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Original Article

Longitudinal Changes in Bone Density in Hyperparathyroidism

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Abstract

Primary hyperparathyroidism (HPTH) is a known risk factor for cortical bone loss. The primary objective of this study was to examine the time course and location of changes in bone mass within the first year after parathyroidectomy (PTX). The secondary goal was to evaluate the efficacy of combined estrogen therapy and parathyroidectomy in postmenopausal women. Thirty-two subjects with primary HPTH participated in a prospective, longitudinal study for at least 1 yr. Twenty-seven subjects underwent PTX, while five received no therapy (control). Among the PTX patients, 21 were postmenopausal women, and 8 of these women also received estrogen. Subjects had serial measurements of parathyroid hormone levels, serum chemistries, and bone density at multiple sites. Among all PTX patients, lumbar spine, hip, and whole body bone mineral content increased significantly (3.8–6%; $p < 0.005$) at 12 mo, with most of the increments observed by 3 mo. In postmenopausal women, estrogen treatment resulted in higher increments in the femoral neck ($8.6 \pm 2\%$ vs $4.9 \pm 1.2\%$, respectively; $p = 0.07$) and the whole body ($6 \pm 2\%$ vs 2.4 ± 1.6 %, respectively; $p = 0.07$). In HPTH, early and generalized increments in bone mass follow PTX, and the combination of surgery with estrogen therapy may be superior to surgery without estrogen treatment. A randomized, controlled trial including PTX, estrogen, and a combination of the two is needed to determine the optimal therapy in postmenopausal women.

Key Words: Hyperparathyroidism; surgery; hormone replacement therapy; bone density; bone turnover; guidelines.

Introduction

Hyperparathyroidism (HPTH) is the third most common endocrine disorder and presents as asymptomatic disease in the majority of patients *(1).* A significant number of asymptomatic patients have osteopenia, which may be accentuated at skeletal sites enriched in cortical bone *(1–7).* The optimal treatment of asymptomatic HPTH is debatable *(8–10).* Studies evaluating the effect of no intervention on bone mass have yielded conflicting results *(3,11–15);* however, prospective studies of patients undergoing parathyroidectomy (PTX) have shown significant increments in bone mineral density (BMD), although BMD is not restored to normal *(3–6,16–18).* The temporal onset of BMD increments within the first year after PTX, and the impact

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of surgery on whole body bone mineral content (WB BMC) is unclear.

HPTH is especially common among postmenopausal women, a group already at elevated risk for osteoporosis. Such patients who have even mild HPTH may be at particular risk for bone loss faster than that in age-matched, eucalcemic controls subjects *(15).* Hormone replacement therapy (HRT) increases BMD in patients with HPTH *(3,7,19–21).* A recent nonrandomized study suggested that the efficacy of HRT in increasing BMD was comparable to that of PTX *(3).* Two preventive studies of osteoporosis in early postmenopausal women suggested that a combined approach using two antiresorptive agents, namely estrogen with calcitonin or etidronate, increased BMD more than treatment with one agent alone *(22,23).* PTX can be likened to the administration of an antiresorptive agent in that it decreases the bone resorptive pool. Estrogen administration in combination with PTX may therefore raise BMD more than PTX alone. However, this hypothesis has never been tested.

In 1990 a panel of experts published guidelines for the management of asymptomatic HPTH *(24).* The Consensus Development Conference Panel recommended considering PTX for patients meeting any of the following criteria:

1. A serum Ca level exceeding 12 mg/DL
2. A history of acute hypercalcemic crisis, hypercalciuria, kidney stones, or nephrocalcinosis
3. Reduced creatinine clearance with no known explanation
4. A BMD more than 2 standard deviations (SDs) below that of age-matched control subjects
5. An age of <50 yr

Although some physicians abide by these BMD guidelines, several investigators have followed a less conservative approach, intervening when bone loss was less severe *(3,5,18,21,25).*

This study aimed primarily to evaluate the following questions: (1) What is the temporal onset of BMD changes within the first year after PTX? and (2) Does PTX increase BMD at all sites at which measurements are made? These were secondary questions: (1) Is a combined approach with PTX and estrogen therapy superior to PTX alone? and (2) Is the BMD response to PTX of subjects who do not meet the expert panel's BMD criterion for surgical intervention ($Z > -2$) similar to that of patients who do ($Z < -2$)?

Materials and Methods

Design

This longitudinal, prospective, observational study included patients diagnosed with HPTH who received their care at the Brigham and Women's Hospital (BWH) between 1991 and 1995.

Subjects

All individuals who were diagnosed with HPTH and who were receiving their care through the Endocrine-Hypertension Division and the Surgery Department at BWH were invited to participate in the study. The decision about whether to treat a given patient conservatively (without intervention; control group), with PTX, or with PTX and estrogen (PTX/E) was made by the subject's primary care physician independent of study entry.

Before enrollment, each subject underwent a physical examination and a laboratory evaluation that included a multichannel serum chemistry analysis, a complete blood count with differential, and an intact parathyroid hormone (iPTH) determination. Exclusion criteria included a history of bisphosphonate or fluoride intake within 1 yr of the start of this protocol or the use of any medications that can affect bone turnover (vitamin D, >1000 IU/day; vitamin A, >5000 IU/day; anabolic steroids, glucocorticoids, anticonvulsants, thiazides, and calcitonin). Patients with rheumatoid arthritis or excessive alcohol intake (>2 drinks per day) were also excluded. The data presented pertain to the 32 subjects who completed at least 1 yr of the study. Nineteen other subjects enrolled but did not complete 1 yr: 4 subjects in the control group (1 premenopausal woman and 3 postmenopausal women) and 15 subjects in the PTX group (12 women—5 pre-, 1 peri-, and 6 postmenopausal—and 3 men). The main reason for failing to complete 1 yr of study was unwillingness to return for BMD measurements because of the time commitment involved ($n = 13$). In addition, one subject had severe tremor leading to motion artifacts that rendered BMD measurements impossible, four subjects were started on antiresorptive therapy, and

Table 1
Baseline Characteristics of All Study Subjects[a]

All study participants	PTX (n = 27)	Control (n = 5)
Female/male *(n)*	25/2	2/3
Age (yr ± SD)	56.7 ± 9.7	64.6 ± 12.6
Weight (lb ± SD)	163 ± 39.2	165 ± 17.3
Dietary Ca intake (mg/d)	765 ± 80	450 ± 35
Serum Ca level (mg/dL)	10.6 ± 0.12	10.9 ± 0.23
Serum iPTH level (pg/mL)	96.6 ± 8.1	127.4 ± 31.2
Serum 25(OH)D level (ng/mL)	14.9 ± 1.0	15.7 ± 3.8
Serum 1,25$(OH)_2$D level (pg/mL)	55.8 ± 4.0	55.8 ± 11.1
Osteocalcin (ng/L)	14.2 ± 2.2	12.3 ± 3.3
Postmenopausal women	**PTX/E (n = 8)**	**PTX (n = 13)**
Age (yr ± SD)	55.8 ± 8.9	60.1 ± 5.5
Postmenopausal (yr ± SD)	9.7 ± 7.0	13.6 ± 10.1
Weight (lb ± SD)	150 ± 12.6	162 ± 45.1
Dietary Ca intake (mg/d)	686 ± 135	774 ± 122
Serum Ca level (mg/dL)	10.8 ± 0.12	10.6 ± 0.22
Serum iPTH level (pg/mL)	83.3 ± 11.0	102.5 ± 14.5
Serum 25(OH)D level (ng/mL)	13.7 ± 1.8	14.0 ± 1.7
Serum 1,25$(OH)_2$D level (pg/mL)	62.8 ± 5.7	46.8 ± 7.3
Osteocalcin level (ng/L)	15.5 ± 5.4	12.6 ± 2.0

[a] Values are mean ± SEM unless otherwise noted.

one subject had severe joint pain and shortness of breath after PTX. The baseline characteristics of these subjects including BMD measurements were not significantly different from those of study participants (as outlined in Tables 1 and 2) except that the WB BMC was higher in PTX patients who dropped out.

The study was reviewed and approved by the Committee for the Protection of Human Subjects at BWH. Informed written consent was obtained from each subject before participation.

Procedures

All subjects had lumbar spine, femoral neck, trochanter, and forearm ($^1/_3$ radius) BMD as well as WB BMC measured by dual X-ray absorptiometry (model QDR 1000W/2000, Hologic, Waltham, MA) at study entry and at 3, 6, and 12 mo thereafter. Eleven subjects had all of their measurements taken with the QDR 1000W, 9 subjects had their measurements taken with both the QDR 1000W and the QDR 2000, and 12 subjects had their measurements taken with the QDR 2000. As a result of careful cross-calibration of machines, no stepwise changes were introduced into the BMD measurements at the lumbar spine, femoral neck, and trochanter or into the measurements of WB BMC. A conversion formula derived at our institution from the cross-calibration procedure was used for forearm BMD measurements. The precision for spine and proximal femur BMD measurements at our center is 1.2% *(26)* and for total body BMC is 0.99% *(27)*.

The BMD values measured are presented in actual units (g/cm^2), as Z scores (number of SDs below values for age-matched controls), and as T scores (number of SDs below peak BMD values). The lumbar spine BMD values for five subjects (two in the control group, three in the PTX group) with severe osteophytes of the vertebrae, vertebral fractures, and/or fusion of lumbar vertebrae were not included in the analyses; however, their values for the other sites were evaluated and included.

Table 2
Baseline BMD Data for All Study Subjects

	PTX	Control
Lumbar spine		
BMD (g/cm^2)[a]	0.86 ± 0.03	1.12 ± 0.22
Z score[a]	–0.58 ± 0.25	1.39 ± 1.56
T score[a]	–1.67 ± 0.29	0.49 ± 1.93
Femoral neck		
BMD (g/cm^2)	0.64 ± 0.02	0.76 ± 0.10
Z score[a]	–1.15 ± 0.16	0.07 ± 0.59
T score	–2.58 ± 0.19	–1.77 ± 0.80
Trochanter		
BMD (g/cm^2)[a]	0.57 ± 0.02	0.69 ± 0.10
Z score	–0.94 ± 0.18	0.03 ± 0.77
T score	–1.78 ± 0.20	–0.84 ± 0.89
Forearm ($^1/_3$ radius)		
BMD (g/cm^2)	0.60 ± 0.02	0.62 ± 0.04
Z score	–0.66 ± 0.29	–0.87 ± 0.82
T score	–1.68 ± 0.33	–2.78 ± 0.61
WB BMC (g)[b]	2053 ± 90	2199 ± 236

[a] $p < 0.05$ PTX compared with control.
[b] *Z* and *T* scores not provided in the current bone densitometer database software.

The subjects' mean dietary Ca intakes were evaluated by a Ca questionnaire generated by the General Clinical Research Center dietitian and administered at study entry and 12 mo afterward.

Laboratory Tests

Serum Ca levels were determined by the clinical chemistry laboratory by a colorimetric method with an Olympus AU-5061 analyzer (Olympus, Lake Success, NY).

Serum iPTH levels were measured by the Allegro immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). The detection limit of the assay is 1.0 pg/mL (normal range: 10–65 pg/mL), and the intra- and interassay coefficients of variation (CV%) are 1.7 and 6.5% at iPTH concentrations of 37.7 and 44.1 pg/mL, respectively.

Serum 25-hydroxyvitamin D [25(OH)D] was measured by a competitive protein-binding assay (normal range: 10–55 ng/mL). A radioreceptor assay kit (Nichols Institute) with the 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] receptor from calf thymus was used for the 1,25(OH)$_2$D assay (normal range: 15–65 pg/mL). For 25(OH)D, the intraassay CV% is between 8.7 and 8.9% at serum concentrations of 12 and 53 ng/mL, respectively, and the interassay CV% is 12% at a serum concentration of 49 ng/mL. For 1,25(OH)$_2$D, the intraassay CV% is 8.7% at a concentration of 34 pg/mL, and the interassay CV% is 13.2% at a concentration of 43 pg/mL. All samples from each patient were run in duplicate and in the same assay.

Serum osteocalcin levels were determined with a radioimmunoassay *(28)*. The detection limit is 0.5 µg/L, and intra- and interassay CV% are 2.3 and 8.3%, respectively. Osteocalcin concentrations range from 2 to 12 µg/L in normal men and premenopausal women, and the upper range is up to 15 µg/L in postmenopausal women.

Parathyroid Exploration

Cervical exploration by a single parathyroid surgeon was performed through a cervical incision with the goal of identifying four parathyroid glands. Abnormal parathyroid glands were removed on the basis of gross comparative appearance as well as frozen-section confirmation. In patients with an adenoma, two or three normal parathyroids were biopsied. In patients with hyperplasia, subtotal PTX was performed. No preoperative imaging studies were routinely conducted.

Statistical Analyses

Baseline characteristics of the study groups were compared by two-tailed *t*-tests. Spearman correlation analyses were performed between baseline variables (BMD, osteocalcin, parathyroid hormone) and percentage of change in BMD at 1 yr. Mixed model analyses using the SAS system (Version 6.11) *(29)* were used to evaluate the effects of the treatments (e.g., PTX, PTX/E, control) between groups and within subjects. Reported *p* values were not adjusted for multiple comparisons of BMD measurements at several skeletal sites. The analyses were performed on absolute BMD values at baseline, 3, 6, and 12 mo. The results are presented as absolute and percentage changes in BMD. To facilitate comparison with other studies, the figures show percentage changes in BMD. Standard errors of the mean are presented unless otherwise stated.

Results

Clinical Characteristics of All Study Subjects

Thirty-one Caucasian subjects and one African American subject completed at least 1 yr of the study. The majority of the 27 patients who underwent PTX were women (4 pre- and 21 postmenopausal). Five subjects (2 men) received no intervention.

Thirty-one subjects had mild HPTH, with a mean serum Ca level of <11.5 mg/dL (Table 1), and one subject had a serum Ca level of 12.2 mg/dL. There were no significant differences in the baseline demographics of the PTX and control groups (Table 1). Twenty-six of the 27 subjects who underwent PTX and all the control subjects were osteopenic (BMD *T* score <–1 SD) at one or more skeletal sites (Table 2) *(30)*. The PTX group was modestly to severely osteopenic, depending on the site measured, whereas the control group had less severe osteopenia. The differences between the two groups were significant at the lumbar spine BMD *T* and *Z* scores, at the femoral neck *Z* score, and at the trochanter BMD (Table 2).

Clinical Characteristics of Postmenopausal Women Who Underwent PTX

Table 1 gives the baseline characteristics of these postmenopausal women who underwent PTX. Of the eight women who underwent PTX and also received estrogen therapy (the PTX/E group), six started taking estrogen within 12 wk after surgery, whereas two had begun taking estrogen 0.5 and 18 yr before surgery, respectively. It is not known whether the expected protective effect of estrogen therapy on BMD in patients undergoing PTX is related or unrelated to the timing of its initiation. Therefore, we included all women taking estrogen in the PTX/E group, whether they started such therapy before or within 12 wk post-PTX. The two women who started taking estrogen before PTX had slightly, although not significantly, higher BMD *T* scores at the lumbar spine, hip, and whole body sites than the six patients who started taking estrogen after PTX ($p = 0.6$, 0.12, and 0.5, respectively). There were no differences in the baseline characteristics of the two groups of postmenopausal women including absolute BMD, *T* scores, and *Z* scores at all sites measured (data not shown).

Calcium and iPTH levels normalized postoperatively in all subjects who underwent PTX. Pathologic studies revealed an adenoma in 21 subjects, double adenomas in 2, glandular hyperplasia in 3, and uncertain pathology (read as adenoma or hyperplasia) in 1. Calcium and iPTH levels in the control group did not change over the course of the year.

Eligibility for Surgery According to Consensus Panel Guidelines

Of the 27 subjects who ultimately underwent PTX, 22 were asymptomatic, 9 had hypercalciuria, 5 were <50 yr of age, 8 had a BMD *Z* score of <–2 SD in at least one skeletal site, 3 had nephrolithiasis, 1 had an elevated serum Ca level >12 mg/dL, and 1 had a fracture. At least one of the panel's criteria guidelines was met by 16 subjects: 11 subjects met only one criterion, 3 met two criteria, and 2 met three criteria.

Changes in BMD

PTX and Controls

For the PTX group, there were significant increments (3.8–6%) in BMD at the lumbar spine, femoral neck, and trochanter as well as in WB BMC ($p < 0.005$; Fig. 1). In contrast, the BMD in the forearm did not change significantly. For the PTX group at 0 and 12 mo, respectively, the lumbar spine BMD values were 0.86 ± 0.03 and 0.90 ± 0.03 g/cm^2, the femoral neck BMD values were 0.64 ± 0.02 and 0.68 ± 0.02 g/cm^2, the trochanter BMD values were 0.57 ± 0.02 and 0.59 ± 0.02 g/cm^2, and the WB BMC values were 2053 ± 90 and 2107 ± 102 g. The increments in BMD were substantial by 3 mo (varying between 4.7 and 6.7%, depending on the skeletal site) and were almost at their maximum 6 mo after PTX. Controls showed a decrease in lumbar spine BMD and WB BMC by 12 mo of 3 and 2.4%, respectively, which was almost significant for the WB BMC ($p = 0.051$). For the control group, the lumbar spine, femoral neck, and trochanter BMD values and total body mineral content at 0 and 12 mo were 1.12 ± 0.22 and 1.09 ± 0.2 g/cm^2, 0.76 ± 0.1 and 0.79 ± 0.11 g/cm^2, 0.69 ± 0.1 and 0.72 ± 0.12 g/cm^2, and 2199 ± 236 and 2139 ± 212 g.

PTX/E vs PTX Only

There were significant increments in lumbar spine, femoral neck, and trochanter BMD in the PTX

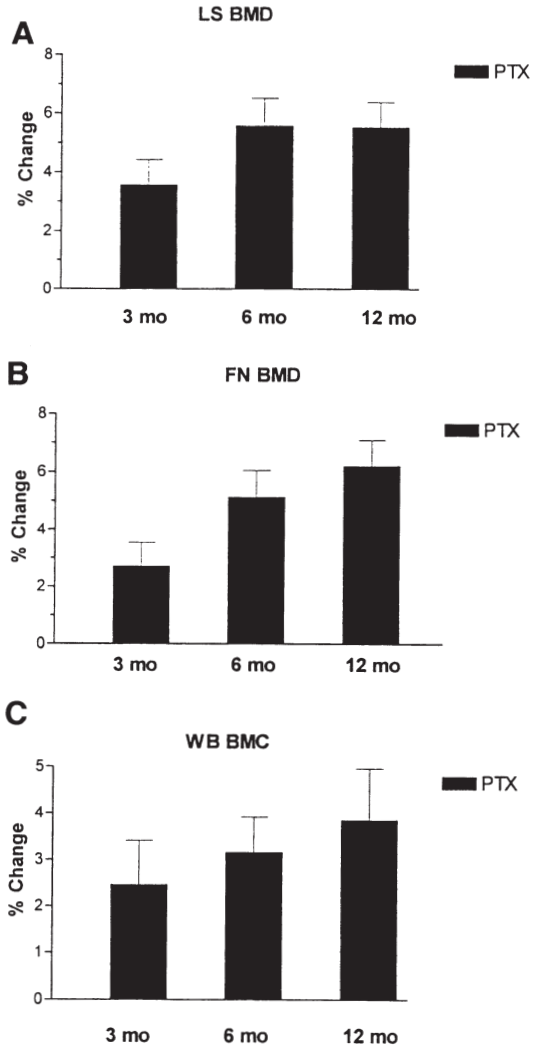

Fig. 1. (A) Comparison of changes of lumbar spine (LS) BMD, **(B)** femoral neck (FN) BMD, and **(C)** whole body bone mineral content (WB) BMC in parathyroidectomized (PTX) patients. $p < 0.005$ vs baseline for all time points and skeletal sites.

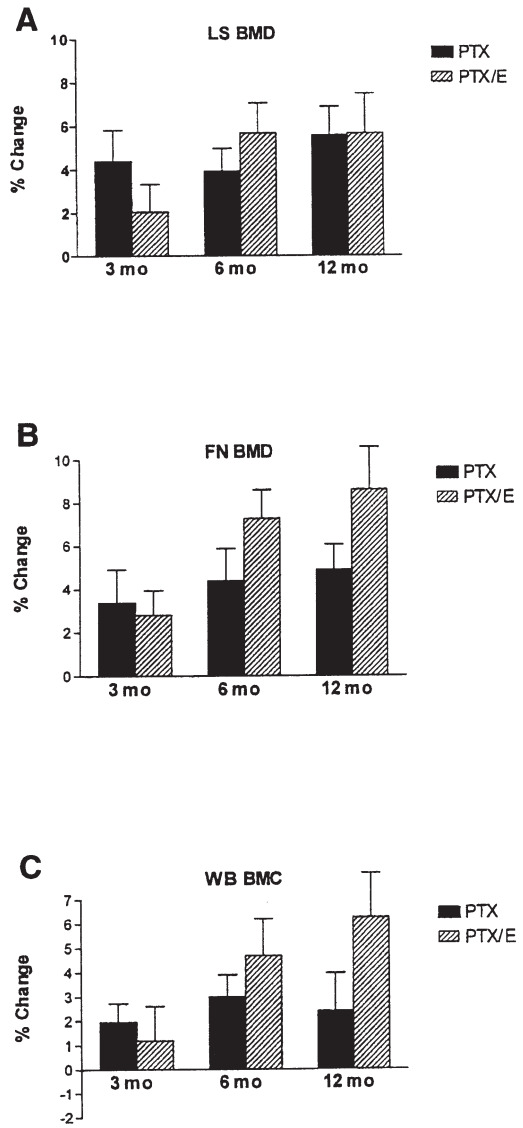

Fig. 2. (A) Comparison of changes in the lumbar spine (LS) BMD, **(B)** femoral neck (FN) BMD, and **(C)** whole body mineral content (WB) BMC in subjects who received parathyroidectomy (PTX) and PTX and estrogen (PTX/E). $p < 0.002$ vs baseline for the PTX group at all time points and skeletal sites; $p < 0.02$ vs baseline for the PTX/E group at all time points and skeletal sites.

group (2.0–5.6%, $p < 0.002$) and the PTX/E group (5.0–8.6%, $p < 0.02$) (Fig. 2). The forearm BMD did not change significantly in either group. For the PTX group at 0 and 12 mo, respectively, the lumbar spine BMD values were 0.77 ± 0.03 and 0.81 ± 0.03 g/cm^2, the femoral neck BMD values were 0.61 ± 0.02 and 0.64 ± 0.02 g/cm^2, the trochanter BMD values were 0.53 ± 0.02 and 0.55 ± 0.02 g/cm^2, and the WB BMC values were 1851 ± 100 and 1911 ± 111 g. For the PTX/E group at 0 and 12 mo, the corresponding pairs of values were 0.88 ± 0.053 and 0.93 ± 0.053 g/cm^2, 0.64 ± 0.04 and 0.69 ± 0.032 g/cm^2, 0.57 ± 0.03 and 0.60 ± 0.03 g/cm^2, and 2109 ± 126 and 2206 ± 184 g. Comparison of the two groups revealed slightly higher increments in BMD for the femoral neck and the WB BMC in the PTX/E group

($p = 0.07$). This trend was present at other sites measured (lumbar spine and trochanter), although it was not significant.

Evaluation of Patients BMD Response Stratified by Consensus Panel Guidelines

Nineteen of the 27 subjects who ultimately underwent PTX in our study did not meet the Consensus Development Conference Panels BMD criterion for surgical intervention (i.e., did not have a *Z* score <–2) in any of the skeletal sites measured *(24).* Forty-seven percent of these subjects were osteopenic and 53% were osteoporotic by World Health Organization (WHO) criteria *(30).* Of those who did not have a *Z* score of <–2, *T* scores were <–2.5 (osteoporotic by WHO criteria; *see* ref. *30*) in two, two, and nine subjects at the lumbar spine, trochanter, and femoral neck sites, respectively.

The BMD percentage change values in the 19 subjects not fulfilling the panels BMD criterion for surgery (*Z* score >–2) were 4.8% for the lumbar spine, 5.8% for the femoral neck, 4.3% for the trochanter, –0.5% for the forearm, and 2.6% for WB BMC. For the eight subjects who did meet the panel's BMD criterion (i.e., *Z* score <–2), their respective values were 7.4%, 7.1%, 6.2%, 2.4%, and 5.7%. The percentage change in BMD at the various sites were not significantly different between the two groups.

Correlation of Baseline Biochemical Parameters and BMD Changes at 1 yr

Baseline iPTH levels were significantly correlated with percentage change in spine and trochanter BMD at 1 yr: $R = 0.49$ ($p = 0.015$) and $R = 0.49$ ($p = 0.01$), respectively. Baseline OC levels were also significantly correlated with percentage change in spine and trochanter BMD at 1 yr: $R = 0.7$ ($p = 0.001$) and $R = 0.49$ ($p = 0.03$), respectively.

Discussion

In this study, we demonstrated that substantial BMD increments occur early (3–6 mo) after PTX at several sites, including the lumbar spine, femoral neck, and trochanter. In addition, we documented significant increases in WB BMC. By contrast, the corresponding values in controls did not change significantly. The consistent trend toward further increments in BMD at all sites except the forearm in postmenopausal women receiving HRT in addition to undergoing PTX is encouraging and needs further evaluation.

The magnitude of increments in BMD after PTX in our study is consistent with results reported by some investigators *(3,5,18)* but is less than that of increments measured in two other studies *(6,17).* The reason for this discrepancy is not clear, but it may be partially explained by the severity of osteopenia in subjects at study entry. Patients with less severe osteopenia (such as the subjects in our study) may gain less bone mass than patients with more severe bone loss *(31,32).* This is further confirmed by the linear inverse relation between baseline forearm and spine BMD and percentage change in BMD at these sites as demonstrated in our study. It was previously reported that most BMD increments occurred by the first year post-PTX *(33),* as early as by 3 mo for spine BMD in seven patients after PTX *(6).* Our study extends these observations to a larger number of subjects and to multiple sites. Indeed, 60% of the 12 mo mean percentage change at the lumbar spine BMD and WB BMC occurred within the first 3 mo, and most increments in femoral neck and trochanter BMD occurred by 6 mo. This observation may be relevant to the management of patients after PTX, particularly with regard to timing of the initiation of antiresorptive therapy in selected patients with severe osteopenia. The slightly higher Ca intake in members of the surgical group may have explained in part their difference from those in the control group in BMD response. In general, Ca may maintain but does not increase bone mass, and it has been shown to have no impact on bone mass in patients with HPTH *(34).*

The correlation between baseline iPTH and ostcocalcin levels and increments in BMD are consistent with previous observations *(18,31,32).* This correlation reflects that the most significant increments in bone mass occur in patients with more severe disease as assessed by iPTH, or bone turnover.

In the control subjects, albeit a small group, BMD measurements showed only a decrease in WB BMC. Bone at this site is mostly cortical—the kind of bone most likely to be affected in HPTH *(1–7).* In two recent studies, WB BMC was the most consistent skeletal site to show a decrement in bone mass in untreated patients, whereas forearm BMD measure-

ment yielded mixed results depending on the study, and lumbar spine BMD did not decrease from baseline *(3,21).* The significant decrements in WB BMC in these two recent studies as well as in our investigation raise the possibility that in addition to BMD in the femur, WB BMC may be the most useful site to monitor in subjects followed conservatively. Three studies of patients followed conservatively have suggested that HPTH is not accompanied by bone loss *(12–14).* In two studies, forearm BMD was measured, a site that may not show significant changes over follow-up of 1 to 2 yr *(12,14).* Indeed, in one of these studies, forearm BMD showed a trend downward that did not reach statistical significance *(12).* However, a great proportion of the subjects in that study were African Americans, a group known to have lower rates of bone turnover *(35)* and skeletal resistance to endogenous *(36)* or exogenous elevations in PTH levels *(37)* compared with Caucasian subjects. Moreover, a follow-up study showed a significant decrease whereas the PTX group showed a significant increase in forearm BMD *(33).* The investigators of these studies recently completed recruitment for a trial randomizing patients to treatment with PTX or observation in order to compare directly the impact of these therapies on BMD *(38).*

It is well recognized that PTX does not completely reverse bone loss in patients with HPTH *(4–6,17).* The further increments in BMD at all sites measured in postmenopausal women who underwent PTX and also took estrogen are therefore encouraging. Further evaluation revealed that the BMD increments in the PTX/E group were twice those in the PTX only group if only the six women in whom HRT was started postoperatively were considered (data not shown). Estrogen deficiency is accompanied by bone loss that may be accelerated in postmenopausal women with HPTH *(15);* this observation strengthens the rationale for the combination of PTX with estrogen therapy. Patients with the lowest BMD have the greatest increments in bone mass in response to antiresorptive therapy *(31,32).* This fact, however, does not explain the further increments in BMD in the PTX/E group because their baseline BMD value was higher, not lower, than that of the group undergoing PTX alone. The increments in lumbar spine and femoral neck BMD noted in our study exceed those reported in osteopenic women in response to estrogen therapy *(39)* and are comparable to those reported in early postmenopausal women receiving combination therapy with HRT/etidronate or HRT/calcitonin to prevent osteoporosis *(22,23).* Thus, combination therapy may be superior to PTX alone in osteopenic postmenopausal women with HPTH. Our study did not have the power to show a significant difference between PTX/E and PTX alone; however, the inclusion of two women who were taking estrogen prior to PTX may have blunted the overall observed BMD response in the PTX/E group.

In the largest study evaluating prospective changes in bone mineral density post-PTX, subjects were operated on if they had a BMD $Z < -2$ *(17).* Patients with less severe bone loss also experience significant increments in bone mass *(2,5,18,21,25)* that do not take place in the absence of intervention *(3,8,13,21).* The ideal BMD cutoff at which to intervene surgically is unclear. However, an approach that uses a Z score may be suboptimal because it would imply that the incidence of osteoporosis would not rise with age, although bone mass decreases and fracture incidence increases with aging *(30).* Our study raises the possibility that a less conservative BMD criterion than the one suggested by the National Institues of Health (NIH) consensus panel may be indicated. Otherwise, a significant number of symptomatic patients with HPTH and osteopenia or osteoporosis would not be recommended for a PTX and therefore may be deprived of significant increments in bone mass *(8).*

We believe that the patient group we studied is representative of the general population of patients suffering from HPTH and that the results are therefore generalizable. Indeed, even though our patients were recruited from a tertiary referral hospital, they presented with very mild or no symptoms of HPTH—currently the most common presentation of this condition. Their baseline calcium, PTH levels, and BMD measurements were comparable to those reported in a larger cohort of hyperparathyroid subjects *(1).* All subjects diagnosed with HPTH were offered the chance to participate, and the investigators had no part in planning any patient's treatment at any time during the study. A large proportion of the original study group, 37% of the overall group

and 50% of the surgical group, did not complete the study. However, they did so mostly because of the time commitment involved and did not differ overall in their characteristics from the subjects included in the analyses. Nevertheless, bias may still have existed; therefore, a randomized trial is necessary to confirm the findings described herein.

In conclusion, within the first year of our study, early and generalized increments in bone mass were documented at several skeletal sites in patients who underwent PTX; the values that increased included NB BMC, thus documenting that the site-specific increments (spine, hip) did not reflect a redistribution of bone mineral. By contrast, maintenance of bone mass or bone loss was documented in the control group. In postmenopausal women who took estrogen in addition to undergoing PTX, there were further increments at most sites than those undergoing PTX alone. HPTH is the third most common endocrine disease and is a known risk factor for osteoporosis and possibly for fractures *(40,41)*. This study raises key questions regarding optimal treatment of HPTH and identifies the need for a multicenter randomized trial including PTX, HRT, and combination therapy. Only through such a trial will the optimal therapy for this asymptomatic but potentially costly disease be determined.

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References

1. Silverberg SJ, Shane E, De La Cruz L, Dempster DW, Feldman F, Seldin D, et al. 1989 Skeletal disease in primary hyperparathyroidism. J Bone Miner Res 4:283–290.
2. Grey AB, Evans MC, Stapleton JP, Reid IR. 1994 Body weight and bone mineral density in postmenopausal women with primary hyperparathyroidism. Ann Intern Med 121:745–749.
3. Guo C-Y, Thomas WEG, A1-Dehaimi AW, Assiri AMA, Eastell R. 1996 Longitudinal changes in bone mineral density and bone turnover in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab 81:3487–3491.
4. Martin P, Bergmann P, Gillet C, Fuss M, Corvilain J, Van Geertruyden J. 1990 Long-term irreversibility of bone loss after surgery for primary hyperparathyroidism. Arch Intern Med 150:1495–1497.
5. Mole PA, Walkinshaw MH, Gunn A, Paterson CR. 1992 Bone mineral content in patients with primary hyperparathyroidism: a comparison of conservative management with surgical treatment. Br J Surg 79:263–265.
6. Abugassa S, Nordenstrom J, Eriksson S, Mollerstrom G, Alveryd A. 1990 Skeletal remineralization after surgery for primary and secondary hyperparathyroidism. Surgery 107:128–133.
7. McDermott MT, Perloff JJ, Kidd GS. 1994 Effects of mild asymptomatic primary hyperparathyroidism on bone mass in women with and without estrogen replacement therapy. J Bone Miner Res 9:509–514.
8. Marcus R. Editorial: 1995 bone of contention: the problem of mild hyperparathyroidism. J Clin Endocrinol Metab 80:720–722.
9. Coe FL, Favus MJ, Parks JH. 1986 Is estrogen preferable to surgery for postmenopausal women with primary hyperparathyroidism? N Engl J Med 314:1508, 1509.
10. Silverberg SJ, Bilezikian JP. 1996 Extensive personal experience: evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 81:2036–2040.
11. Leppla DC, Snyder W, Pak CYC. 1982 Sequential changes in bone density before and after parathyroidectomy in primary hyperparathyroidism. Investigat Radiol 6:604–606.
12. Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM. 1988 Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic hyperparathyroidism: evidence for biphasic disease course. J Clin Endocrinol Metab 67:1294–1298.
13. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, Bilezikian JP. 1995 Longitudinal measurements of bone density and biochemical indices in untreated primary hyperparathyroidism. J Clin Endocrinol Metab 80:723–728.
14. Warner J, Clifton-Bligh P, Posen S, McElduff A, Delbridge L, Reeve T. 1991 Longitudinal changes in forearm bone mineral content in primary hyperparathyroidism. J Bone Miner Res 6:S91–S95.
15. Grey AB, Stapleton JP, Evans MC, Reid IR. 1996 Accelerated bone loss in post-menopausal women with mild primary hyperparathyroidism. Clin Endocrinol 44(6):697–702.
16. Mautalen C, Reyes HR, Ghiringhelli G, Fromm G. 1986 Cortical bone mineral content in primary hyperparathyroidism: changes after parathyroidectomy. Acta Endocrinol 111(4):494–497.
17. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, et al. 1995 Increased bone mineral density after

parathyroidectomy in primary hyperparathyroidism. J Clin Endocrinol Metab 80:729–734.
18. Garton M, Martin J, Stewart A, et al. 1995 Changes in bone mass and metabolism after surgery for primary hyperparathyroidism. Clin Endocrinol 42(5):493–500.
19. Marcus R, Madvig P, Crim M, Pont A, Kosek J. 1984 Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. Ann Intern Med 100:633–640.
20. Selby PL. Peacock M. 1986 Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. N Engl J Med 314:1481–1485.
21. Grey AB, Stapleton JP, Evans MC, Tatnell MA, Reid IR. 1996 Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism: a randomized, controlled trial. Ann Intern Med 125(5):360–368.
22. Meschia M, Brincat M, Barbacini P, Crossignani PG, Albisetti W. 1993 A clinical trial of the effects of a combination of elcatonin and conjugated estrogens on vertebral bone mass in early postmenopausal women. Calcif Tissue Int 53:17–20.
23. Wimalawansa SJ. 1998 A four year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 104:219–226.
24. Consensus Development Conference Panel. 1991 Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. Ann Intern Med 114:593–597.
25. Silverberg SJ, Lock FG, Bilezikian JP. 1996 Vertebral osteopenia: a new indication for surgery in primary hyperparathyroidism. J Clin Endocrinol Metab 81:4007–4012.
26. El-Hajj Fuleihan G, Testa MA, Angell JE, Porrino N, LeBoff MS. 1995 Reproducibility of DXA absorptiometry: a model for bone loss estimates. J Bone Miner Res 10:1004–1014.
27. Byrne TA, Morrissey TB, Gatzen C, Benfell K, Nattakom T, Schletinga MR, LeBoff MS, Ziegler TR, Wilmore DW. 1993 Anabolic therapy with growth hormone accelerates protein gain in surgical patients requiring nutritional rehabilitation. Ann Surg 218:400–418.
28. Calvo MS, Eyre DR, Gundberg CM. 1996 Molecular basis in clinical application of biological markers of bone turnover. Endocr Rev 17:333–368.
29. SAS Institute. 1996 SAS/STAT software changes and enhancement: 1996 the MIXED procedure. Cary, North Carolina Sas Institute.
30. Kanis JA, Melton J III, Christiansen C, Johnston CC, Khaltae N. 1994 Perspective: the diagnosis of osteoporosis. J Bone Miner Res 9:1137–1141.
31. Bergenfelz A, Lindergard B, Ahren B. 1993 Prediction of changes in bone density after operation for primary hyperparathyroidism. Ann Chir Gynaecol 82:245–249.
32. Minisola S, Rosso R, Romagnoli E, Pacitti MT, Scarnecchia L, Carnevale V, Mazzuoli G. 1993 Trabecular bone mineral density in primary hyperparathyroidism: relationship to clinical presentation and biomarkers of skeletal turnover. Bone Miner 20:113–123.
33. Rao DS, Antonelli R, Phillips ER, Parfitt AM, Divine G, Jacobsen G. 1996 Does parathyroidectomy attenuate the age related bone loss in patients with primary hyperparathyroidism? J Bone Miner Res 11(S1): T751 (abstract).
34. Locker FG, Silverberg SJ, Bilezikian JP. 1996 Influence of dietary calcium intake on bone mineral density and biochemical parameters in primary hyperparathyroidism. J Bone Miner Res 11(Suppl 1): T747 (abstract).
35. Weinstein RS, Bell NH. 1988 Diminished rates of bone formation in normal black adults. N Engl J Med 319:1698–1701.
36. El-Hajj Fuleihan GE-H, Gundberg CM, Gleason R, et al. 1994 Racial differences in parathyroid hormone dynamics. J Clin Endocrinol Metab 79:1642–1647.
37. Cosman F, Morgan DC, Nieves JW, Shen V, Luckey MM, Dempster DW, Lindsay R, Parisien M. 1997 Resistance to bone resorbing effects of PTH in black women. J Bone Miner Res 12:958–966.
38. Rao DS, Phillips ER, Honasoge M, Divine GW, Talpos GB, Bone HG. 1997 Feasiblity of a randomized trial of parathyroidectomy (PTX) in mild primary hyperparathyroidism (PHPT). J Bone Miner Res 12(Suppl):S681 (abstract).
39. Mazess RB, Gallagher C, Notelovitz M, Schiff I, Utian W. 1989 Monitoring skeletal response to estrogen. Am J Obstet Gynecol 161:843–848.
40. Larsson K, Ljunghall S, Krusemo UB, Naessen T, Lindh E, Persson I. 1993 The risk of hip fractures in patients with primary hyperparathyroidism: a population-based cohort study with a follow-up of 19 years. J Intern Med, 234(6):585–593.
41. Melton LJ III, Atkinson EJ, O'Fallon WM, Heath H III. 1992 Risk of age-related fractures in patients with primary hyperparathyroidism. Arch Intern Med 152(11):2269–2273.