	4/14 (28.6)	5/14 (35.7)	NS[b]
Very active	2/15 (13.3)	3/14 (21.4)	2/14 (14.3)	
Etiology				
Graves' disease	14/15 (93.3)	13/14 (92.8)	12/14 (85.7)	
Toxic nodular goiter	1/15 (6.6)	1/14 (7.2)	2/14 (14.3)	NS[b]
Serum free T4 (pmol/L)	3.10 ± 2.32	4.30 ± 4.31	2.91 ± 2.04	NS[a]
TSH (mIU/L)	0.98 ± 1.91	1.22 ± 2.77	1.44 ± 3.55	NS[a]
LS BMD (z-score)	−1.15 ± 0.83	−0.78 ± 0.98	−0.89 ± 1.17	NS[a]
FN BMD (z-score)	−0.85 ± 1.24	−0.55 ± 0.69	−1.14 ± 1.22	NS[a]
WT BMD (z-score)	−0.78 ± 1.32	−0.73 ± 0.59	−1.00 ± 1.40	NS[a]

Group A, Controls; group B, low dose CT; group C, high dose CT. BMI, Body mass index. LS, lumbar spine; FN, femoral neck; WT, Ward's triangle; BMD, bone mineral density. Data are shown as the mean ± SD, with the percentage in *parentheses*.

[a] By one-way ANOVA.

[b] By χ^2-Fisher test.

sex-matched controls. The euthyroid state was attained [F_{EXP} = 9.34 (6, 240) df; $P < 0.001$] at the 3 month evaluation without differences among the three groups [F_{EXP} = 1.60 (2, 40) df; $P = 0.21$; Fig. 1, A and B]. The lumbar and femoral BMD increased significantly [LS: F_{EXP} = 15.88 (2, 48) df; $P < 0.001$; FN: F_{EXP} = 13.84 (2, 48) df; $P < 0.001$; WT: F_{EXP} = 5.96 (2, 48) df; $P < 0.01$] at the 9 month evaluation without later gain (Fig. 2, A–C). No significant difference was observed among the three groups [LS: F_{EXP} = 0.22 (2, 24) df; $P > 0.70$; FN: F_{EXP} = 0.45 (2, 24) df; $P > 0.40$; WT: F_{EXP} = 0.10 (2, 24) df; $P > 0.50$]. Three of 43 patients failed to increase lumbar and femoral BMD, 1 of 15 in group A and 1 of 14 in groups B and C, all of whom were premenopausal females. Bone turnover markers were elevated at baseline when compared with the final value, but there was no significant difference among groups in the follow-up period. TOTALALP and BGP decreased significantly into the normal range at the fourth visit (9 months; Fig. 3, A and B). BONEALP remained elevated at visit 2 (3 months) and decreased significantly at visit 3 (6 months; Fig. 3C). On the other hand, bone resorption markers decreased significantly at visit 2 (3 months; Fig. 4, A–C) to normal values, except for ICTP which normalized at visit 3 (6 months).

The adjustment by serum free T_4 levels (by analysis of covariance) was significant for BGP [F_{EXP} = 7.83 (6, 239) df; $P < 0.01$], ICTP [F_{EXP} = 166.77 (6, 239) df; $P < 0.001$], and OHP/Cr [F_{EXP} = 59.79 (6, 239) df; $P < 0.001$] and near significant for BONEALP [F_{EXP} = 3.69 (6, 239) df; $P = 0.05$]. No changes in significant differences were observed; nevertheless, this analysis allowed us to generate an evolutive model of the changes in the bone mineral metabolism for hyperthyroid patients receiving standard medical treatment (Fig. 5).

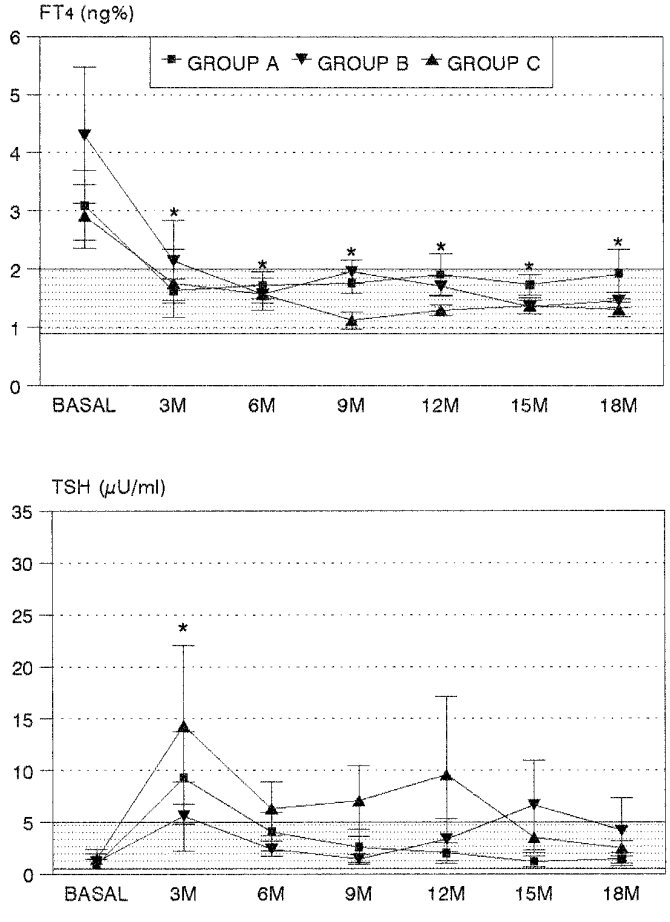

FIG. 1. Evolution of thyroid function tests during the follow-up. Data are shown as the mean ± sem. Group A, Without CT; group B, low dose CT; group C, high dose CT. M, Month of follow-up. *, $P < 0.05$ *vs.* basal.

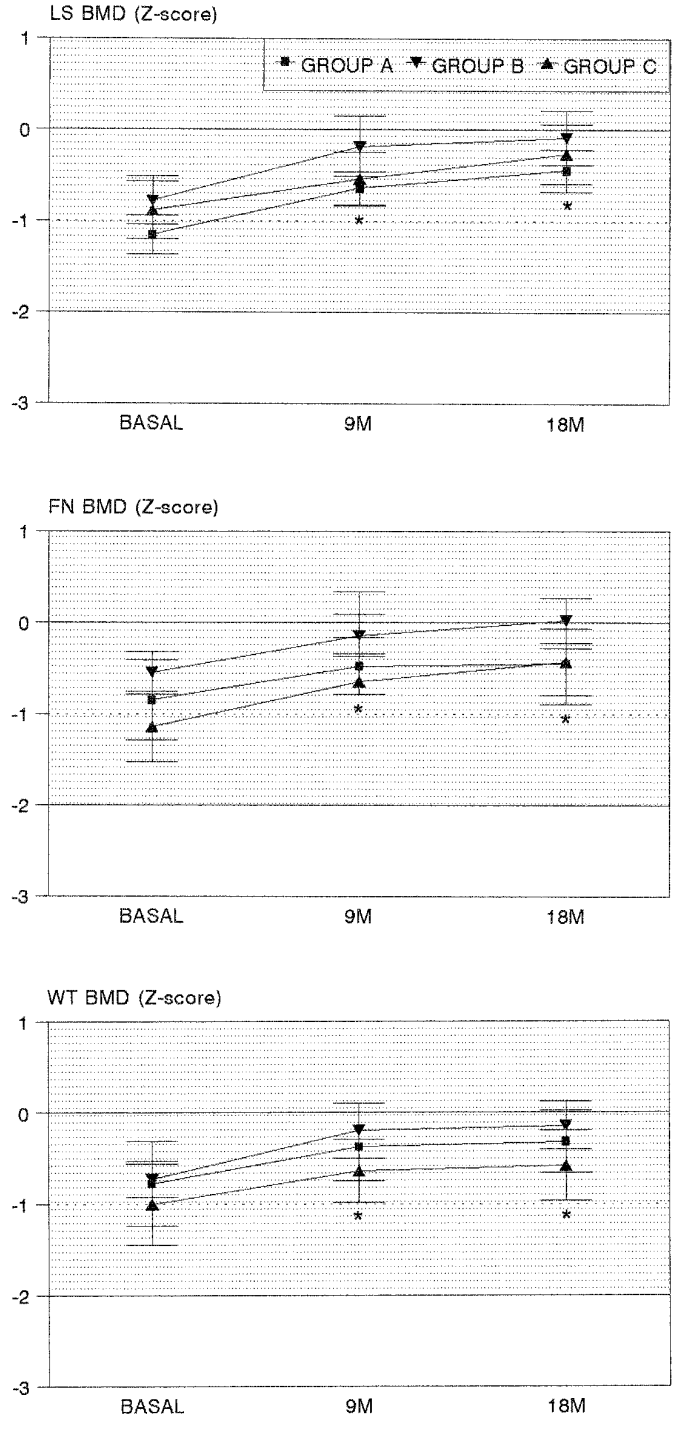

FIG. 2. Evolution of the BMD during the follow-up. Data are shown as the mean ± SEM. Group A, Without CT; group B, low dose CT; group C, high dose CT. M, Month of follow-up. *, $P < 0.05$ *vs.* basal.

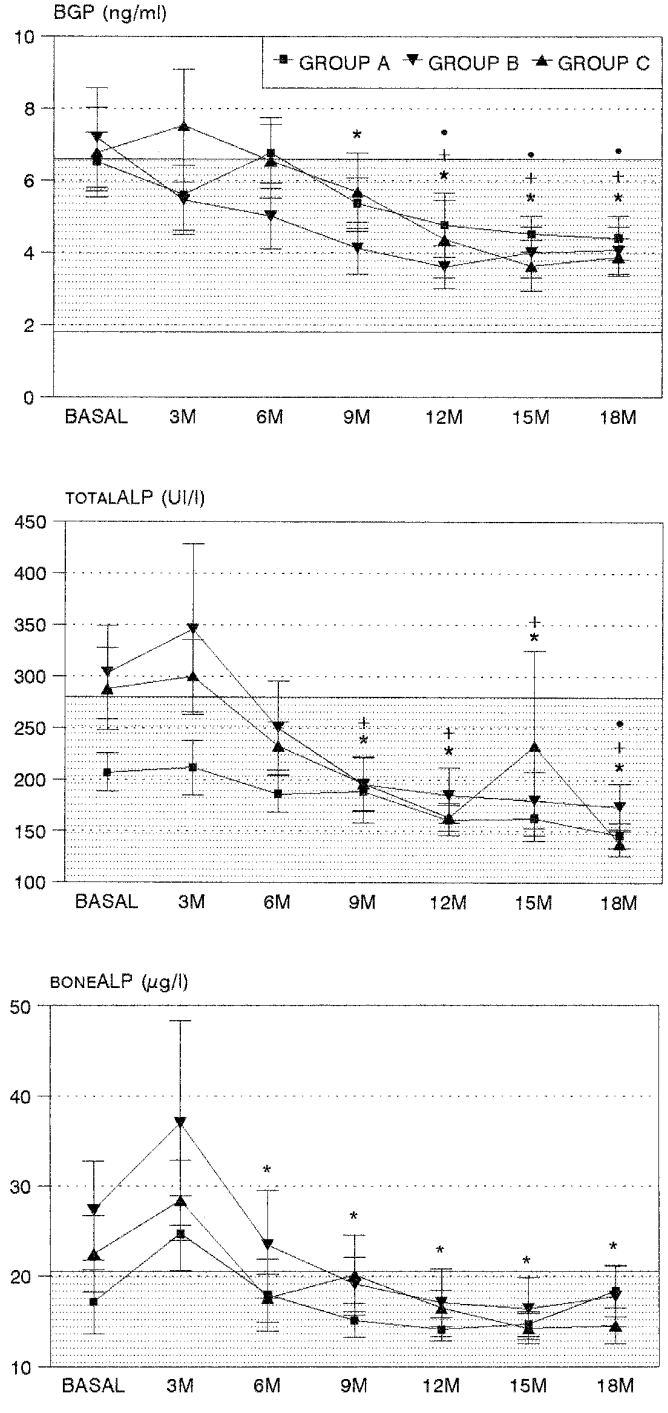

FIG. 3. Evolution of bone formation markers during the follow-up. Data are shown as the mean ± SEM. Group A, Without CT; group B, low dose CT; group C, high dose CT. M, Month of follow-up. *, $P < 0.05$ *vs.* basal; +, $P < 0.05$ *vs.* 3 months; ●, $P < 0.05$ *vs.* 6 months.

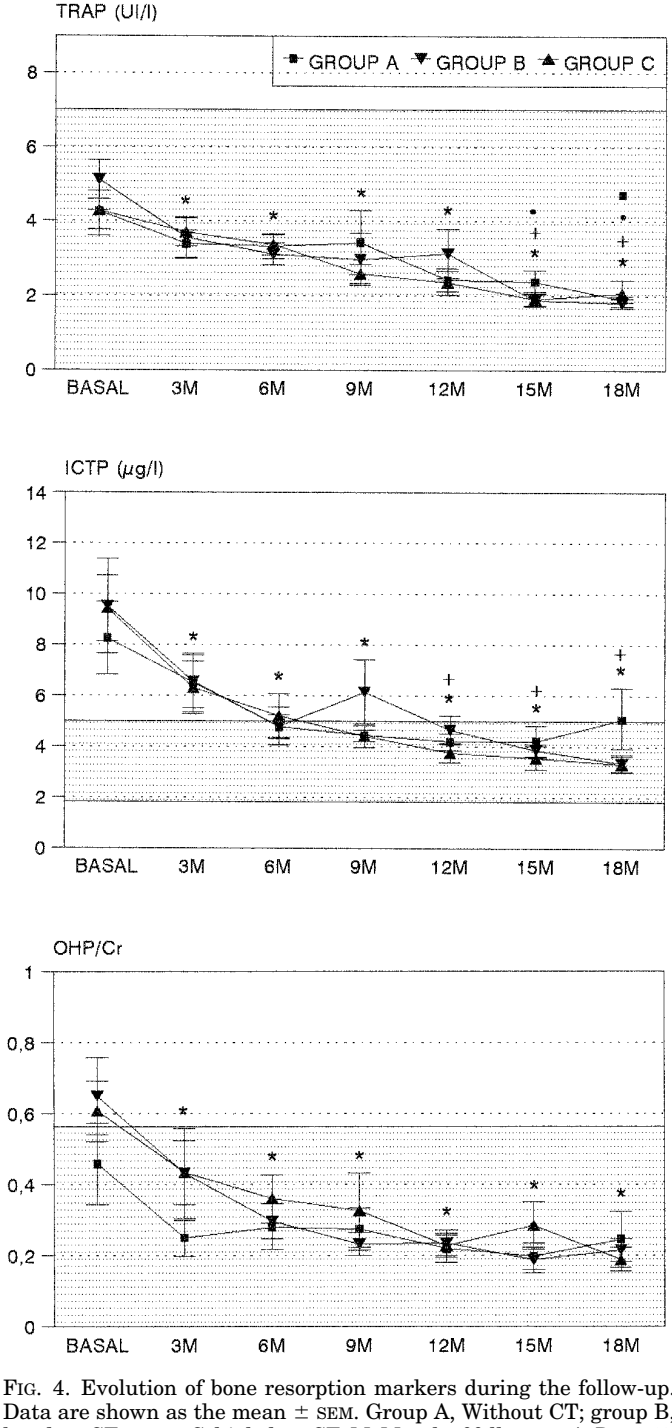

FIG. 4. Evolution of bone resorption markers during the follow-up. Data are shown as the mean ± SEM. Group A, Without CT; group B, low dose CT; group C, high dose CT. M, Month of follow-up. *, $P < 0.05$ *vs.* basal; +, $P < 0.05$ *vs.* 3 months; ●, $P < 0.05$ *vs.* 6 months; ■, $P < 0.05$ *vs.* 9 months.

The extent and degree of adverse events are shown in Table 2. These events were mild, and medication did not have to be discontinued.

Discussion

We demonstrate, as did other groups using similar methodology (6, 7, 15), a significant reduction in axial BMD in hyperthyroid patients. This reduction was similar in magnitude to that observed previously and was partially restored after attainment of the euthyroid state. Even so, after the 18-month period of follow-up, this recovery was incomplete, with a 5% deficit compared to values in sex- and age-matched controls. Some studies with smaller number of patients (15) and using different methodologies (14) have suggested a potential reversibility of hyperthyroid bone disease. Our

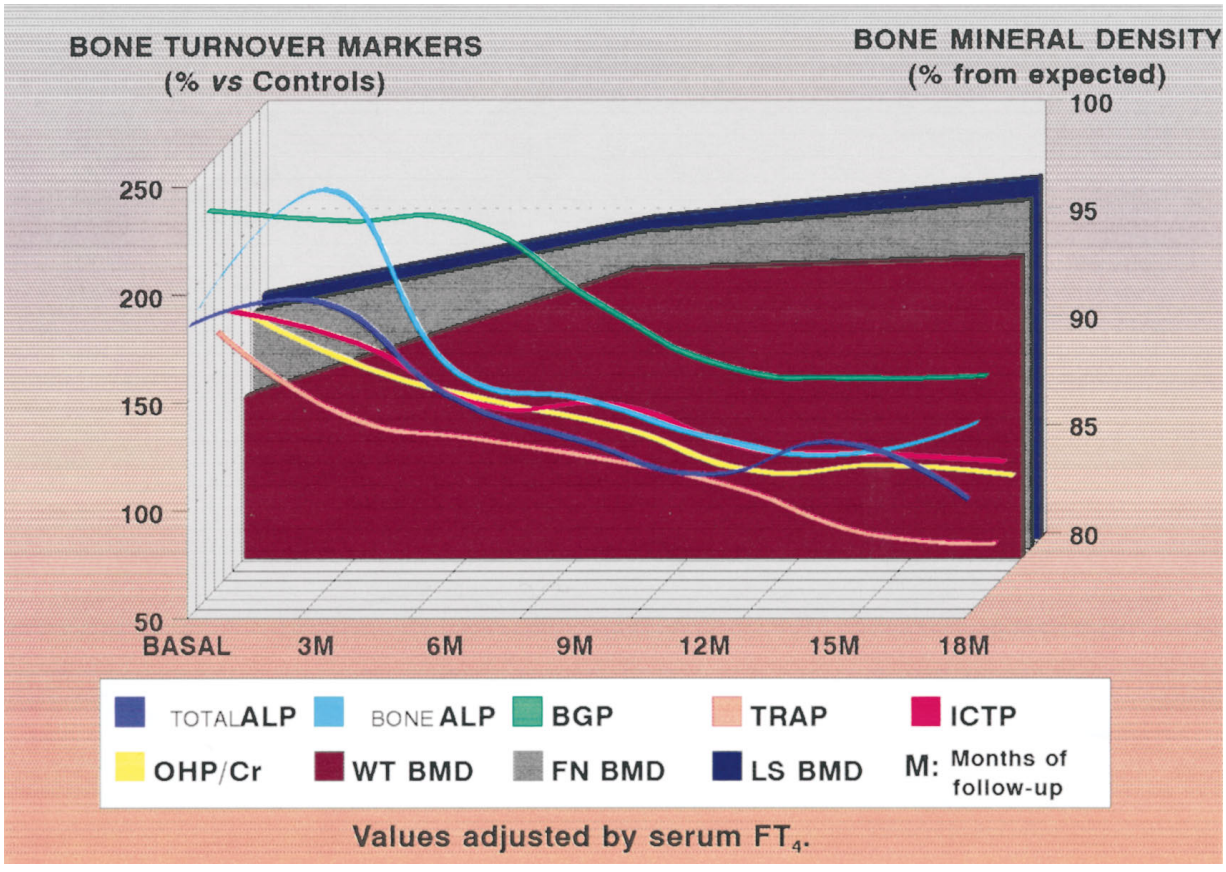

FIG. 5. Model of bone and mineral metabolism evolution in hyperthyroid patients receiving standard medical treatment.

TABLE 2. Adverse events in hyperthyroid patients receiving CT treatment

	Group	n (%)	Duration	Severity
Digestive	B	1/14 (7.1)	Intermittent	Mild
Discomfort, nausea	C	3/14 (21.4)	Intermittent	Mild[a]
Skin	B	1/14 (7.1)	Intermittent	Mild
Facial flushing	C	2/14 (14.3)	Intermittent	Mild
ORL	B	1/14 (7.1)	Days	Mild
Aquous rhinorrhea	C	1/14 (7.1)	Intermittent	Mild
Nervous system:				
Headache	C	1/14 (7.1)	Intermittent	Medium[a]
None	B	11/14 (78.6)		
	C	10/14 (71.4)		

Group B, Low dose CT; group C, high dose CT.
[a] Medium intensity in one patient at 18 months evaluation.

data show a significant increase limited to the first 9 months of treatment, so it seems uncommon to expect a total recovery of bone mass. In this sense, an initial increase in bone mass can be due to the filling of bone spaces that are undergoing exaggerated remodeling. This mechanism, because of the increase in active remodeling units that characterizes hyperthyroid osteopenia, make the interpretation of short term studies difficult. Moreover, even a small deficit may leave these patients at jeopardy for fracture in their lifetimes.

Although CT given intranasally has been shown to be an effective treatment for postmenopausal osteoporosis (23), we have failed to prove any significant effect on bone metabolism in hyperthyroid bone disease, which is also characterized by increased bone turnover (3). Even with a stratified design to control the influence of sex and menopause, no significant difference was observed in the evolution of bone mass or in the bone metabolism markers assayed. Moreover, there was no significant difference in osteoporosis risk factors or in biochemical characteristics among the three groups at baseline. On the other hand, several male and postmenopausal female patients have been included in this study; although they did not influence the results, our conclusions do not apply specifically to male or menopausal female subjects. The lack of effect of CT may be due to the low number of patients included or to the low dose, high catabolism (24), or lack of effectiveness of CT in the hyperthyroid state as has been shown in animal studies (25). Our data suggest that the effect of restoration of the euthyroid state is greater than the potential benefits of CT at the doses employed. This agrees with the lack of influence of the menopause in the BMD from patients with active hyperthyroidism (8). So, hyperthyroidism exerts a profound alteration in bone dynamics and surpasses the effects of sex, menopause, and antiresorptive treatment with CT at the doses used in this study. In our opinion, the efforts might be directed to the early restoration of euthyroidism and to the correction of risk factors for osteoporosis. Nevertheless, the doses of CT used were relatively low (800 and 1400 IU/month) compared with the FDA-approved dose for the treatment of osteoporosis (3000 IU/month).

As expected, the baseline levels of formation (TOTALALP, BONEALP, and BGP) and resorption (tartrate-resistant acid

phosphatase, ICTP, and OHP/Cr) bone turnover markers were elevated. A direct correlation between several bone turnover markers and thyroid hormone levels has been shown in different studies (4, 12). This is esspecially true for ICTP, which has been suggested to be a good indirect marker of thyroid status (26). It was necessary, therefore, to control BMD values and bone turnover markers by thyroid hormone levels to search for subtle differences. The reconstruction of the changes in bone metabolism of hyperthyroid patients once adjusted by serum FT_4 showed the presence of a recovery period, apparently limited to the first 9 months of treatment. This period is characterized by increased levels of bone formation markers during 3–6 months that return to normal values thereafter. Osteocalcin showed delayed evolution, as expected from its direct relation with the mineralization process (11). On the other hand, bone resorption markers tend to normalize earlier in the follow-up. Again, CT treatment did not change the evolution of bone turnover markers, a process totally dependent on thyroid function status. Moreover, BMD increased significantly at the 9 month evaluation. Overall, this picture suggests that the main changes in bone mineral metabolism in hyperthyroid patients occur in the first 9–12 months of medical treatment according to observations after radioiodine treatment (12), but these changes are insufficient to normalize BMD. The final bone loss, although mild, could account for the higher risk of developing osteoporotic fractures observed in epidemiological studies (27).

In summary, this study shows that restoration of the euthyroid state partially reduces hyperthyroidism-associated osteopenia, with a bone mass recovery period focused on the first 6–9 months of effective treatment. This recovery phase is characterized by elevated levels of bone formation markers and reduced bone resorption markers. The treatment with nasal CT at the doses assayed has no additional effect over attainment of the euthyroid state.

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