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Original Article

Hylonome

Bone mineral density in hypoparathyroid women on LT_4 suppressive therapy. Effect of calcium and 1,25$(OH)_2$ vitamin D_3 treatment

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Abstract

Our aim was to study the bone mineral density (BMD) of patients with chronic hypoparathyroidism (hypoPTH) after long-term calcium and vitamin D treatment. Twenty hypoPTH women (mean±SD, aged 50±15 years, iPTH 4±6 pg/ml) and 20 matched euparathyroid women (euPTH) after near total thyroidectomy for thyroid cancer, completed with I-131 ablation and on suppressive therapy with L-Thyroxine (LT_4), were studied. In addition eight hypoPTH patients who were receiving LT_4 replacement therapy after surgery for compressive goiter were simultaneously studied. The hypoPTH patients were on calcium and 1,25$(OH)_2$ vitamin D_3 therapy to normalize serum calcium. Bone mineral density (BMD) (DXA, at the lumbar spine [L_2-L_4, LS], femoral neck [FN] and Ward triangle [WT]), serum and urine calcium, serum phosphorus, TOTALALP and osteocalcin were measured. Patients with hypoPTH showed greater lumbar BMD than euPTH patients on suppressive therapy (Z-score; 1.01±1.34 vs. -0.52±0.70, $p<0.05$). Serum osteocalcin levels were higher in hypoPTH patients on suppressive therapy compared to hypoPTH patients on replacement therapy. The LS BMD from hypoPTH patients correlated with calcium supplements ($r=0.439$; $p=0.02$), 1,25$(OH)_2D_3$ dose ($r=0.382$; $p=0.04$) and LT_4 dose ($r=0.374$; $p=0.05$). Our data suggest that long-term treatment with calcium and 1,25$(OH)_2$ vitamin D_3 supplements in hypoPTH patients on suppressive LT_4 therapy results in increased BMD when compared with patients with normal PTH levels.

Keywords: Hypoparathyroidism, Thyroid Hormones, Calcium, 1,25$(OH)_2$ Vitamin D_3, Bone Density, Bone Markers

Introduction

The adverse effects of L-Thyroxine (LT_4) therapy on bone mass and mineral metabolism are controversial. Although excess thyroid hormone stimulates bone resorption resulting in increased bone turnover and bone loss[1,2], the effect of prolonged LT_4 suppressive therapy on the skeleton has been reported from being neutral[3] to inducing a decrease in axial and appendicular bone mass[4]. Confounding variables such as parathyroid function, menopausal status, and prior history of hyperthyroidism may be partially responsible for such differences[5]. On the other hand, the treated hypoparathyroid (hypoPTH) condition could provide protection against age-related cortical and trabecular bone loss, due to the attenuation of the high turnover bone loss that occurs after menopause, and to the induction of a positive calcium balance[6-10].

The purpose of this study was to assess bone mineral density (BMD) and the osteoblastic function of thyroidectomized women with and without hypopararathyroidism, receiving suppressive doses of LT_4 due to thyroid cancer, and also to compare them with hypoPTH women on LT_4 replacement therapy after compressive goiter surgery, matched by sex, age, body mass index (BMI) and menopausal status.

Subjects and methods

Patients

Twenty hypoPTH female patients and twenty euparathyroid (euPTH) female patients (matched by age, body mass index

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	EuPTH on ST (n=20)	HypoPTH on ST (n=20)	HypoPTH on RT (n=8)
Age (years)	50±15	50±15	56±12
Postmenopausal Rate (%)	65.0	65.0	87.5
Duration of Menopause (years)	11±9	12±9	9±5
BMI (kg/m^2)	28.5±6,4	27.4±3.4	28.2±3.4
Duration of Hypo PTH (months after surgery)	--	78±46	78±86
LT4 Dose Dose (mg)	160±32*	160±33*	112±33
Accumulated Dose (mg)	325±215	389±260	218±233
Ca Dose (g/d)	--	2.35±0.43*	1.81±0.65
$1,25(OH)_2D_3$ Dose (μg/d)	--	0.52±0.20	0.53±0.25

HypoPTH: hypoparathyroid patients; EuPTH: patients with normal parathyroid function.
ST: Suppressive therapy; RT: Replacement therapy. *$p<0.05$ versus HypoPTH on RT.
Data are expressed as mean ± SD except for % values.

Table 1. Clinical characteristics of patients.

(BMI, calculated as BMI = weight (kg) / height^2 (m^2)) and menopausal status) after near total thyroidectomy for thyroid cancer completed with I-131 ablation and on LT_4 suppressive therapy were studied. Eight women with hypoparathyroidism secondary to debulking surgery for compressive goiter who were receiving LT_4 or replacement therapy were also evaluated in the same period. All patients were Caucasians and were regularly followed at our clinic. The study period comprised six months. All hypoPTH patients were receiving calcium (Calcium Sandoz Forte, Novartis) and $1,25(OH)_2$ vitamin D_3 (Rocaltrol, Roche) therapy to normalize serum calcium. The diagnosis of hypoparathyroidism was based upon low serum calcium and PTH levels on several different measurements, relief of muscular spasms by treatment with calcium and vitamin D, and inability to maintain normal serum calcium levels with a rapid return of symptoms when treatment was withdrawn. No patient was taking oral contraceptives, estrogen replacement therapy or any other medications that might affect bone density. None had a history of hepatic disease, alcoholism, osteoporotic fracture, early menopause or any other major medical condition. Patients with previous hyperthyroidism were excluded. All patients were informed about the nature of the study and gave informed consent. Our ethical committee approved the study.

Blood and urine analysis

Serum samples were obtained between 08:00 and 09:00 hours after overnight fast and were immediately processed and kept frozen at -20°C until the assays. Basal serum TSH assay was performed by IRMA (Medgenix Diagnostics, Belgium; lower detection limit 0.02μU/ml) and serum free thyroxine (FT_4) by RIA (Diagnostic Products Corporation, USA). Calcium, phosphate, and alkaline phosphatase (ALP) were measured by autoanalyzer (DAX 72 calorimetric method). Osteocalcin and intact parathyroid hormone (IPTH) were assayed by RIA (Nichols Institute Diagnostics, USA). Blood extraction was done the same day that bone densitometry was performed.

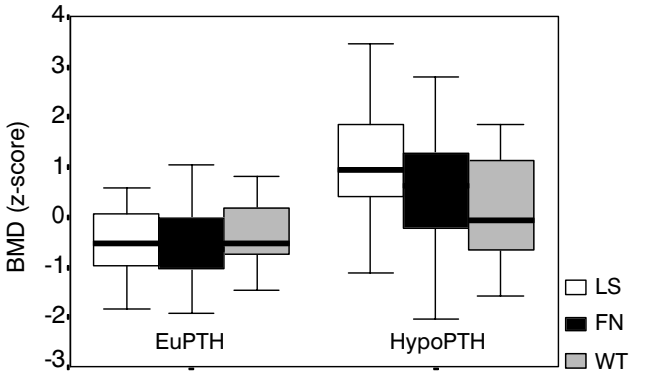

Figure 1. Bone mineral density (BMD, z-score) in treated hypoparathyroid (HypoPTH) and Euparathyroid (EuPTH) women on suppressive therapy with LT_4. LS: Lumbar spine (L_1-L_4); FN: femoral neck; WT: Ward triangle. *$p<0.05$ versus EuPTH; [#]$p<0.05$ versus 0.

Bone densitometry

Bone mineral density (BMD) was measured by dual X-ray absorptiometry using a QDR 1000/w absorptiometer (Hologic Inc., Waltham, MA, USA) in the lumbar spine (L_2-L_4; LS), femoral neck (FN) and Ward triangle (WT). The coefficient of variation for the BMD measurement at our center is 1.31% in the LS and 1.88% in the FN[11]. One thousand three hundred and thirty-one healthy Spanish females served to establish the mean BMD in the healthy population and to calculate the z-score for each BMD measurement (number of reference population standard deviations between the patient's BMD and the age- and sex-matched reference mean value)[12].

Statistical analysis

Results were analyzed using unpaired t-test to compare the mean of LS, FN and WT BMD expressed as z-score versus 0, one way analysis of variance to assess the differences among groups: eu- and hypoPTH patients on LT_4 suppressive therapy and hypoPTH patients on LT_4 replacement therapy, and simple regression analysis or Spearman correlation analysis to assess the relationship between BMD and different variables) as appropriate, using SPSS (8.0 for Windows) software (SPSS Inc., Chicago, IL).

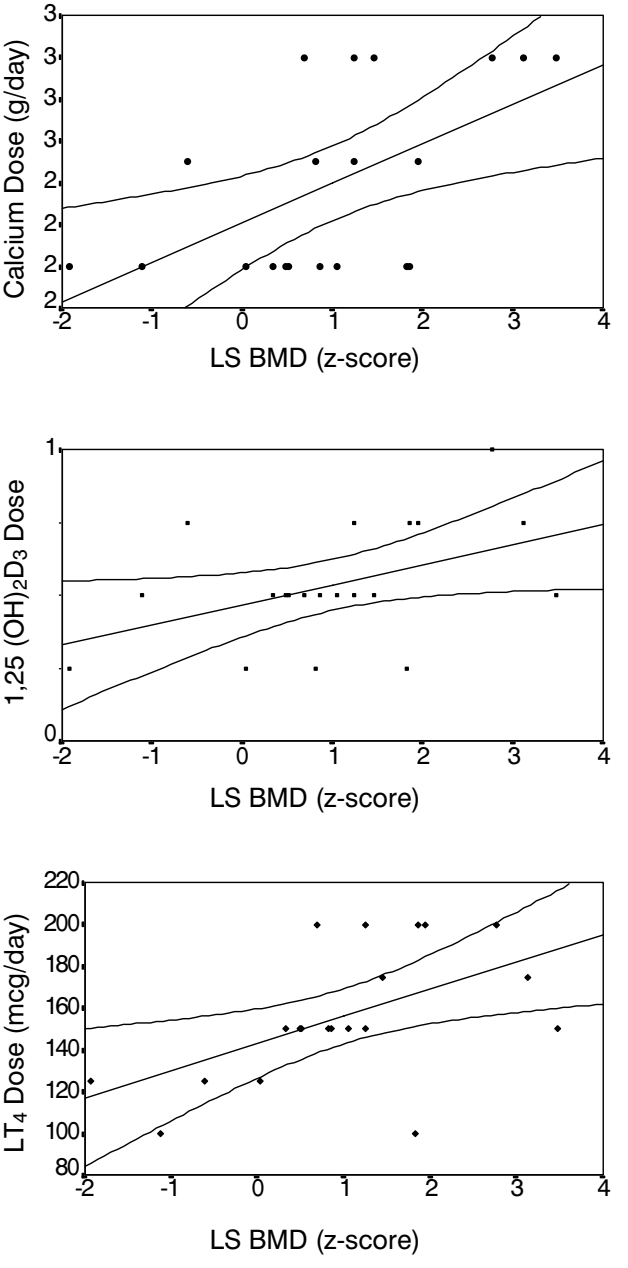

Figure 2. Correlation between lumbar spine BMD (LS, L_1-L_4, z-score) with calcium supplements (CS; $r=0.439$; $p=0.02$), $1,25(OH)_2$ vitamin D_3 supplements (DS; $r=0.382$; $p=0.04$) and LT_4 dose (TD; $r=0.374$; $p=0.05$).

Results

The clinical characteristics of the patients are shown in Table 1. As expected from matched selection, hypoPTH and euPTH patients on LT_4 suppressive therapy showed similar age, percentage of posmenopausal women, duration of menopause, BMI, LT_4 dose and accumulated LT_4 dose. HypoPTH patients on LT_4 replacement therapy were somewhat older and the percentage of postmenopausal women was higher, but these differences did not reach statistical significance. LT_4 dose was significantly lower in hypoPTH patients on replacement therapy.

Biochemical and bone mass data are shown in Table 2. Serum calcium, phosphorus, IPTH and 24h urine calcium were significantly different between euPTH and hypoPTH patients. HypoPTH patients on LT_4 replacement therapy showed higher TSH and lower osteocalcin levels than the patients on suppressive therapy. LS and FN BMD were higher in hypoPTH

	EuPTH on ST (n=20)	HypoPTH on ST (n=20)	HypoPTH on RT (n=8)
sCa (mg/dl)	9.3±0.6*	8.5±0.7	8.9±0.6
sP (mg/dl)	4.1±0.8*H	4.4±0.6	4.6±0.8
iPTH (pg/ml)	48±24*H	4±6	3±4
FT_4 (ng/dl)	1.92±0.46	2.01±0.57	1.54±0.28
TSH (μU/ml)	0.22±0.39H	0.42±0.47H	1.92±1.26
Osteocalcin (ng/ml)	5.2±1.7	6.5±4.4	2.6±2.2*
ALP (U/I)	97±37	95±15	113±22
24h uCa (mg/24h)	126±83*	219±90	285±126
LS BMD (z-score)	-0.52±0.70*I	1.01±1.34I	0.48±0.97
FN BMD (z-score)	-0.37±1.06	0.55±1.14*	0.57±1.23
WT BMD (z-score)	-0.33±0.66I	0.12±1.07	-0.10±0.93

HypoPTH: hypoparathyroid patients; EuPTH: patients with normal parathyroid function. ST: Suppressive therapy; RT: Replacement therapy. *p<0.05 versus HypoPTH on ST; Hp<0.05 versus HypoPTH on RT; Ip<0.05 versus 0. Reference values: Serum Calcium (sCa): 8.4-10.2 mg/dl; serum phosphorus (sP): 2.3-4.6 mg/dl; iPTH 13-54 pg/ml; FT_4: 0.85-2.01 ng/dl; TSH: 0.5-5.0 μU/ml; osteocalcin: 2.4-10.0 ng/ml; alkaline phosphatase (ALP): 30-115 U/I, 24 hours urine calcium (24hUCa):<250 mg/24h. LS-BMD: Lumbar spinal, FN-BMD: Femoral neck, WT: Ward triangle bone mineral density. Data are expressed as mean ± SD.

Table 2. Biochemical and densitometrical characteristics of patients.

females on suppressive therapy (95% confidence interval (CI), LS: (0.38; 1.64), FN: (0.01;1,08)), whereas LS and WT BMD were lower in euPTH females on suppressive therapy (95% CI, LS: (-0.85; -0.20), WT: (-0.64; -0.02)). HypoPTH females on LT_4 replacement therapy showed normal BMD. When direct comparisons where made, only lumbar bone mass was significantly higher in hypoPTH females on LT_4 suppressive therapy compared to euPTH females on LT_4 suppressive therapy (Figure 1).

FN BMD from hypoPTH patients significantly correlated with the BMI (r=0.367, p=0.05), meanwhile the LS BMD showed positive correlation with calcium supplements (r=0.439; p=0.02) and $1,25(OH)_2D_3$ supplements (r=0.382; p=0.04) (Figure 2).

Discussion

Up to now, few data are available regarding the bone effects of calcium and $1,25(OH)_2$ vitamin D_3 therapy in hypoPTH. We have shown a slightly decreased FN BMD in euPTH women on LT_4 suppressive therapy, a normal FN and LS BMD in hypoPTH women on LT_4 replacement therapy and an elevated LS BMD in treated hypoPTH women receiving suppressive doses of LT_4 (p<0.05 vs. hypoPTH with suppressive LT_4 therapy). These elevated BMD values are probably multifactorial in their origin. We confirm, therefore, earlier findings in patients with primary and secondary hypoPTH after thyroid or parathyroid surgery that have shown higher bone mass when treated with calcium and vitamin D analogs[6,7,10,13,14].

In hypoPTH menopausal women on LT_4 suppressive therapy after total thyroidectomy due to thyroid carcinoma, calcium and 1-α(OH) vitamin D_3 treatment has been associated with higher bone density and lower spinal deformation index[6]. It is possible that the accelerated bone loss after menopause can be attenuated in these patients, indicating a reduced remodeling rate with this therapy. The hypothetical PTH-independent effects of vitamin D analogs to reduce bone turnover in this setting can not be discarded. In our study, calcium and $1,25(OH)_2D_3$ supplements correlated with LS BMD, although these correlations are likely to reflect the severity of hypoPTH or other interfering, underlying conditions. In fact, vitamin D receptors have been found in osteoblasts, and, in normal subjects, vitamin D stimulates both the number and activity of osteoblasts[15,16]; nevertheless a skeletal anabolic effect *in vivo* has never been demonstrated. On the other hand, the femoral neck BMD correlated with BMI showing the well-known protective effect of body weight on bone mass[17].

It is well known that thyroid hormone excess can stimulate bone turnover, with increased serum calcium and reduced serum levels of PTH and $1,25(OH)_2D_3$[18], resulting in bone loss[1,2] even after euthyroidism is attained[19]. In this setting of low levels of active vitamin D and PTH, hypoPTH patients on LT_4 suppressive therapy could be especially sensitive to the skeletal effects of the active vitamin D[20], a therapy, at least in part, substitutive.

This fact may explain the low levels of serum osteocalcin, a reflex of osteoblast activity and bone remodeling, that has been previously described in hypoPTH patients on LT_4 replacement therapy[6,7], and the differences shown in the present study between osteocalcin levels from hypoPTH patients on LT_4 suppressive or replacement therapy. These data also confirm the lack of $1,25(OH)_2D_3$ stimulating effect on osteocalcin secretion in the absence of PTH[7,9]. Histomorphometrical studies have also shown that vitamin D alone is not able to restore the normal bone turnover in hypoPTH patients[21]. Thus the osteocalcin-stimulatory effect of vitamin D is missing when PTH is absent, but may be partially restored in the high turnover state induced by suppressive therapy with LT_4 in these patients. Nevertheless, the long-term stimulatory effect of $1,25(OH)_2D_3$ treatment on osteocalcin production has never been shown. Actually there is evidence that it decreases bone turnover and osteocalcin levels in euthyroid people.

To limit potential biases in the selection of the study population, we have only excluded men, patients with previous hyperthyroidism who show long-term bone loss and a higher risk to present osteoporotic fractures[22], as well as patients with previous primary hyperparathyroidism, who show net gain of bone mass after surgical treatment[23]. All the patients included in the present series were postmenopausal women on long-term LT_4 suppressive therapy, and were compared with a matched population of euPTH patients who were also on LT_4 suppressive therapy. None of the patients was taking estrogens or medications that might affect bone density other than calcium, thyroid hormones and $1,25(OH)_2D_3$ and none of them had a history of early menopause. Our study, although cross-sectional, included patients with a long-term therapy period and z-scores were obtained using national standards.

In conclusion, long-term treatment with calcium and $1,25(OH)_2$ vitamin D_3 supplements in hypoPTH women on LT_4 suppressive therapy results in increased BMD, meanwhile hypoPTH women on LT_4 replacement therapy show normal bone mass and euPTH women on LT_4 suppressive therapy show low bone mass. The higher BMD observed in hypoPTH women may be related to a global skeletal effect of LT_4 suppressive and $1,25(OH)_2$ vitamin D_3 therapies. Further studies with longer follow-up and larger samples are probably necessary to establish if bone loss is reduced in hypoPTH subjects with LT_4 therapy and combined calcium and vitamin D treatment as suggested in our study.

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