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Trabecular bone score and bone mineral density in patients with postsurgical hypoparathyroidism after total thyroidectomy for differentiated thyroid carcinoma

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ABSTRACT

Background: Although bone mineral density is reported to be increased in patients with postsurgical hypoparathyroidism (postsurgical HypoPT), the effect of HypoPT on trabecular bone score remains unknown. This study evaluated the long-term effects of HypoPT secondary to total thyroidectomy for differentiated thyroid cancer on trabecular bone score, bone mineral density, and bone turnover markers with a similar group of patients without HypoPT.

Methods: Women with resected differentiated thyroid cancer and either postsurgical HypoPT ($n=25$; 8 premenopausal and 17 postmenopausal) or euparathyroid function ($n=98$; 14 premenopausal and 84 postmenopausal) were matched for age and body mass index. Patients received thyroid-stimulating hormone suppression during follow-up. The bone mineral density and trabecular bone score were analyzed using dual x-ray densitometry and Med-Imaps software at baseline (1–3 months postsurgery) and at the final study visit.

Results: Follow-up duration was similar in studied groups (median 10 years). Baseline bone mineral density and trabecular bone score were similar between HypoPT and non-HypoPT patients, regardless of menopausal status. At study end, postmenopausal HypoPT patients had greater bone mineral density versus the non-HypoPT patients at the lumbar spine, hip, and distal radius ($P=.001$), and a greater trabecular bone score (1.31 ± 0.09 vs 1.24 ± 0.12, $P=.0184$). Premenopausal patients with and without HypoPT had similar bone mineral density values at the final evaluation. The bone turnover markers (osteocalcin, bone-specific alkaline phosphatase, and β-crosslaps) were less in postmenopausal HypoPT patients, reflecting decreased bone turnover.

Conclusion: Postmenopausal patients who underwent a total thyroidectomy for differentiated thyroid cancer with postsurgical HypoPT have greater trabecular bone score and bone mineral density compared with euparathyroid patients, suggesting that HypoPT protects against the negative effects of long-term thyroid-stimulating hormone suppression treatment on bone.

Introduction

Postsurgical hypoparathyroidism (HypoPT) results from resection of, direct injury to, or devascularization of the parathyroid glands and is one of the most common complications after total thyroidectomy. Operative injury of the parathyroid glands resulting in transient HypoPT is the most common acquired cause of HypoPT in adults, with incidence rates of 19%–38%; permanent HypoPT in patients undergoing cervical surgery for thyroid cancer is much less common with an incidence of <3%.[1] Fortunately, one-third of patients with HypoPT recover within 6 months of a thyroid or parathyroid operation[2]; the overall prevalence of postsurgical

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HypoPT is estimated at 22 per 100,000 inhabitants in Denmark and 29 per 100,000 inhabitants in the United States.[3,4]

Many long-term challenges may develop in patients treated for HypoPT, including soft-tissue calcification attributable to persistently high serum-phosphate levels, renal calcification, and increased bone mineral density (BMD).[5] In cross-sectional studies, increased BMD has been observed in idiopathic, autoimmune, and postsurgical HypoPT, a finding that would suggest a decrease in the risk of fracture.[6] The few studies that have evaluated fracture risk in postsurgical HypoPT found either an increased or normal fracture risk.[7,8] These findings may reflect that bone strength comprises not only BMD but also bone quality, of which microarchitecture is a major variable along with mineralization and bone turnover.

A recently developed, noninvasive technique—trabecular bone score (TBS)—allows the evaluation of bone microarchitecture. This approach analyzes the texture of gray-level images generated in a dual-energy x-ray absorptiometry (DXA) spine scan, thereby giving information regarding bone quality. A low TBS suggests deterioration of the trabecular microarchitecture and has been verified to predict the risk of vertebral fractures independent of BMD.[9]

For patients who have undergone total thyroidectomy for differentiated thyroid cancer (DTC), the combined effects of permanent postsurgical HypoPT and thyroid-suppressive treatment with levothyroxine (L-T4) are of special concern because of the potential deleterious effects of the latter therapy on bone loss. In a cross-sectional retrospective study of postmenopausal women with DTC, normal parathyroid function, and a median duration of 4.2 years of thyroid suppression therapy, deterioration of TBS without an associated decrease in BMD was reported.[10] In fact, recent guidelines recommend less aggressive suppression with L-T4 in subjects with thyroid cancer.[11] To our knowledge, long-term studies of bone microarchitecture with TBS in HypoPT patients after total thyroidectomy for DTC have not been reported.

The aim of this study was to compare the changes in BMD and bone microarchitecture assessed with TBS in premenopausal and postmenopausal women with DTC and permanent HypoPT with a matched group of non-HypoPT after total thyroidectomy and treated with thyroid suppressive therapy (median of 10 years).

Materials and Methods

Diagnosis and follow-up of all patients occurred at a single center (Thyroid Cancer Unit, University Hospital 12 Octubre, Madrid, Spain). A subgroup of 170 of the 1,747 women diagnosed with DTC who had undergone a total thyroidectomy followed with ^{131}I ablation when indicated and who had received long-term thyroid suppressive therapy with L-T4 for more than 10 years according to guidelines[11] and had a DXA scan performed 1–3 months after total thyroidectomy were invited to participate in the study. Additional inclusion criteria were as follows: (1) serum thyroid-suppressing hormone (TSH) levels suppressed to $<$0.5 IU/ml, and (2) a diagnosis of postsurgical HypoPT, with low levels of serum calcium ($\leq$1.88 mmol/dl) and serum intact parathyroid hormone (PTH) requiring oral calcium and calcitriol therapy for 1 year after total thyroidectomy.[2] Exclusion criteria included the use of antiresorptives drugs (bisphosphonates, raloxifene, denosumab, estrogen/progestin, etc), recombinant PTH, diuretics, or glucocorticoids, and the presence of diseases affecting bone metabolism or malignant neoplasms.

A total of 25 of the 30 patients with controlled postsurgical HypoPT and 98 of the 140 control patients matched for age and body mass index (BMI) without HypoPT provided informed consent to participate and had the final DXA scan at the end of the study. All patients with postsurgical HypoPT received treatment with calcium (1.5–3.0 g of elementary calcium/day) and 1,25-dihydroxycholecalciferol (calcitriol 0.25–1.00 μg/day), which was adjusted during their regular visit every 4–6 months. Treatment was titrated to maintain serum calcium levels (adjusted for serum albumin) toward the lower limit of the reference range, with patients being free of symptoms of hypocalcemia.

This study was approved by the Ethical Review Board of the University Hospital 12 de Octubre, Madrid, Spain. Informed consent was obtained from all enrolled patients. Clinical data were retrieved, using the information collected in patient files. In those patients who reported pain suggestive of clinical vertebral fracture, incident vertebral fractures were assessed using a conventional spinal x-ray and were interpreted visually.

Hormonal and biochemical parameters

Fasting serum samples were obtained between 8 AM and 9 AM at baseline and at the final study visits. Samples were frozen immediately at −70°C until the assays were performed. Serum levels of calcium (corrected for levels of serum albumin), phosphate, and creatinine were measured by automated standard laboratory methods (Modular P800 Chemistry Analyzer, Roche Diagnostics, Basil, Switzerland) and 24-hour urinary calcium excretion by the colorimetric method. Serum TSH was measured by chemiluminescence (Architect TSH reagent, Abbot Laboratories, San Francisco, CA, USA) and free thyroxine (T4) by electrochemiluminescence (Elecsys T4, Roche Diagnostics, Basil, Switzerland; functional sensitivity $<$0.01 μg/mL). Serum intact PTH (normal range: 7–57 pg/ml) were determined using chemiluminescent immunoassays with an Immulite 2000 (Siemens Healthcare, Erlangen, Germany). Serum 25–hydroxyvitamin D3 (25OHD) was measured by (IDS-iSYS, Immunodiagnostic Systems Limited, Boldon. United Kingdom), with normal values 13–59 ng/ml. Analyzed serum bone markers included osteocalcin (baseline evaluation: competitive radioimmunoassay-coated tube [Brahms Diagnostics, Berlin, Germany], normal values 4.0–12.0 ng/ml; final evaluation: N-MID Osteocalcin, [Roche Diagnostics, Basil, Switzerland], normal values: 8–48 ng/ml); bone-specific alkaline phosphatase (BAP) (Ostase BAP, Inmunodiagnostic System, Boldan, UK), normal values: 15–40 U/L, and; β-crosslaps: (β- CTX) (Elecsys 1010, Roche Diagnostics, Basil, Switzerland); normal range: 0.200–0.704 ng/ml.

Assessment of BMD and TBS

BMD was assessed with a QDR 4500 densitometer (Hologic Inc, Waltham, MA) at the lumbar spine (LS-BMD), femoral neck (FN-BMD), total hip (TH-BMD), and distal third of the radius (1/3 DR-BMD). The same equipment was used during the entire study. The coefficient of variation was 0.95% at LS-BMD and 2.1% at FN-BMD. BMD values are expressed as absolute values (g/cm^2) and as standard deviations (SD) from the expected peak adult BMD. Reference values for BMD were obtained from a Spanish, multicenter study with 1,305 healthy women aged 20–80 years.[12] Normal BMD (T score $>$ −1), osteopenia (T score −1 $\leq$ and $>$ −2.5) and postmenopausal osteoporosis (T score $\leq$ −2.5) were characterized using criteria of the World Health Organization.[13] TBS measurements were performed on the LS-BMD DXA scan using TBS iNsight2.0 software (Med-Imaps, Geneva, Switzerland). Lumbar TBS was calculated as the mean value of individual measurements for vertebraL1-L4. We characterized TBS by the following values: normal ($\geq$1.35), partially degraded microarchitecture ($\geq$1.20 and $<$1.35), and degraded microarchitecture ($<$1.20).[9] The coefficient of variation of TBS calculated from 3 repeated measurements in 15 women was 0.89%.

Table 1
Baseline clinical and biochemical characteristics of premenopausal and postmenopausal women who have undergone total thyroidectomy for differentiated thyroid cancer*

Parameters (mean ± SD)	Premenopausal DTC patients			Postmenopausal DTC patients		
	Non-HypoPT ($n=14$)	HypoPT ($n=8$)	*P* value	Non-HypoPT ($n=84$)	HypoPT ($n=17$)	*P* value
Age (years)	35 ± 7	37 ± 10.	.3728	59 ± 9	56 ± 7	.1396
BMI (kg/m^2)	22 ± 2	26 ± 3	.0505	28 ± 4	27 ± 4	.5020
Serum creatinine (mg/dL)	0.79 ± 0.10	0.71 ± 0.15	.2132	0.76 ± 0.18	0.75 ± 0.11	.8851
Serum calcium (mg/dL)	9.07 ± 0.36	8.24 ± 0.37	.0017	9.26 ± 0.56	8.56 ± 0.76	.0006
Serum phosphate (mg/dL)	3.5 ± 0.7	4.3 ± 0.98	.0519	3.6 ± 0.5	4.3 ± 0.67	.0011
Serum 25-OH-D (ng/dL)	29.3 ± 9.5	19.3± 13.3	.2207	27.11 ± 12.4	31.92 ± 12.8	.3417
Serum intact PTH (pg/mL)	32.7 ± 13.8	14.1 ± 3.4	.0034	36.7 ± 16.4	9.3 ± 8.1	< .0001
Serum BAP (U/L)	10.7 ± 7.6	6.7 ± 1.1	.8137	12.1 ± 4.8	7.3 ± 3.2	.0022
Serum osteocalcin (ng/mL)	6.0 ± 2.2	4.37 ± 0.9	.1330	9.16 ± 6.8	5.4 ± 5.0	.0025
Urinary calcium (mg/24 hours)	154 ± 101	203 ± 179	.7079	164 ± 104	178 ± 80	.4168
FT4 (ng/dL)	1.61 ± 0.43	1.40 ± 0.28	.6318	1.65 ± 0.41	1.78 ± 0.43	.1838
L-T4 dose/weight (μg/kg per day)	2.58 ± 0.65	2.61 ± 0.62	.6799	2.15 ± 0.58	2.13 ± 0.46	.5342
Serum TSH (IU/mL)	0.22 ± 0.46	0.24 ± 0.26	.5264	0.27 ± 0.53	0.46 ± 0.76	.7667

BAP, bone alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; DTC, differentiated thyroid cancer; F-T4, free thyroxine; HypoPT, patients with hypoparathyroidism; L-T4, levothyroxine; Non-HypoPT, patients without hypoparathyroidism; PTH, parathyroid hormone; TBS, trabecular bone score; TSH, thyroid stimulating hormone; 25-OH-D, 25hydroxyvitamin D3.
* According to the presence of postsurgical hypoparathyroidism.

Table 2
Baseline bone densitometry and TBS values of premenopausal and postmenopausal patients who had undergone total thyroidectomy for differentiated thyroid cancer*

Parameters (mean ± SD)	Premenopausal DTC patients			Postmenopausal DTC patients		
	Non-HypoPT ($n=14$)	HypoPT ($n=8$)	*P* value	Non-HypoPT ($n=84$)	HypoPT ($n=17$)	*P* value
LS-BMD (g/cm^2)	0.99 ± 0.11	1.07 ± 0.10	.1831	0.84 ± 0.15	0.93 ± 0.15	.0473
FN-BMD (g/cm^2)	0.77 ± 0.12	0.91 ± 0.13	.2008	0.67 ± 0.11	0.71 ± 0.10	.4433
TH-BMD (g/cm^2)	0.89 ± 0.09	0.98 ± 0.12	.2008	0.80 ± 0.10	0.79 ± 0.09	.6207
1/3 DR-BMD (g/cm^2)	0.63 ± 0.04	0.68 ± 0.06	.1336	0.55 ± 0.04	0.58 ± 0.05	.6547
TBS	1.48 ± 0.08	1.52 ± 0.08	.7353	1.31 ± 0.12	1.32 ± 0.09	.8836

DTC, differentiated thyroid cancer; HypoPT, patients with hypoparathyroidism; FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar bone mineral density; Non-HypoPT, patients without hypoparathyroidism; TBS, trabecular bone score; TH-BMD, total hip bone mineral density; 1/3 DR-BMD, distal third of the radius bone mineral density.
* According to the presence of postsurgical hypoparathyroidism.

Statistical analysis

Quantitative variables are expressed as mean and SDs or as medians with interquartile range. Normality of the data was confirmed using the Kolmogorov-Smirnov test. Qualitative variables were described using absolute and relative percentages. Contingency tables and the χ^2 or Fisher tests were used to compare categorical parameters. The nonparametric Wilcoxon test or the Kruskal-Wallis test were used for the cross-sectional study and Student *t* test for the longitudinal study. The Pearson test was performed to evaluate the correlations between clinical parameters and DXA and TBS parameters. Multiple lineal regression was performed to evaluate the dependence and influence between variables. Adjusted covariates included menopausal status and body weight. A level of $\alpha = 0.05$ was considered statistically significant in all statistical procedures. The Bonferroni correction was used in analysis of variance (ANOVA) tests. All data were analyzed using SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline clinical and biochemical characteristics

Of the 170 women invited to participate, 25 of the 30 patients with HypoPT and 98 of the 140 control patients completed the study. Baseline characteristics of the study cohort are summarized represented in Tables 1 and 2. At baseline, 8 patients were premenopausal and 17 were postmenopausal in the HypoPT group, and 14 patients were premenopausal and 84 were postmenopausal in the control group. During follow-up, 5 premenopausal HypoPT patients became postmenopausal. No patients in the control group transitioned from premenopausal to postmenopausal. Premenopausal and postmenopausal HypoPT patients had lesser levels of serum calcium and greater serum phosphate levels compared with non-HypoPT patients. Serum creatinine and urinary calcium daily excretion were within normal limits in all groups. Lesser levels of PTH were found in HypoPT patients. The L-T4 prescribed per kg body weight was similar in premenopausal and postmenopausal patients regardless of the status of parathyroid function.

Final clinical and biochemical characteristics

The duration of follow-up (ie, the period between the baseline visit to the final visit) was similar in the four groups. For patients in the postmenopausal HypoPT and non-HypoPT groups, mean follow-up was: 11.1 ± 6.5 years and 11.3 ± 5.9 years, respectively. For patients in the premenopausal HypoPT and non-HypoPT groups, mean follow-up was 15.7 ± 9.2 years and 10.6 ± 6.7 years, respectively.

At the end of follow-up, age and BMI were similar in patients with or without HypoPT, despite the change in the menopausal status of 5 patients (Tables 3 and 4). Serum calcium values were less and levels of phosphate were greater in HypoPT patients compared with non-HypoPT patients, although the values were still within the normal reference limits (Table 3). PTH levels for each group were relatively unchanged from baseline. The dosage of L-T4 prescribed per kg/body weight was similar in premenopausal patients, but slightly greater in postmenopausal HypoPT versus non-HypoPT patients (1.81 ± 0.37 mg/kg vs 1.63 ± 0.4 mg/kg, respectively, $P = .0412$). Serum TSH levels were not significantly

Table 3
Final clinical and biochemichal characteristics of premenopausal and postmenopausal women who have undergone total thyroidectomy for differentiated thyroid cancer*

Parameters (mean ± SD)	Premenopausal DTC patients			Postmenopausal DTC patients		
	Non-HypoPT ($n=14$)	HypoPT ($n=3$)	P value†	Non-HypoPT ($n=84$)	HypoPT ($n=22$)	P value
Age (years)	46 ± 4	46 ± 5	0.7042	67 ± 8	65 ± 8	.6509
BMI (kg/m^2)	24 ± 4	31 ± 4	0.0778	29 ± 5	28 ± 5	.4102
Serum creatinine (mg/dL)	0.70 ± 0.11	0.58 ± 0.06	0.0689	0.78 ± 0.21	0.77 ± 0.12	.6262
Serum calcium (mg/dL)	9.0 ± 0.3	6.9 ± 1.8	0.0181	9.1 ± 0.4	8.4 ± 0.7	< .0001
Serum phosphate (mg/dL)	3.3 ± 0.4	4.7 ± 1.1	0.0287	3.4 ± 0.5	4.3 ± 0.7	< .0001
Serum 25-OH-D (ng/dL)	23.7 ± 5.5	19.4 ± 9.0	0.3865	22.9 ± 8.4	25.9 ± 9.9	.2209
Serum intact PTH (pg/mL)	41.9 ± 12.8	8.9 ± 0.9	0.0317	52.8 ± 22.9	15.5 ± 11.8	< .0001
Serum BAP (U/L)	23.5 ± 10.0	19.2 ± 7.4	0.0481	26.2 ± 11.1	21.9 ± 11.8	.0543
Serum osteocalcin (ng/mL)	21.31 ± 13.5	17.53 ± 2.7	0.99	21.0 ± 7.1	15.4 ± 2.9	.0009
β-CTX (ng/mL)	0.40 ± 0.45	0.28 ± 0.12	0.99	0.35 ± 0.19	0.12 ± 0.10	.0512
Urine calcium (mg/24 h)	165.4 ± 46.7	101.6 ± 56.4	0.091	152.2 ± 166.0	191.6 ± 92.6	.0245
F-T4 (ng/dL)	1.61 ± 0.38	1.33 ± 0.09	0.1386	1.63 ± 0.26	1.69 ± 0.25	.3078
L-T4 dose/weight (μg/kg per day)	1.82 ± 0.56	1.84 ± 0.35	0.8997	1.63 ± 0.41	1.81 ± 0.37	.0412
Serum TSH (IU/mL)	0.41 ± 0.57	0.94 ± 0.91	0.2009	1.23 ± 2.03	0.77 ± 1.04	.5485

BAP, bone alkaline phosphatase; β-CTX, β-cross laps; BMD, bone mineral density; BMI, body mass index; DTC, differentiated thyroid cancer; F-T4, free thyroxine; HypoPT, patients with hypoparathyroidism; L-T4, levothyroxine; Non-HypoPT, patients without hypoparathyroidism; PTH, parathyroid hormone; TBS, trabecular bone score; TSH, thyroid stimulating hormone; 25-OH-D, 25hydroxyvitamin D3.

* According to the presence of postsurgical hypoparathyroidism.

† n value too small to do statistics. β-CTX, β-cross laps

Table 4
Final bone densitometry and TBS values of premenopausal and postmenopausal patients who have undergone total thyroidectomy for differentiated thyroid cancer*

Parameters (mean ± SD)	Premenopausal DTC patients			Postmenopausal DTC patients		
	Non-HypoPT ($n=14$)	HypoPT ($n=3$)	P value†	Non-HypoPT ($n=84$)	HypoPT ($n=22$)	P value
LS-BMD (g/cm^2)	1.00 ± 0.12	1.17 ± 0.32	0.3135	0.86 ± 0.12	0.99 ± 0.15	.0001
FN-BMD (g/cm^2)	0.78 ± 0.11	0.97 ± 0.27	0.2568	0.68 ± 0.11	0.78 ± 0.11	.0007
TH-BMD (g/cm^2)	0.95 ± 0.10	1.11 ± 0.22	0.1856	0.84 ± 0.13	0.94 ± 0.13	.0027
1/3 DR-BMD (g/cm^2)	0.71 ± 0.04	0.69 ± 0.07	0.3135	0.59 ± 0.06	0.66 ± 0.05	< .0001
TBS	1.46 ± 0.08	1.43 ± 0.15	0.99	1.24 ± 0.12	1.31 ± 0.09	.0184
Duration (years)	10.6 ± 6.7	15.7 ± 9.2	0.4029	11.3 ± 5.9	11.1 ± 6.6	.7599
Incident Fractures‡	4 (29)	0	0.2230	18 (21)	3 (14)	.4143

DTC, differentiated thyroid cancer; HypoPT, patients with hypoparathyroidism; FN-BMD, femoral neck bone mineral density; LS-BMD, lumbar bone mineral density; Non-HypoPT, patients without hypoparathyroidism; TBS, trabecular bone score; TH-BMD, total hip bone mineral density; 1/3 DR-BMD, distal third of the radius bone mineral density.

* According to the presence of postsurgical hypoparathyroidism.

† n value too small to do statistics.

‡ Data presented as number (percentage).

different in either premenopausal or postmenopausal patients or in those with or without HypoPT (Table 3). The incidence of clinical vertebral fractures was numerically less in HypoPT patients, independent of their menopausal status (postmenopausal 3 and premenopausal none), compared with non-HypoPT patients (postmenopausal 18 and premenopausal 4) during the the study.

BMD, TBS, and bone turnover markers

At baseline, no significant differences were seen in BMD for premenopausal patients regardless of their parathyroid status (Table 2). In postmenopausal patients, no differences in baseline BMD were seen between HypoPT groups, except for LS-BMD (0.8 4 ± 0.15 g/cm^2 vs 0.93 ± 0.15 g/cm^2 for non-HypoPT and HypoPT patients, respectively; $P=.0473$).

At the final study visit, HypoPT status was not associated with differences in BMD or premenopausal patients (Table 4). In contrast, postmenopausal patients with HypoPT had greater BMD values compared with postmenopausal patients at all measured locations (LS-BMD (0.99 ± 0.15 g/cm^2 vs 0.86 ± 0.12 g/cm^2), FN-BMD (0.78 ± 0.11 g/cm^2 vs 0.68 ± 0.11 g/cm^2), TH-BMD (0.94 ± 0.13 g/cm^2 vs 0.84 ± 0.13 g/cm^2, and 1/3 R BMD (0.66 ± 0.05 g/cm^2 vs 0.59 ± 0.06 g/cm^2; $P < .0003$ each; Table 4). The percent change from baseline to the end of follow-up (Fig. 1) was greater in premenopausal patients with HypoPT compared with non-HypoPT patients at FN-BMD (17.1 ± 12.1% vs −2.6 ± 6.8%, $P=.0455$) and TH-BMD (23.9 ± 11.3 % vs 5.7 ± 6.8%, $P=.0451$). Baseline TBS measurements showed no HypoPT-associated differences in premenopausal or postmenopausal patients (Table 2). At the final study visit, HypoPT status was not associated with a difference in TBS in premenopausal patients, and the mean TBS of both groups was within the normal range (Table 4). Postmenopausal patients had TBS values consistent with a partially degraded microarchitecture, regardless of their HypoPT status. Mean TBS in postmenopausal patients was less for patients in the non-HypoPT group (1.24 ± 0.12) versus the HypoPT group (1.31 ± 0.09, $P=.0184$).

At baseline, serum levels of osteocalcin and BAP were not different in premenopausal patients, regardless of HypoPT status (Table 2). In postmenopausal patients, baseline osteocalcin levels were less in patients with HypoPT (5.36 ± 4.95 ng/ml), compared with non-HypoPT patients (9.16 ± 6.77 ng/ml, $P=.002$), as were baseline levels of BAP (7.34 ± 3.24 U/L vs 12.05 ± 4.83 U/Lm respectively, $P=.0022$), reflecting decreased bone turnover in those with HypoPT. At the final study visit, serum osteocalcin levels remained similar in premenopausal patients regardless of HypoPT status, although BAP levels were decreased in those with HypoPT versus non-HypoPT (19.2 ± 7.4 U/L vs 23.5 ± 10.0 U/L, respectively, $P=.0481$; Table 3). Final osteocalcin levels were also significantly less in postmenopausal HypoPT patients (15.4 ± 2.9 ng/ml)

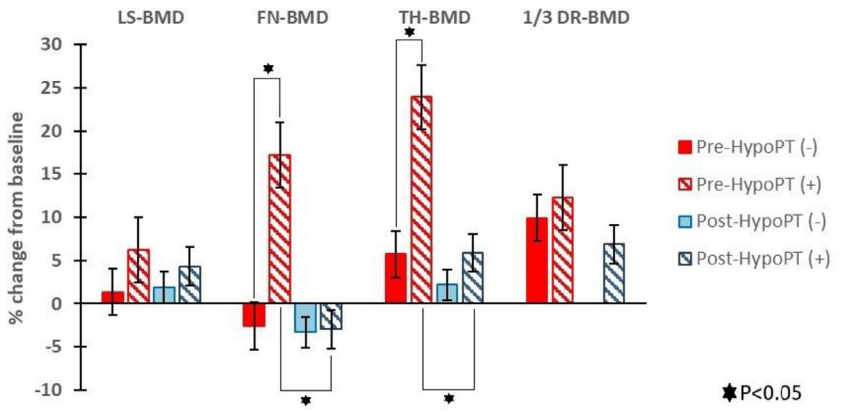

Fig. 1. Percent change from baseline in bone mineral density according to menopausal status and presence of hypoparathyroidism. Pre-hypoPT (–), premenopausal patients without hypoparathyroidism; pre-HypoPT (+), premenopausal patients with hypoparathyroidism; post-HypoPT (–), posmenopausal patients without hypoparathyroidism; post-HypoPT (+), postmenopausal patients with hypoparathyroidism. *FN-BMD*, femoral neck bone mineral density; *LS-BMD*, lumbar bone mineral density; *TH-BMD*, total hip bone mineral density; *1/3 DR-BMD*, distal third of the radius bone mineral density. Values are mean ± SD.

compared with non-HypoPT patients (21.0 ± 7.1 ng/ml, $P = .0009$), and BAP levels tended to be less in postmenopausal HypoPT patients compared with non-HypoPT patients (21.9 ± 11.8 U/L vs 26.2 ± 11.1 U/L, respectively, $P = .054$; Table 3). β-cross laps (β-CTX) values that were only measured in the final visit were not different in premenopausal patients, regardless of HypoPT status. In Postmenopausal patients with HypoPT, β-CTX values were not different from patients with non-HypoPT (0.12 ± 0.10 ng/ml vs 0.35 ± 0.19 ng/ml, respectively, $P = .0512$). Suppressed serum values of TSH were not different in HypoPT or non-HypoPT patients independent of their menopause status.

Association between BMD/TBS and clinical and biochemical characteristics

Age tended to be negatively correlated with TBS in patients with HypoPT ($r = -0.44$, $P = .0534$) and negatively correlated with non-HypoPT ($r = -0.50$, $P \leq .001$). BMI was only correlated with LS-BMD in postmenopausal patients ($r = 0.25$, $P = .0107$). There was a positive correlation between TBS and LS-BMD in patients with HypoPT ($r = 0.71$, $P = .0006$) and non-HypoPT patients ($r = 0.43$, $P \leq .0001$). Positive correlations were also found with other BMD sites (data not presented). Serum levels of free T4 were not associated with BMD or TBS. In contrast, LS-BMD was correlated with TSH levels ($r = 0.42$, $P = .0495$) in postmenopausal patients with HypoPT and with the duration of thyroid suppression therapy ($r = 0.42$, $P = .0342$) in premenopausal patients with HypoPT. TSH levels were not correlated with TBS.

Multiple linear regression analyses were performed to evaluate the independent association of clinical parameters with BMD and TBS. Age was associated with LS-BMD and TBS in postmenopausal patients with non-HypoPT ($\beta = 0.046$, $P \leq .0001$ and $\beta = 0.0033$, $P \leq .0001$, respectively). BMI was also associated to LS-BMD and TBS in postmenopausal patients with postsurgical non-HypoPT ($\beta = 0.0129$, $P \leq .0001$ and $\beta = 0.0033$, $P \leq .0001$, respectively). Serum levels of 25-OH-D did not modify associations in the multiple regression analysis. The association between the duration of thyroid suppressive therapy and BMD was not maintained after adjustment for age and BMI. No association with other bone parameters and TSH levels or doses were found after adjusting for BMI and the duration of thyroid suppressive therapy.

Discussion

To our knowledge, this is the first long-term study (>10 years) showing that compared with body weight–matched and age-matched postmenopausal non-HypoPT patients and postmenopausal patients with HypoPT attributable to a DTC–associated total thyroidectomy have significantly greater BMD and TBS measures. Moreover, this is one of the few studies that considers the effect of L-T4 and postsurgical HypoPT on the bone mass, bone turnover markers, and bone quality, with respect to menopausal status in patients for DTC. Of note, we observed that postsurgical HypoPT patients had a similar incidence of densitometric osteoporosis both at baseline and at follow-up (12% vs 12%), and in non-HypoPT patients, there was a deterioration in bone densitometry and an increase in osteoporosis comparing baseline to follow-up (19%–39%).

Other studies have shown similar results regarding the increased bone mass in patients with HypoPT. In a cross-sectional study using photon absorptiometry and spine dual-photon absorptiometry, Seeman et al[14] described a greater increase in axial BMD than in the appendicular skeleton in 15 patients with HypoPT secondary to operations for thyroid carcinoma. In this early study, duration of L-T4 therapy, duration of the disease, and level of thyroid suppressive therapy were considered. In another cross-sectional study, bone mass was also found to be greater (21%–28% in lumbar, proximal femur, and distal radius) by dual-photon absorptiometry in 13 HypoPT patients after total thyroidectomy compared with a control group without HypoPT.[15] All patients in this study were postmenopausal and were studied 9 years after total thyroidectomy. Although the authors suggested that the long-term use of L-T4 at doses that suppressed endogenous TSH was not associated with a decrease in bone mass, the study lacked baseline data as a comparator. Our own previous work in which we compared the effects on BMD in 20 HypoPT and 20 non-HypoPT women matched for age and BMI after a total thyroidectomy for thyroid cancer found both LS-BMD and FN-BMD to be increased in the HypoPT patients who were on L-T4 suppressive therapy compared with patients with normal parathyroid function after a mean follow-up of 78 months.[16]

Our present results are also consistent with previous reports of decreased bone remodeling in patients with HypoPT. A study by Duan et al[17] reported an increased BMD in the lumbar spine and proximal femur in eight patients with HypoPT who underwent a thyroid operation for thyroid cancer after 5 years of follow-up. The authors suggested that decreased PTH may decrease the bone loss associated with aging. These findings were supported in a later study by Chan et al,[18] who studied eight patients with idiopathic HypoPT and six with postsurgical HypoPT. Both groups of patients had increased BMD, which was attributed to an increase in bone mineralization secondary to suppressed bone turnover, as

suggested by the decreased levels of BAP. It should be noted, however, that in the study by Chan et al,[18] the age of patients ranged 23–57 years, but the menopausal status was not considered. In the present study, we found decreased levels of bone formation markers (osteocalcin and BAP) after more than a 10-year follow-up, which reinforces the hypothesis that bone remodeling is decreased in patients with postsurgical HypoPT. These findings are also consistent with bone histomorphometry studies that have shown an absence of detectable cell-based remodeling in patients with HypoPT treated with vitamin D.[19]

More recently, Kim et al[20] reported the effect of HypoPT on bone mass in 6 premenopausal and 50 postmenopausal women who had undergone total thyroidectomy for thyroid cancer after a follow-up of 12–18 months. Compared with patients with the same conditions, but with normal parathyroid function, women with postsurgical HypoPT had significantly greater values of BMD at the total hip, despite serum bone markers not showing any significant change during the follow-up period, in contrast to our and other studies.[16–18]

The reasons for the increase in bone mass and TBS in postmenopausal women with HypoPT after total thyroidectomy for DTC are unclear. As discussed earlier in this report, the lack of PTH in HypoPT patients induces a state of chronically low bone turnover in the spine, which is linked to increased BMD and distorted bone microarchitecture.[19] Furthermore, suppressive therapy with L-T4 could contribute to the alterations in the trabecular microstructure. Indeed, patients receiving L-T4 secondary to an operation for thyroid cancer have been found to have a greater risk of osteoporosis and fractures.[21,22] Despite these observations, there are controversial results regarding the fracture risk in postsurgical HypoPT. A decreased incidence of spinal deformity and greater BMD have been reported in patients with HypoPT after thyroidectomy for thyroid carcinoma.[23] Mendonça et al[8] reported recently an increased frequency of morphometric vertebral fractures in 16 postmenopausal women with postsurgical HypoPT compared with 17 age-matched and weight-matched controls, despite the absence of observable, between-group differences in LS-BMD or TH-BMD. In contrast, a large study of 688 postsurgical HypoPT patients found no difference in fracture risk compared with the general population.[7] In our study we found a numerically less incidence of vertebral fractures in postsurgical HypoPT patients compared with non-HypoPT patients, although the low sample size prevents a reliable statistical analysis of fracture risk in this population. In addition to the relatively low sample size, another limitation of our study is the absence of a control group of patients with a less aggressive dosing regimen of L-T4 replacement and, therefore, a decreased level of TSH suppression.

In summary, we found that after a long-term TSH suppression in postmenopausal patients with HypoPT after total thyroidectomy for thyroid cancer, there was less deterioration of bone microarchitecture by TBS and an increase in BMD compared with postmenopausal patients with normal parathyroid function. Our findings suggest that the lack of PTH provides protection against bone loss in postmenopausal patients with thyroid suppressive therapy and postsurgical HypoPT because of thyroid cancer.

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