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. 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 (osteocalcin, 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)

**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.
TABLE 1. Baseline characteristics of the raloxifene and control groups

<table>
<thead>
<tr>
<th>Index</th>
<th>Raloxifene group (n = 9)</th>
<th>Control group (n = 9)</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62 ± 4</td>
<td>62 ± 3</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.69 ± 0.05</td>
<td>2.65 ± 0.03</td>
<td>2.10–2.44</td>
</tr>
<tr>
<td>Serum PTH (pmol/liter)</td>
<td>25.9 ± 0.1</td>
<td>20.7 ± 4.4</td>
<td>2.4–15.9</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/liter)</td>
<td>0.78 ± 0.03</td>
<td>0.87 ± 0.03</td>
<td>0.81–1.39</td>
</tr>
<tr>
<td>Total alkaline phosphatase (IU/liter)</td>
<td>99 ± 9</td>
<td>95 ± 8</td>
<td>33–96</td>
</tr>
<tr>
<td>Serum 1,25-dihydroxyvitamin D (pmol/liter)</td>
<td>141 ± 17</td>
<td>115 ± 9.6</td>
<td>43–149</td>
</tr>
<tr>
<td>Serum osteocalcin (nmol/liter)</td>
<td>11.4 ± 1.6</td>
<td>11.0 ± 1.4</td>
<td>1.5–11.0</td>
</tr>
<tr>
<td>Serum N-telopeptide (nmol BCE/liter)</td>
<td>21.2 ± 3.4</td>
<td>21.1 ± 3.1</td>
<td>8.7–19.8</td>
</tr>
<tr>
<td>Urinary calcium (mmol/liter)</td>
<td>6.1 ± 1.0</td>
<td>5.9 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Bone mineral density (g/cm², T-score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.995 ± 0.1, -0.7 ± 0.6</td>
<td>0.848 ± 0.1, -2.2 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>Total hip</td>
<td>0.835 ± 0.1, -0.9 ± 0.4</td>
<td>0.773 ± 0.1, -1.4 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Distal radius (1/3 site)</td>
<td>0.537 ± 0.1, -1.2 ± 0.3</td>
<td>0.619 ± 0.1, -1.3 ± 0.4</td>
<td></td>
</tr>
</tbody>
</table>

*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 ± 4.2 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 (F2, 23.0 = 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 raloxifene 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);...
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 turnover 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.

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