Raloxifene Lowers Serum Calcium and Markers of Bone Turnover in Postmenopausal Women with Primary Hyperparathyroidism

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Estrogen replacement therapy (ERT) decreases total serum calcium by about 0.5 mg/dl in postmenopausal women with primary hyperparathyroidism (PHPT). We investigated the ability of raloxifene, which has skeletal antiresorptive properties similar to those of ERT, to decrease serum calcium concentrations and markers of bone turnover in PHPT. Eighteen postmenopausal women with asymptomatic PHPT were randomized to 8 wk of raloxifene (60 mg/d) or placebo, followed by a 4-wk washout. At baseline, the groups were well matched. The calcium concentration decreased significantly by 8 wk of raloxifene administration (10.8 ± 0.2 to 10.4 ± 0.2 mg/dl; $P < 0.05$), as did markers of bone resorption and formation [os-

teocalcin, 11.4 ± 1.6 to 9.9 ± 1.6 nmol/liter ($P < 0.05$); serum N-telopeptide, 21.2 ± 3.4 to 17.3 ± 2.8 nmol bone collagen equivalents/liter ($P < 0.05$)]. Four weeks after raloxifene was discontinued, indices were indistinguishable from baseline. Raloxifene administration did not affect serum PTH, 1,25-dihydroxyvitamin D, total alkaline phosphatase, or urinary calcium excretion. Calcium and bone marker changes were therefore similar to those observed with ERT in PHPT. This short-term study suggests that raloxifene may be a useful approach to the treatment of postmenopausal women with mild PHPT. (*J Clin Endocrinol Metab* 88: 1174–1178, 2003)

MOST PATIENTS WITH primary hyperparathyroidism are women, with the majority being in their postmenopausal years (1, 2). As primary hyperparathyroidism (PHPT) frequently surfaces in the decade following the menopause, a possible relationship between estrogen deficiency and the unmasking of hypercalcemia has been postulated (3). Data on the effect of estrogen replacement therapy (ERT) on the hypercalcemia of PHPT date back to the 1970s (4–7). Studies have shown a modest (~0.5 mg/dl) reduction in total serum calcium levels in postmenopausal women with PHPT who receive ERT, without a change in serum PTH (4, 6–8). Markers of bone turnover, which are generally elevated, but only modestly, in PHPT, appear to decline (6–8).

No controlled clinical trials have been conducted to assess the potential of raloxifene, a selective estrogen receptor modulator (SERM), to control indexes of PHPT. Raloxifene acts as an estrogen agonist in bone, with similar antiresorptive properties (9). We therefore considered the possibility that raloxifene has an estrogen-like effect in PHPT. In this current study we tested the hypothesis that a short-term course of raloxifene will reduce the serum calcium concentration and biochemical markers of bone turnover in postmenopausal women with mild PHPT.

Subjects and Methods

Patients and study design

We studied 18 postmenopausal women with asymptomatic primary hyperparathyroidism. These women were selected because they did not meet the guidelines of the NIH for parathyroidectomy (10), had refused

surgery, or had previously undergone unsuccessful surgery. Women treated with estrogen, raloxifene, or bisphosphonates within 3 months of enrollment were excluded, as were those treated with agents that are associated with elevated PTH levels (lithium and thiazide diuretics). Menopausal status was confirmed by gonadotropins in the postmenopausal range in the women who had menstruated within the previous 12 months. All of the women gave written informed consent for the study, which was approved by the institutional review board of Columbia-Presbyterian Medical Center.

The study was a randomized, placebo-controlled, double-blind trial. Patients received raloxifene (60 mg daily) or an identical-appearing placebo tablet (provided by Eli Lilly & Co., Indianapolis, IN) for an 8-wk period, followed by a 4-wk washout period. Measurements were obtained at baseline and 1, 4, 8, and 12 wk after study initiation. The indices measured were serum calcium, PTH, serum phosphorous, and 1,25-dihydroxyvitamin D levels and urinary calcium excretion. Triplicate assays for serum calcium were performed at 0 and 8 wk to minimize the error of the measurement and thus increase statistical power (11). The urinary calcium data were adjusted to creatinine excretion. The bone formation marker was osteocalcin; the bone resorption marker was serum N-telopeptide (NTX). Normal ranges for these measurements are provided in Table 1. Baseline bone density by dual energy x-ray absorptiometry (model QDR-4500 bone densitometer, Hologic, Inc., Waltham, MA) was determined in 15 women.

Biochemical analyses

Serum total calcium and phosphorus, and urea nitrogen and creatinine concentrations were measured by automated techniques (Technicon Instruments, Tarrytown, NY), and urinary calcium was measured by atomic absorption spectrophotometry. Serum PTH was measured by immunoradiometric assay (interassay coefficient of variation, 3.0%) (12), and serum 1,25-dihydroxyvitamin D was measured as previously described (interassay coefficient of variation, 7.7%) (13). Serum osteocalcin was measured by RIA (interassay coefficient of variation, 13.0%) (14). Serum NTX was measured by ELISA [interassay coefficient of variation, 12.3% at 7.5 nmol/BCE/liter, 4.7% at 27.7 nmol/bone collagen equivalents (BCE)/liter]. Serum NTX has less intrasubject variability than urinary NTX in postmenopausal women (15, 16). All samples from each woman were analyzed at the same time in each assay.

Abbreviations: BCE, Bone collagen equivalents; ERT, estrogen replacement therapy; NTX, N-telopeptide; PHPT, primary hyperparathyroidism; SERM, selective estrogen receptor modulator.

TABLE 1. Baseline characteristics of the raloxifene and control groups[a]

Index	Raloxifene group (n = 9)	Control group (n = 9)	Normal range
Age (yr)	62 ± 4	62 ± 3	
Serum calcium (mmol/l)	2.69 ± 0.05	2.65 ± 0.03	2.10–2.44
Serum PTH (pmol/liter)	25.9 ± 6.1	20.7 ± 4.4	2.4–15.9
Serum phosphorus (mmol/liter)	0.78 ± 0.03	0.87 ± 0.03	0.81–1.39
Total alkaline phosphatase (IU/liter)	99 ± 9	95 ± 8	33–96
Serum 1,25-dihydroxyvitamin D (pmol/liter)	141 ± 17	115 ± 9.6	43–149
Serum osteocalcin (nmol/liter)	11.4 ± 1.6	11.0 ± 1.4	1.5–11.0
Serum N-telopeptide (nmol BCE/liter)	21.2 ± 3.4	21.1 ± 3.1	8.7–19.8
Urinary calcium (mmol/liter)	6.1 ± 1.0	5.9 ± 1.1	
Bone mineral density (g/cm^2, T-score)			
Lumbar spine	0.995 ± 0.1, −0.7 ± 0.6	0.848 ± 0.1, −2.2 ± 0.4	
Total hip	0.835 ± 0.1, −0.9 ± 0.4	0.773 ± 0.1, −1.4 ± 0.2	
Distal radius (1/3 site)	0.537 ± 0.1, −1.2 ± 0.3	0.619 ± 0.1, −1.3 ± 0.4	

[a] No baseline differences between the two groups were significant. Data represent mean ± SEM.

Statistical analysis

Comparisons between groups of women were made using unpaired *t* tests, whereas within-group estimates of change in indices from baseline were assessed with paired *t* tests. All statistical tests were two-sided. Replicate measurements were used to reduce the influence of measurement error, according to the Spearman-Brown formula (11). Two of 18 patients did not complete the study. The data were analyzed using both intention to treat strategy as well as excluding the subjects who did not complete the study.

Results

Eighteen women (mean age, 64 ± 2 yr; range, 52–83) were randomized to receive raloxifene or placebo. At baseline, the groups were well matched (Table 1). There were no significant differences in baseline serum calcium, PTH, urinary calcium excretion, or markers of bone turnover. PTH was slightly higher in the raloxifene-treated group (25.9 ± 6.1 *vs.* 20.7 ± 4.4 pmol/liter; 106 ± 25 *vs.* 85 ± 18 pg/ml; $P = 0.49$). Bone mineral density measurements at the lumbar spine, hip, and radius were also similar between the two groups of patients.

Nine patients received raloxifene, and nine received placebo. One woman taking placebo experienced chest discomfort during the first week of the study and withdrew. Evaluation for an etiology of the chest pain was unrevealing. A second patient (taking raloxifene) withdrew after 1 wk, citing an increase in hot flashes.

Serum calcium

Serum calcium concentrations decreased significantly by 8 wk of raloxifene administration (from 2.69 ± 0.05 to 2.59 ± 0.05 mmol/liter; 10.8 ± 0.2 to 10.4 ± 0.2 mg/dl; $P < 0.05$), whereas there was no significant change in the control group (2.65 ± 0.03 to 2.59 ± 0.05 mmol/liter; 10.6 ± 0.1 to 10.4 ± 0.2 mg/dl; $P = $ NS; Fig. 1). In the raloxifene group, the mean change in serum calcium was −0.10 ± 0.05 mmol/liter (−0.4 ± 0.2 mg/dl). In the placebo group, the mean change in serum calcium was −0.05 ± 0.05 mmol/liter (−0.2 ± 0.2 mg/dl). When the rate of change in serum calcium was compared between the two groups, significant between-group differences were confirmed. The time × treatment interaction tested significant ($F_{(2,30)} = 5.38$; $P < 0.01$) in a mixed model analysis with fixed effect of treatment and random effects of time and subject. After 4 wk without ralox-
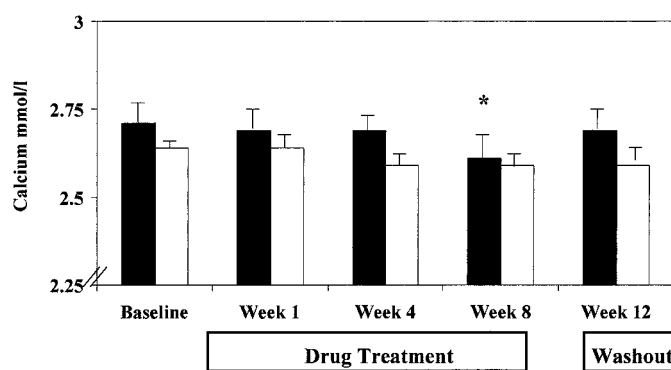

FIG. 1. Changes in serum calcium after raloxifene treatment in women with PHPT. Serum calcium levels were determined in women receiving raloxifene (■) and in controls (□). Results are shown as the mean ± SEM. *, $P < 0.05$ for the change from baseline measure.

ifene administration (the washout period), serum calcium concentrations returned to baseline in the raloxifene group (2.69 ± 0.03 mmol/liter; 10.8 ± 0.1 mg/dl), whereas there continued to be no change in the control group (2.59 ± 0.05 mmol/liter; 10.4 ± 0.2 mg/dl). Although data are presented from the intention to treat analysis of all patients, results did not differ in an efficacy analysis, including only the 16 patients (raloxifene, n = 8; placebo, n = 8) who completed the study.

Markers of bone turnover

Markers of bone formation and resorption decreased by wk 8 in patients receiving raloxifene. Serum osteocalcin fell from 11.4 ± 1.6 to 9.9 ± 1.6 nmol/liter ($P < 0.05$), and serum NTX decreased from 21.2 ± 3.4 to 17.3 ± 2.8 nmol BCE/liter ($P < 0.05$; Fig. 2). There was no change in either bone turnover marker in the control group [osteocalcin, 11.0 ± 1.4 to 11.5 ± 1.7 nmol/liter ($P = $ NS); serum NTX, 21.1 ± 3.1 to 20.4 ± 3.0 nmol BCE/liter ($P = $ NS)]. Both markers trended upward toward baseline levels when raloxifene was discontinued. By 4 wk after stopping the drug, neither osteocalcin (11.1 ± 2.1 nmol/liter) nor serum NTX (18.2 ± 2.3 nmol BCE/liter) was significantly below baseline levels. Serum total alkaline phosphatase was unchanged during the 8 wk of the study [raloxifene, 99 ± 9 to 101 ± 10 IU/liter ($P = $ NS);
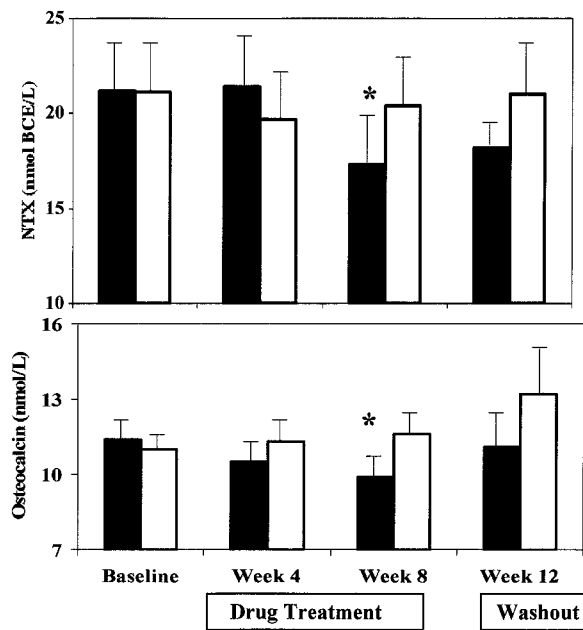
FIG. 2. Changes in serum NTX and osteocalcin after raloxifene treatment in women with primary hyperparathyroidism. Serum NTX and osteocalcin levels were determined in women receiving raloxifene (■) and in controls (□). Results are shown as the mean ± SEM. *, $P < 0.05$ for change from the baseline measure.

placebo, 95 ± 8 to 93 ± 9 IU/liter (P = NS)]. Bone-specific alkaline phosphatase was not measured.

Other indexes of calcium metabolism

Serum PTH did not change in the raloxifene group (25.9 ± 6.1 to 29.8 ± 7.6 pmol/liter; 106 ± 25 to 122 ± 31 pg/ml; P = NS) or in the control group (20.7 ± 4.4 to 22.0 ± 4.4 pmol/liter; 85 ± 18 to 90 ± 18 pg/ml; P = NS). Urinary calcium excretion also did not change in the raloxifene group (6.1 ± 1.0 to 6.1 ± 0.9 mmol/liter; 243 ± 40 to 242 ± 37 mg/g creatinine; P = NS) or in the control group (5.9 ± 1.1 to 5.8 ± 1.3 mmol/liter; 237 ± 45 to 233 ± 52 mg/g creatinine; P = NS). Serum phosphorous levels did not change in the raloxifene group (0.78 ± 0.03 to 0.74 ± 0.07 mmol/liter; 2.5 ± 0.2 to 2.3 ± 0.2 mg/dl; P = NS) or in the control group (0.87 ± 0.03 to 0.90 ± 0.03 mmol/liter; 2.7 ± 0.1 to 2.8 ± 0.1 mg/dl; P = NS). 1,25-Dihydroxyvitamin D levels did not change in the raloxifene group (141 ± 17 to 132 ± 10 pmol/liter; 59 ± 7 to 55 ± 4 pg/ml; P = NS) or in the control group (115 ± 9.6 to 110 ± 7.2 pmol/liter; 48 ± 4 to 46 ± 3 pg/ml]; P = NS).

Discussion

The results of this small study demonstrate that raloxifene is associated with reductions in serum calcium levels and markers of bone turnover in postmenopausal women with mild PHPT. These changes are similar to those reported with estrogen therapy. Like ERT, there is no alteration in PTH levels and the calcium and bone marker changes return to baseline with discontinuation of raloxifene.

Most patients with PHPT in the United States are asymptomatic (17). However, even patients with mild, asymptomatic PHPT have evidence of skeletal involvement. Bone turn-

over is increased, with higher levels of both bone resorption and formation markers (18). By dual energy x-ray absorptiometry, bone mass is relatively well preserved in the cancellous skeleton, with minimal differences compared with age- and sex-matched controls, but in the predominantly cortical skeleton (the distal one third radius site) it is typical to detect substantial bone loss (13, 19). These findings have been substantiated in detailed histomorphometric studies (20). It is not clear whether there is an increase in fracture incidence in PHPT (21–25).

Surgery remains the only option for cure of PHPT (26). Yet most agree that surgery is not indicated in all patients, especially in many patients without symptoms. An effective medical therapy would provide an option not only for some asymptomatic patients, but also for those in whom parathyroid surgery is contraindicated because of intercurrent medical conditions, those with previously unsuccessful surgery, and those who decline surgery (27).

An efficacious nonsurgical therapy is not yet available. Oral phosphate, which can lead to potentially dangerous ectopic soft tissue calcification, is not recommended (28, 29). Calcitonin is not useful either. Recent data on a calcimimetic agent (30–32) and alendronate treatment (33, 34) have shown promise.

A relationship between estrogen deficiency and the unmasking of hypercalcemia was first postulated over 50 yr ago (3) based on the increased frequency of PHPT in postmenopausal women. The concept is that estrogen in these women provided a control, as an inhibitor of bone resorption, for the actions of PTH. During the menopause, it was speculated, the estrogen deficiency state removed this controlling influence, thus allowing PTH to exert its full effect on bone. The resultant effect is the development of hypercalcemia. This hypothesis is supported by the observation that the estrogenized postmenopausal skeleton is less sensitive to the bone-resorbing effects of acutely administered PTH than is the postmenopausal skeleton (35).

Estrogens were first used in the treatment of PHPT in 1972. Gallagher *et al.* (4) found that estrogen administration to 10 postmenopausal women with symptomatic PHPT resulted in a prompt decrease in serum calcium concentrations after 1 wk of therapy, with continued reductions at 4 wk. Decreases in serum calcium concentrations of approximately 0.5 mg/dl were observed in subsequent studies of postmenopausal women with PHPT treated with ERT (6, 7, 36). In the largest study, 42 women were randomly assigned to receive conjugated estrogens (0.625 mg) and medroxyprogesterone acetate (5 mg daily) or placebo for 2 yr (8). A decrease in total serum calcium was found in patients treated with ERT, although the difference between the treatment and placebo groups was not significant. In these studies hypercalcemia rapidly recurred when therapy was discontinued.

Other effects of estrogen therapy were observed in women with mild PHPT. Urinary calcium excretion (6–8) and serum phosphorous levels (4, 6, 7) decreased, as did markers of bone turnover (including alkaline phosphatase activity, urinary hydroxyproline, and urinary NTX) (6–8). Studies of bone mineral density in estrogen-treated patients with primary hyperparathyroidism documented a salutary effect of treatment on bone mineral density at the lumbar spine and fem-

oral neck (8, 36). In a cross-sectional study, estrogen therapy protected the skeleton from bone loss in women with mild asymptomatic PHPT (37). However, no changes in PTH and vitamin D levels have been associated with ERT in PHPT in the studies in which these measurements were performed (6–8).

Raloxifene is a SERM that exhibits tissue-specific estrogen agonist or antagonist activity. It binds to the estrogen receptor and targets a distinct DNA element, acting as an estrogen agonist on bone and lipid metabolism and as an estrogen antagonist in the breast and uterus. It is currently approved for both prevention and treatment of postmenopausal osteoporosis and has been shown to reduce the incidence of vertebral fractures in osteoporotic women (38).

Raloxifene appears to have similar effects as estrogen on calcium metabolism in healthy postmenopausal women. When raloxifene was compared with estrogen in a short-term, 8-wk study in healthy postmenopausal women, reductions in bone turnover variables and urinary calcium excretion were similar for estrogen and raloxifene (39). Balance studies showed both medications to induce positive calcium balance at 1 and 7 months, although at the 7 month point, remodeling suppression was greater for estrogen than for raloxifene (39). Urinary calcium declined equally at the 1 month analysis and was sustained for 7 months.

Recently, three women with mild PHPT were treated with raloxifene for 1 yr (40). Although the study was not randomized or placebo-controlled, a decrease in total serum calcium level was found (11.0 to 10.3 mg/dl) along with increases in bone density of the lumbar spine and femoral neck. PTH did not change.

In our study, raloxifene caused a modest decline in serum calcium concentrations and markers of bone turnover in postmenopausal women with mild PHPT. Serum calcium levels and bone markers returned to baseline soon after discontinuation of raloxifene. As with estrogen therapy, the decrease in serum calcium seemed to be due to the skeletal antiresorptive effects of raloxifene. After estrogen, the serum calcium concentration has been reported to fall as early as 1 or 4 wk, whereas the reduction in calcium in response to raloxifene did not occur until wk 8. It is not clear whether the apparent difference in time course between estrogen and raloxifene reflects an intrinsic difference in the kinetics of actions. Estrogen and raloxifene have different affinities for the two estrogen receptor subtypes, α and β (41). Moreover, they elicit opposite effects on gene transcription depending on the receptor to which they are bound (42). It is also possible that a more rapid fall in serum calcium was observed with estrogen because the initial hypercalcemia was more severe in the estrogen-treated patients (4). Experimental design discrepancies may also account for some of the differences. Another difference between estrogen and raloxifene is that urinary calcium falls with estrogen treatment. It is possible that estrogen has an additional effect on calcium reabsorption in the kidney in women with PHPT (43) that does not occur with raloxifene.

This short-term study suggests that raloxifene may be a useful approach for postmenopausal women with mild PHPT. The effect of raloxifene to lower serum calcium levels in these patients seems to occur as a result of the inhibition of bone turnover. Whether long-term administration of raloxifene in this disorder will be associated with a salutary effect on bone density remains to be seen.

References

1. **Silverberg SJ** 2000 Natural history of primary hyperparathyroidism. Endocrinol Metab Clin North Am 29:451–464
2. **Palmer M, Jakobsson S, Akerstrom G, et al.** 1988 Prevalence of hypercalcaemia in a health survey: a 14-year follow-up study of serum calcium values. Eur J Clin Invest 18:39–46
3. **Albright F, Reifenstein EC** 1948 The parathyroid glands and metabolic bone disease. Baltimore: Williams & Wilkins
4. **Gallagher JC, Nordin BE** 1972 Treatment with with oestrogens of primary hyperparathyroidism in post-menopausal women. Lancet 1:503–507
5. **Nordin BE, Need HA, Morris M, et al.** 1991 Evidence for a renal calcium leak in postmenopausal women. J Clin Endocrinol Metab 72:401–407
6. **Marcus R, Madvig P, Crim M, et al.** 1984 Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. Ann Intern Med 100:633–640
7. **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
8. **Grey AB, Stapleton JP, Evans MC, et al.** 1996 Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism. A randomized, controlled trial. Ann Intern Med 125:360–368
9. **Draper MW, Flowers DE, Huster WJ, et al.** 1996 A controlled trial of raloxifene (LY139481) HCl: impact on bone turnover and serum lipid profile in healthy postmenopausal women. J Bone Miner Res 11:835–842
10. **NIH** 1991 NIH conference: diagnosis and management of asymptomatic primary hyperparathyroidism—consensus development conference statement. Ann Intern Med 114:593-597
11. **Fleiss JL** 1986 The design and analysis of clinical experiments. New York: Wiley & Sons; 14–17
12. **Nussbaum SR, Zahradnik RJ, Lavigne JR, et al.** 1987 Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. Clin Chem 33:1364–1367
13. **Silverberg SJ, Shane E, de la Cruz L, et al.** 1989 Skeletal disease in primary hyperparathyroidism. J Bone Miner Res 4:283–291
14. **Gundberg CM, Wilson PS, Gallop PM, et al.** 1985 Determination of osteocalcin in human serum: results with two kits compared with those by a well-characterized assay. Clin Chem 31:1720–1723
15. **Greenspan SL, Rosen HN, Parker RA** 2000 Early changes in serum N-telopeptide and C-telopeptide cross-linked collagen type 1 predict long-term response to alendronate therapy in elderly women. J Clin Endocrinol Metab 85:3537–3540
16. **Eastell R, Mallinak N, Weiss S, et al.** 2000 Biological variability of serum and urinary N-telopeptides of type I collagen in postmenopausal women. J Bone Miner Res 15:594–598
17. **Silverberg SJ, Bilezikian JP** 1996 Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 81:2036–2040
18. **Seibel MJ, Gartenberg F, Silverberg SJ, et al.** 1992 Urinary hydroxypyridinium cross-links of collagen in primary hyperparathyroidism. J Clin Endocrinol Metab 74:481–486
19. **Bilezikian JP, Silverberg SJ, Shane E, et al.** 1991 Characterization and evaluation of asymptomatic primary hyperparathyroidism. J Bone Miner Res 6(Suppl 2):S85–S89; S121–S124
20. **Parisien M, Silverberg SJ, Shane E, et al.** 1990 The histomorphometry of bone in primary hyperparathyroidism: preservation of cancellous bone structure. J Clin Endocrinol Metab 70:930–938

21. **Khosla S, Melton III LJ, Wermers RA, et al.** 1999 Primary hyperparathyroidism and the risk of fracture: a population-based study. J Bone Miner Res 14:1700–1707
22. **Kochersberger G, Buckley NJ, Leight GS, et al.** 1987 What is the clinical significance of bone loss in primary hyperparathyroidism? Arch Intern Med 147:1951–1953
23. **Larsson K, Ljunghall S, Krusemo UB, et al.** 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 234:585–593
24. **Wilson RJ, Rao S, Ellis B, et al.** 1988 Mild asymptomatic primary hyperparathyroidism is not a risk factor for vertebral fractures. Ann Intern Med 109:959–962
25. **Kenny AM, MacGillivray DC, Pilbeam CC, et al.** 1995 Fracture incidence in postmenopausal women with primary hyperparathyroidism. Surgery 118:109–114
26. **Clark OH, Wilkes W, Siperstein AE, et al.** 1991 Diagnosis and management of asymptomatic hyperparathyroidism: safety, efficacy, and deficiencies in our knowledge. J Bone Miner Res 6(Suppl 2):S135–S142; S151–S152
27. **(No Authors Listed)** 1984 Medical management of primary hyperparathyroidism. Lancet 2:727–728
28. **Broadus AE, Magee JS, Mallette LE, et al.** 1983 A detailed evaluation of oral phosphate therapy in selected patients with primary hyperparathyroidism. J Clin Endocrinol Metab 56:953–961
29. **Vernava III AM, O'Neal LW, Palermo V** 1987 Lethal hyperparathyroid crisis: hazards of phosphate administration. Surgery 102:941–948
30. **Silverberg SJ, Bone III HG, Marriott TB, et al.** 1997 Short-term inhibition of parathyroid hormone secretion by a calcium-receptor agonist in patients with primary hyperparathyroidism. N Engl J Med 337:1506–1510
31. **Peacock M, Shoback DM, Greth WE, et al.** The calcimimetic AMG 073 reduces serum calcium (ca) in patients with primary hyperparathyroidism (PHPT) (abstract). Proc of the 23rd Annual Meeting of the American Society for Bone and Mineral Research, 2001, p 1106
32. **Shoback DM, Firek AF, Mims RB, et al.** An evaluation of the calcimimetic AMG 073 in patients with hypercalcemia and primary hyperparathyroidism

(PHPT) [Abstract]. Proc of the 23rd Annual Meeting of the American Society for Bone and Mineral Research, 2001, p SA 462
33. **Khan A, Bilezikian JP, Kung A, et al.** A double blind randomized placebo controlled trial of alendronate in primary hyperparathyroidism [Abstract]. Proc of the 23rd Annual Meeting of the American Society for Bone and Mineral Research, 2001, p F464
34. **Rossini M, Gatti D, Isaia G, et al.** 2001 Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. J Bone Miner Res 16:113–119
35. **Cosman F, Shen V, Xie F, et al.** 1993 Estrogen protection against bone resorbing effects of parathyroid hormone infusion. Assessment by use of biochemical markers. Ann Intern Med 118:337–343
36. **Diamond T, Ng AT, Levy S, et al.** 1996 Estrogen replacement may be an alternative to parathyroid surgery for the treatment of osteoporosis in elderly postmenopausal women presenting with primary hyperparathyroidism: a preliminary report. Osteop Int 6:329–333
37. **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
38. **Ettinger B, Black DM, Mitlak BH, et al.** 1999 Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 282:637–645
39. **Heaney RP, Draper MW** 1997 Raloxifene and estrogen: comparative bone-remodeling kinetics. J Clin Endocrinol Metab 82:3425–3429
40. **Zanchetta JR, Bogado CE** 2001 Raloxifene reverses bone loss in postmenopausal women with mild asymptomatic primary hyperparathyroidism. J Bone Miner Res 16:189–190
41. **Kuiper GG, Lemmen JG, Carlsson B, et al.** 1998 Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β. Endocrinology 139:4252–4263
42. **Paech K, Webb P, Kuiper GG, et al.** 1997 Differential ligand activation of estrogen receptors ERα and ERβ at AP1 sites. Science 277:1508–1510
43. **Brown EM, Pollak M, Seidman CE, et al.** 1995 Calcium-ion-sensing cell-surface receptors. N Engl J Med 333:234–240