0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 11
Printed in U.S.A.

# Vertebral Osteopenia: A New Indication for Surgery in Primary Hyperparathyroidism*

SHONNI J. SILVERBERG, FLORE G. LOCKER, AND JOHN P. BILEZIKIAN

*Departments of Medicine (S.J.S., F.G.L., J.P.B.) and Pharmacology (J.P.B.), Columbia University College of Physicians and Surgeons, New York, New York 10032*

**ABSTRACT**

Most patients with primary hyperparathyroidism have reduced radial and preserved vertebral bone density. We have identified a subset of patients with low lumbar spine bone density at diagnosis. This study assessed the effect of parathyroidectomy (undertaken based upon accepted surgical guidelines) or nonintervention on bone mineral density (BMD) in these patients.

Twenty-two of 143 (15%) patients with mild primary hyperparathyroidism had lumbar spine BMD more than 1.5 SD below the mean for an age- and sex-matched population (z-score). Fourteen underwent parathyroidectomy, whereas 8 were followed with no intervention. All had annual BMD measurements for 4 yr after enrollment or after surgery. After parathyroidectomy, there was a brisk sustained rise in lumbar spine BMD [yr 1, 15 ± 3% ($P < 0.005$); yr 4, 21 ± 4% ($P < 0.01$)]. In those followed without surgery, BMD did not change significantly at any site. Postmenopausal women showed the same pattern as the cohort as a whole, *i.e.* increased BMD after surgery [yr 1, 13 ± 3% ($P < 0.01$); yr 4, 16 ± 5% ($P < 0.01$)], but no worsening was found with nonintervention despite the passage of years in the menopause.

We conclude that parathyroidectomy markedly improves lumbar spine BMD in patients with vertebral osteopenia. It is proposed that reduced cancellous bone density should become a new indication for surgery in primary hyperparathyroidism. (*J Clin Endocrinol Metab* **81:** 4007–4012, 1996)

PRIMARY hyperparathyroidism is now recognized as a disorder with few overt manifestations, presenting most often as asymptomatic hypercalcemia (1–3). A major challenge in the management of this disease is the decision regarding which patients should undergo parathyroidectomy, the only currently available option for cure (4–8). To that end, the NIH Consensus Development Conference agreed upon a list of guidelines for surgery in primary hyperparathyroidism (9). These include: 1) serum calcium above 2.99 mmol/L (>12 mg/dL), 2) marked hypercalciuria (>9.98 mmol/day [>400 mg/day]), 3) any overt manifestation of primary hyperparathyroidism (nephrolithiasis, osteitis fibrosa cystica, or classic neuromuscular disease), 4) markedly reduced cortical bone density, 5) reduced creatinine clearance in the absence of other cause, and 6) age less than 50 yr. In this study, we report on a finding that suggests a seventh criterion for parathyroidectomy.

Although some overt manifestations of the disease, such as osteitis fibrosa cystica, have all but disappeared from clinical view in the United States, primary hyperparathyroidism continues to have well defined skeletal manifestations (10–16). Most patients with primary hyperparathyroidism have diminution of cortical bone, with relative preservation of cancellous bone. Reduced cortical bone mass, found predominantly in the dense bones of the arms and legs, is an accepted indication for surgical intervention (9). In patients meeting this or other accepted guidelines for surgery, parathyroidectomy is associated with an increase in bone mineral density (BMD) at these cortical sites, as well as at sites containing a preponderance of cancellous bone, such as the lumbar spine (17–21). BMD at the femoral neck, which contains similar amounts of cortical and cancellous elements, also rises after parathyroidectomy (21).

We have recently identified a subgroup of patients whose lumbar spine BMD is low when the diagnosis of primary hyperparathyroidism is made. Although this finding is distinctly unusual in primary hyperparathyroidism, it is a typical presentation of postmenopausal osteoporosis. It was not clear whether this subgroup of patients with primary hyperparathyroidism would respond to surgery or to conservative management in the same manner as those with the more classical pattern of bone loss. Our findings indicate that parathyroidectomy markedly improves lumbar spine BMD in patients with vertebral osteopenia and argue strongly for surgical intervention in such individuals.

## Subjects and Methods

One hundred and forty-three patients are currently enrolled in a longitudinal study of primary hyperparathyroidism. The decision to recommend parathyroidectomy or nonintervention is based upon surgical guidelines as established by the Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism (9). Baseline biochemistries were the mean of three determinations. Thereafter, serum and urine biochemistries were determined every 4 months along with routine clinical evaluation. Serum concentrations of total calcium, phosphorus, and alkaline phosphatase were measured by automated techniques (Technicon Instruments, Tarrytown, NY). PTH was measured by immunoradiometric assay for intact PTH (22). 25-Hydroxyvitamin D and 1,25-dihydroxyvitamin $D_3$ were measured as previously described (10, 23). Urinary calcium was assayed using atomic absorption spectrophotometry. Urinary hydroxypyridinium cross-links of collagen (pyridinoline and deoxypyridinoline) were measured by

Received December 21, 1995. Revision received July 1, 1996. Accepted July 15, 1996.

Address all correspondence and requests for reprints to: Shonni J. Silverberg, M.D., Department of Medicine, PH 8 West, Columbia University College of Physicians and Surgeons, 630 W. 168th Street, New York, New York 10032.

* This work was supported in part by NIH Grants NIDDK 32333, NIAMS 39191, and RR-00645.

high performance liquid chromatography (24). Normal ranges are shown in Table 1.

Bone mineral densitometry was performed at study entry and yearly after baseline measurement or parathyroidectomy. Bone densitometry of the lumbar spine (L2–L4), right femoral neck, and distal third of the nondominant radius were obtained by dual energy x-ray absorptiometry (QDR-1000 Bone Densitometer, Hologic, Waltham, MA). The longitudinal precision of measurements on a spine phantom has a coefficient of variation of 0.43%. Data are expressed as absolute bone density (grams per $cm^2$) and z-score. The z-score is the number of SDs a given measurement differs from the mean for a sex- and age-matched reference population (25). Early data were obtained using single and dual photon absorptiometry techniques (SP2 and DP3, Lunar Radiation Corp., Madison, WI). Data were compared with a series of equations developed at our own site, very similar to those generated by Hologic, relating measurements on the two systems to one another, as previously described (21, 26). The newer dual energy x-ray absortiometry technology has been exclusively employed for the past 4 yr. When data are compared for subjects whose longitudinal bone mass measurements were made by dual energy x-ray absortiometry alone to those for subjects whose initial studies employed the earlier techniques, similar patterns were seen. The lack of change in bone density at any site, shown below (see *Results*), in those patients followed without intervention compared with the increase in bone density after parathyroidectomy also speaks against the introduction of a systematic error in the data for patients whose bone density was measured by the two techniques.

All results are expressed as the mean ± SEM for each index. Comparisons of data among surgical and nonsurgical groups were made with Student's unpaired *t* tests, whereas paired *t* tests and ANOVA were used to assess site-specific changes in BMD and z-scores over time. For each person, the bone mineral densitometric measurement obtained at study entry for each site (lumbar spine, femoral neck, and radius) was used to determine the percent change from baseline to each year of follow-up. This study was performed in the Irving Center for Clinical Research of the Columbia-Presbyterian Medical Center. All patients gave written informed consent for the study, which had the approval of the Columbia-Presbyterian Medical Center institutional review board.

## Results

From a cohort of 143 patients with mild primary hyperparathyroidism, 22 (15%) had lumbar spine z-scores less than −1.5. This group included 7 men, 3 premenopausal women, and 12 postmenopausal women. Their mean age of 53 ± 3 yr was not significantly different from that of the 121 patients with higher, more typical, lumbar spine z-scores. There were no clinically distinctive features among this group; no patient had sustained previous fractures or had a history of alcoholism or use of drugs affecting mineral metabolism. There was no family history of primary hyperparathyroidism or multiple endocrine neoplasia.

At the time of presentation (Fig. 1, *top panel*), osteopenia was most prominent at the lumbar spine (z-score, −2.285 ± 0.15), with less osteopenia seen at the femoral neck (z-score, −1.695 ± 0.17) and radius (z-score, −1.522 ± 0.32). The opposite profile was seen in the vast majority of primary hyperparathyroid patients (85%; n = 121) with vertebral z-scores higher than −1.5, in whom bone loss was most prominent at the more highly cortical distal radius site (Fig. 1, *bottom panel*). In this larger group, lumbar spine BMD was well preserved, with a mean z-score of −0.061 ± 0.15. Within both sets of patients, z-scores at the lumbar spine differed from those at the other measured sites (by ANOVA, $P < 0.01$).

Fourteen of the 22 patients in the subgroup underwent parathyroidectomy according to accepted surgical guidelines. Five had serum calcium levels greater than 2.99 mmol/L (12 mg/dL), 2 had marked hypercalciuria [urinary calcium excretion, >9.98 mmol/day (400 mg/day)], 2 had nephrolithiasis, 8 had z-scores at the radius less than −2, and 5 were less than 50 yr of age. Seven patients met 1 criterion for surgery (see introduction), whereas 7 others met 2 criteria for parathyroidectomy. Eight patients with low lumbar spine z-scores were followed with no intervention. Three of these patients met the criteria for surgery, but chose to be followed without parathyroidectomy. Of these, 1 had hypercalcemia and hypercalciuria in the surgical range, whereas 2 others had low radius BMD. The 2 groups of patients (see Table 1) differed from each other only in that patients who underwent parathyroidectomy were younger than those followed with no intervention (49 ± 3 *vs.* 60 ± 3 yr) and had higher serum calcium levels [2.89 ± 0.1 *vs.* 2.77 ± 0.1 mmol/L (11.6 ± 0.3

**TABLE 1.** Baseline data by treatment modality

| | Surgery | No surgery | Normal range |
|---|---|---|---|
| No. of patients | 14 | 8 | |
| Age (yr)[a] | 49 ± 3 | 60 ± 3 | |
| Serum index | | | |
| Calcium[a] | 2.89 ± 0.1 | 2.77 ± 0.1 | 2.17–2.67 mmol/L |
| Alkaline phosphatase | 108 ± 10 | 115 ± 14 | <100 IU/L |
| PTH | 28.9 ± 3.7 | 35.9 ± 14.4 | 2.4–15.9 pmol/L |
| 25-Hydroxyvitamin D | 60 ± 5 | 62 ± 8 | 22–130 nmol/L |
| 1,25-Dihydroxyvitamin $D_3$ | 156 ± 19 | 144 ± 24 | 36–156 pmol/L |
| Urinary Index | | | |
| Calcium | 7.4 ± 0.7 | 6.5 ± 1.5 | <6.2 mmol/day |
| Collagen cross-links: | | | |
| PYD | 52.0 ± 4.8 | 50.6 ± 5.0 | <51.8 nmol/mmol creatinine |
| DPD | 19.5 ± 1.8 | 17.9 ± 3.0 | <14.6 nmol/mmol creatinine |
| Bone mineral density ($g/cm^2$) | | | |
| Lumbar spine | 0.718 ± 0.03 | 0.706 ± 0.03 | |
| Femoral neck | 0.623 ± 0.02 | 0.618 ± 0.02 | |
| Radius | 0.552 ± 0.03 | 0.559 ± 0.03 | |
| z-Score | | | |
| Lumbar spine | −2.401 ± 0.18 | −2.064 ± 0.20 | |
| Femoral neck | −1.905 ± 0.14 | −1.320 ± 0.31 | |
| Radius | −1.763 ± 0.47 | −1.191 ± 0.43 | |

[a] Groups differ at $P < 0.05$.

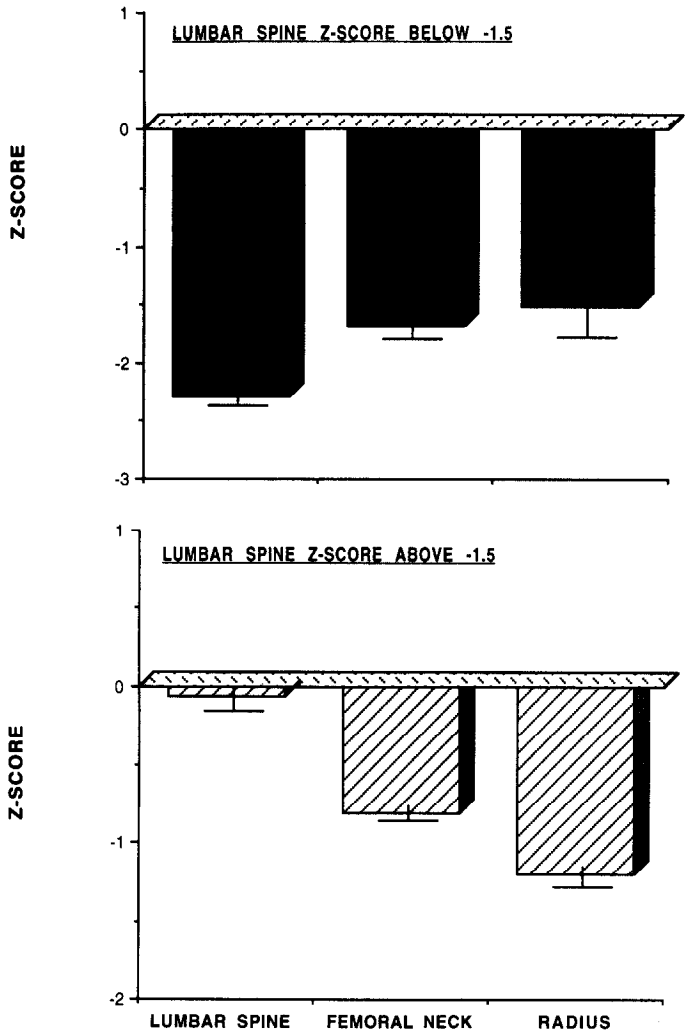


FIG. 1. Baseline bone densitometry z-scores by site in 143 patients with primary hyperparathyroidism. *Top panel*, Patients with lumbar spine osteopenia (z-score below −1.5; n = 22). *Bottom panel*, Patients with lumbar spine z-score above −1.5 (n = 121).

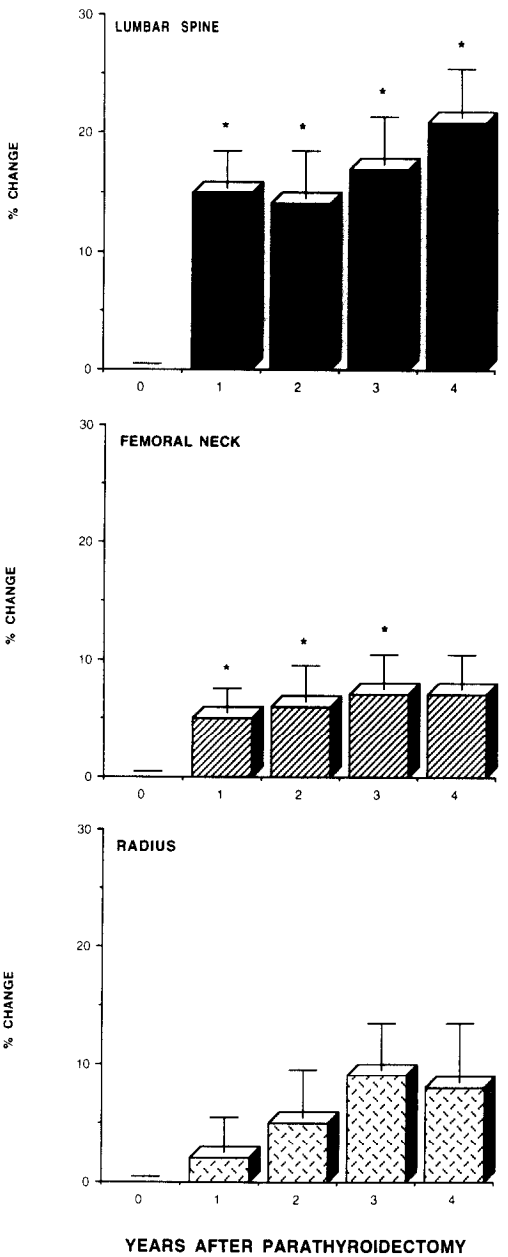


FIG. 2. BMD after parathyroidectomy in 14 primary hyperparathyroid patients with vertebral osteopenia. The cumulative percent change from yr 0 baseline by site is shown. *, Change from baseline, $P < 0.05$.

*vs.* 11.1 ± 0.3 mg/dL)]. Those who underwent parathyroidectomy could not be distinguished from those followed without intervention by any other demographic, biochemical, or bone densitometric index.

An annual BMD was determined for 4 yr after baseline measurement or surgery. After parathyroidectomy, lumbar spine BMD rose 15 ± 3% at yr 1 ($P < 0.005$), reaching 21 ± 4% above the baseline by yr 4 ($P < 0.01$; Fig. 2, *top panel*). The mean z-score rose from −2.401 ± 0.18 to −1.134 ± 0.40 by yr 4 at the lumbar spine (a 53% increase; $P < 0.0005$), actually rising into the normal range. In the seven postmenopausal women who underwent parathyroidectomy, lumbar spine BMD rose in a similar fashion, increasing by 13 ± 3% at the end of 1 yr and rising to 16 ± 5% above baseline by 4 yr ($P < 0.01$; Fig. 3). In contrast to the vigorous rise seen at the lumbar spine, a more modest rise in BMD was noted at the femoral neck (Fig. 2, *middle panel*): 5 ± 2% at yr 1 ($P = 0.011$) and 7 ± 3% by yr 4 ($P = 0.05$). Although no significant change in BMD was seen at the distal radius, there was a trend toward increasing BMD as was seen at the other sites (Fig. 2, *bottom panel*).

In the eight patients followed with no intervention, BMD did not show a significant change at any site (Fig. 4). Again, despite the passage of 4 yr, the five postmenopausal women in this group also showed no decline in lumbar spine BMD (data not shown).

## Discussion

The decision to opt for surgery in primary hyperparathyroidism is often a difficult one. To date, surgical guidelines have been targeted to symptoms of the disease (nephroli-

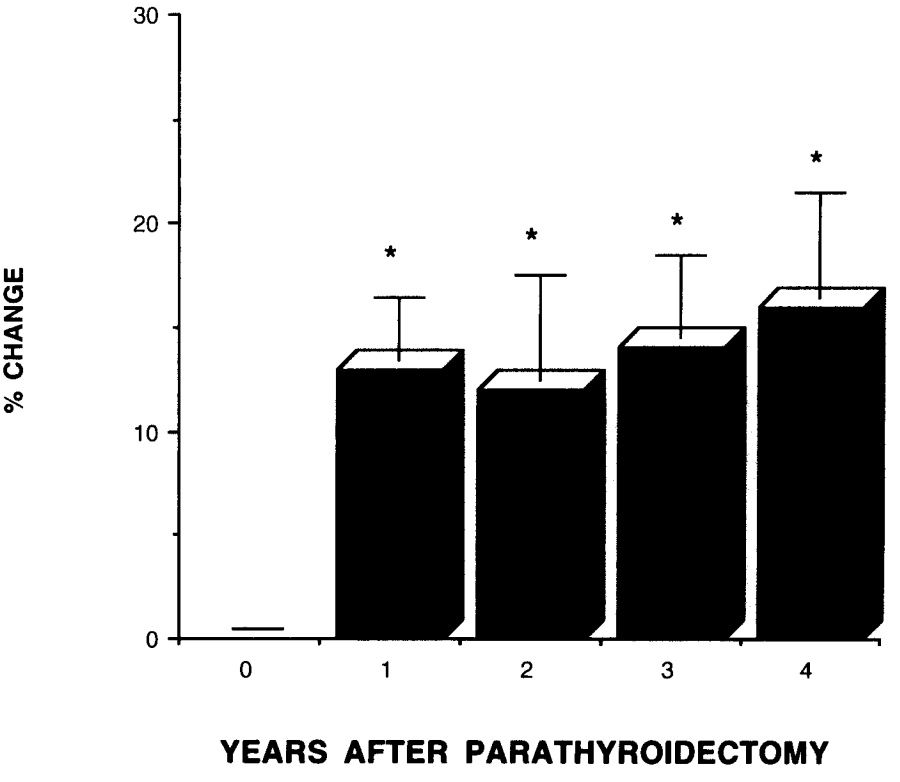


FIG. 3. Lumbar spine bone density after parathyroidectomy in postmenopausal primary hyperparathyroid women with vertebral osteopenia. The cumulative percent change from yr 0 baseline is shown. *, Change from baseline, $P < 0.05$.

thiasis, osteitis fibrosa cystica, classic neuromuscular disease), anticipated length of exposure to (young age), and severity of known effects of excess PTH (elevated serum or urinary calcium; reduced cortical bone density). The results of this study suggest that another criterion for parathyroidectomy be added, namely reduced vertebral bone density. Unlike previous guidelines for parathyroidectomy, this criterion is not readily explained by the classical actions of PTH on bone.

PTH is known to have a dual effect on the skeleton: a catabolic effect on cortical bone and an anabolic effect on cancellous bone (27–30). In the typical patient with primary hyperparathyroidism, the densitometric pattern resulting from PTH excess is that of reduced density at cortical sites (*i.e.* the distal radius) and normal density at cancellous sites (*i.e.* the lumbar spine) (10). Preservation of cancellous elements has also been well documented by histomorphometric analysis of bone biopsy specimens (11, 15, 16). In addition, in contrast to the normal aging skeleton, trabecular connectivity is maintained with advancing age in primary hyperparathyroidism (31, 32).

The patients described here exhibit a skeletal profile unlike that of the usual patient with primary hyperparathyroidism. In these patients there is a reversal of the pattern of primary hyperparathyroid bone loss described above, with bone density highest at the more cortical radius, intermediate at the femoral neck, and lowest at the more cancellous site, the lumbar spine. This finding would be anomalous for a specific action of PTH and suggests, alternatively, a nonparathyroid cause(s) of reduced cancellous bone. This pattern of bone loss may be the result of different mechanisms in different individuals. In the 12 postmenopausal women, estrogen deficiency may be responsible for reduced lumbar spine bone mass. Other factors contributing to this unusual pattern of bone loss remain to be elucidated.

The effect of parathyroidectomy on the skeletal consequences of primary hyperparathyroidism is of interest in these patients, as it is in all patients with this disorder. Historically, in patients with classical disease, parathyroidectomy led to improvement in the radiological manifestations of osteitis fibrosa cystica, with clear evidence of skeletal remineralization (33). In the present day, after surgery for primary hyperparathyroidism, various radiological and densitometric techniques have shown cortical bone loss to be at least partially reversible (17–20, 34). Data for cancellous sites have emerged only recently. Hesp *et al.* (35) reported an increase in the cancellous, but not the cortical, components of the radius 1–2 yr after parathyroidectomy (by quantitative computerized tomography), whereas Christiansen *et al.* (36) reported increased trabecular bone volume in the early (mean, 7 months) postoperative period. Reporting on 7 patients with primary hyperparathyroidism, Abugassa *et al.* (37) showed a 10% increase in lumbar bone density just 3 months after surgery. We confirmed and extended this observation recently, reporting an increase in lumbar spine, femoral neck, and (more modestly) radial bone density in 34 patients followed for 4 yr after parathyroidectomy (21).

Although there may be more than one mechanism underlying their bone densitometric profiles, patients with low lumbar spine bone density show a typical response to surgery. Parathyroidectomy in these patients is associated with a remarkable improvement in lumbar spine BMD. The significant increase in absolute BMD occurs while normal individuals experience an expected age-related decline in bone mass. This accounts for the rather dramatic improvement of lumbar spine z-scores. Furthermore, the 21% increase in lum-

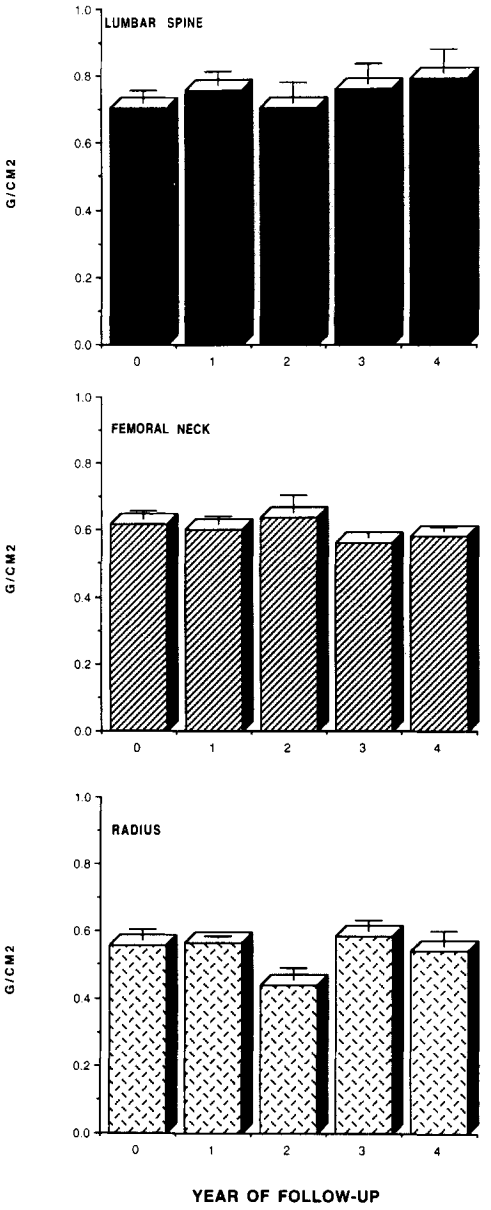


FIG. 4. Annual BMD by site in eight patients with vertebral osteopenia who were followed without treatment for primary hyperparathyroidism.

bar spine BMD after parathyroidectomy in these patients is greater than the 12% rise previously reported in patients with primary hyperparathyroidism whose lumbar spine z-scores are normal (21). This difference reflects a true increase in absolute BMD, not merely a greater percentage due to a lower baseline preoperative value. Indeed, the absolute increase in BMD is nearly one third greater in patients with low vertebral density than that in the previously reported cohort (21). We have shown that patients whose radius BMD is most severely reduced experience the greatest improvement after parathyroidectomy (21). In this study, patients whose lumbar BMD is most severely reduced experience the greatest increase after parathyroidectomy.

There is no clear explanation for the dramatic increase in bone density in these patients after parathyroidectomy. It seems paradoxical that removal of an anabolic agent for the cancellous skeleton, PTH, would lead to such marked anabolic effects at the highly cancellous lumbar spine. If the reduced lumbar BMD were a function of the hyperparathyroid state, reversal of this catabolic element would be beneficial. Remineralization of the enlarged remodeling space could then account for the improved bone density (36, 38). If the catabolic actions of PTH were responsible for the reduced lumbar spine density, however, one would expect the cortical sites (*i.e.* the radius) to be the most severely affected. The reversal of the usual pattern of bone loss, with cancellous bone affected more than cortical bone, strongly suggests another coexisting or antecedant mechanism is to account for the reduced cancellous bone mass in this subset of hyperparathyroid patients.

Finally, patients with low vertebral bone density followed without intervention showed stable nonprogressive BMD measurements over the 4-yr period of observation. This is consistent with the stable longitudinal forearm BMD reported in untreated primary hyperparathyroidism by Rao *et al.* (39) and is similar to the longitudinal data we recently reported in patients whose lumbar spine bone density was not reduced (26). Thus, regardless of the mineralization status of cancellous bone, the hyperparathyroid state appears to provide ongoing protection from expected age- and/or menopause-related bone loss.

The postmenopausal women in this group deserve special mention. In the 1980s, it was suggested that all postmenopausal women with primary hyperparathyroidism should undergo parathyroidectomy to protect them from the superimposed deleterious skeletal effects of the menopause and the hyperparathyroid state. Subsequent studies, from our group and others, have shown primary hyperparathyroidism to afford relative protection against the cancellous bone loss associated with estrogen deficiency (32). Postmenopausal women with primary hyperparathyroidism have higher cancellous bone volume and increased trabecular connectivity than age- and menopause-matched women. The postmenopausal women in this report bear greater resemblance to the typical postmenopausal osteoporotic patient than to the typical primary hyperparathyroid patient. However, nonintervention did not lead to further diminution of bone density, as would be expected in response to the passage of years in the menopause. Moreover, after parathyroidectomy, there was no evidence for renewed postmenopausal bone loss. Just the opposite was seen, with an impressive rise in bone density at the site of greatest bone loss.

On the basis of this new information, we suggest that in

**TABLE 2.** Proposed indications for surgery in primary hyperparathyroidism

1. Serum calcium >2.99 mmol/L (>12 mg/dL)
2. Marked hypercalciuria [>9.98 mmol/day (>400 mg/24 h)]
3. Overt manifestation of primary hyperparathyroidism (nephrolithiasis, *osteitis fibrosa cystica*, classic neuromuscular disease)
4. Markedly reduced cortical bone density
5. Reduced creatinine clearance in the absence of other cause
6. Age <50 yr
7. Markedly reduced cancellous bone density

primary hyperparathyroidism, patients who have low vertebral BMD should be considered for parathyroidectomy and, furthermore, that reduced cancellous bone density should become a new indication for surgery in this disease (Table 2).

## Acknowledgments

We are indebted to the following individuals for their help with this project: Drs. T. Jacobs, E. Shane, and E. Siris for ongoing care of the study patients, and Dr. M. Seibel for performance of the pyridinium cross-link assays.

## References

1. **Heath H, Hodgson SF, Kennedy MA.** 1980 Primary hyperparathyroidism: incidence, morbidity and economic impact in a community. N Engl J Med. 302:189–193.
2. **Mundy GR, Cove DH, Fisken R.** 1980 Primary hyperparathyroidism: changes in the pattern of clinical presentation. Lancet. 1:1317–1320.
3. **Scholz DA, Purnell DC.** 1981 Asymptomatic primary hyperparathyroidism. Mayo Clin Proc. 56:473–478.
4. **Coe FL, Favus MJ.** 1980 Does mild, asymptomatic primary hyperparathyroidism require surgery? N Engl J Med. 302:224.
5. **Hodgson SF, Heath H.** 1981 Asymptomatic primary hyperparathyroidism. Treat or follow? Mayo Clin Proc. 56:521.
6. **Bilezikian JP.** 1985 Surgery or no surgery for primary hyperparathyroidism. Ann Intern Med. 102:402.
7. **Vant Hoff W, Ballardie FW, Bicknell EJ.** 1983 Primary hyperparathyroidism: the case for medical management. Br Med J. 287:1605–1608.
8. **Parfitt AM, Rao DS, Kleerekoper M.** 1991 Asymtomatic primary hyperparathyroidism discovered by multichannel biochemical screening: clinical course and considerations bearing on the need for surgical intervention. J Bone Miner Res. 6(Suppl 2):s97–s101.
9. **Potts JT (ed).** 1991 NIH Consensus Development Conference Statement on Primary Hyperparathyroidism. J Bone Miner Res. 6:s9–s13.
10. **Silverberg SJ, Shane E, de la Cruz L, et al.** 1989 Skeletal disease in primary hyperparathyroidism. J Bone Miner Res. 4:283–291.
11. **Mosekilde L, Melsen F.** 1978 A tetracycline-based histomorphometric evaluation of bone resorption and turnover in hyperthyroidism and hyperparathyroidism. Acta Med Scand. 204:97–102.
12. **Kleerekoper M, Villanueva AR, Mathews CHE, Rao DS, Pumo B, Parfitt AM.** 1983 PTH mediated bone loss in primary and secondary hyperparathyroidism. In: Frame B, Potts JT, eds. Clinical disorders of bone and mineral metabolism. Amsterdam: Excerpta Medica; 200–202.
13. **Eriksen EF, Mosekilde L, Melsen F.** 1986 Trabecular bone remodeling and balance in primary hyperparathyroidism. Bone. 7:213–221.
14. **Delling G.** 1987 Bone morphology in primary hyperparathyroidism: a qualitative and quantitative study of 391 cases. Appl Pathol. 55:147–159.
15. **Parisien M, Silverberg SJ, Shane E, et al.** 1990 The histomorphometry of bone in primary hyperparathyroidism: preservation of cancellous bone. J Clin Endocrinol Metab. 70:930–938.
16. **Christiansen P, Steiniche T, Vesterby A, Mosekilde L, Hessov I, Melsen F.** 1992 Primary hyperparathyroidism: iliac crest trabecular bone volume, structure, remodeling and balance evaluated by histomorphometric methods. Bone. 13:41–49.
17. **Genant HK, Heck LL, Lanzl LH, Rossman K, Horst JV, Paloyan E.** 1973 Primary hyperparathyroidism: a comparative study of clinical, biochemical and radiological manifestations. Radiology. 109:513–524.
18. **Dalen N, Hjern B.** 1974 Bone mineral content in patients with primary hyperparathyroidism without radiological evidence of skeletal changes. Acta Endocrinol (Copenh). 75:297–304.
19. **Leppla DC, Snyder W, Pak CYC.** 1982 Sequential changes in bone density before and after parathyroidectomy in primary hyperparathyroidism. Invest Radiol. 17:604–606.
20. **Mautalen C, Reyes HR, Ghiringhelli G, Fromm G.** 1986 Cortical bone mineral content in primary hyperparathyroidism. Changes after parathyroidectomy. Acta Endocrinol (Copenh). 111:494–497.
21. **Silverberg SJ, Gartenberg F, McMahon DJ, et al.** 1995 Increased bone mineral density following parathyroidectomy in primary hyperparathyroidism. J Clin Endocrinol Metab. 80:729–734.
22. **Nussbaum S, Zahradnik R, Lavigne J, et al.** 1987 Highly sensitive two-site IRMA of parathyrin and its clinical utility in evaluating patients with hypercalcemia. Clin Chem. 33:1364–1367.
23. **Reinhardt TA, Horst RL, Orf JW, Hollis BW.** 1984 A microassay for 1,25-dihydroxyvitamin D not requiring HPLC: application to human studies. J Clin Endocrinol Metab. 58:91–98.
24. **Seibel MJ, Gartenberg F, Silverberg SJ, Ratcliffe A, Robins SP, Bilezikian JP.** 1992 Urinary hydroxypyridinium crosslinks of collagen in primary hyperparathyroidism. J Clin Endocrinol Metab. 74:481–486.
25. **Parfitt AM.** 1990 Interpretation of bone densitomtery measurements: disadvantages of a percentage scale and a discussion of some alternatives. J Bone Miner Metab. 5:537–540.
26. **Silverberg SJ, Gartenberg F, Jacobs TP, et al.** 1995 Longitudinal bone density measurements in untreated primary hyperparathyroidism. J Clin Endocrinol Metab. 80:723–728.
27. **Parfitt AM.** 1987 Surface specific bone remodeling in health and disease. In: Kleerekoper M, Krane S, eds. Clinical disorders of bone and mineral metabolism. New York: Liebert; 7–14.
28. **Reeve J, Meunier PJ, Parsons J, et al.** 1980 Anabolic effect of human parathyroid hormone fragment (hPTH 1–34) therapy on trabecular bone in involutional osteoporosis: a multicenter trial. Br Med J. 280:1340–1344.
29. **Slovik DM, Rosenthal DI, Doppelt SH, et al.** 1986 Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1–34) and 1,25-dihydroxyvitamin D. J Bone Miner Res. 1:377–381.
30. **Marcus R.** 1994 Parathyroid hormone and growth hormone in the therapy of osteoporosis. In: Bilezikian JP, Levine M, Marcus R, eds. The parathyroids. New York: Raven Press: 813–823.
31. **Parisien M, Mellish RWE, Silverberg SJ, et al.** 1992 Maintenance of cancellous bone connectivity in primary hyperparathyroidism: trabecular and strut analysis. J Bone Miner Res. 7:913–920.
32. **Parisien M, Cosman F, Mellish RWE, et al.** 1995 Bone structure in postmenopausal hyperparathyroid, osteoporotic and normal women. J Bone Miner Res. 10:1393–1399.
33. **Albright F, Reifenstein EC.** 1948 The parathyroid glands and metabolic bone disease. Baltimore: Williams and Wilkins.
34. **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.
35. **Hesp R, Tellez M, Davidson L, Elton A, Reeve J.** 1987 Trabecular and cortical bone in the radii of women with parathyroid adenomata. Bone Miner. 2:301–310.
36. **Christiansen P, Steiniche T, Mosekilde L, Hessov I, Melsen F.** 1990 Primary hyperparathyroidism: changes in trabecular bone remodeling following surgical treatment. Bone. 11:75–79.
37. **Abugassa S, Nordenstrom J, Eriksson S, Mollerstrom G, Alveryd A.** 1990 Skeletal remineralization after surgery for primary and secondary hyperparathyroidism. Surgery. 107:128–133.
38. **Heaney RP.** 1994 The bone remodeling transient: implications for the interpretation of clinical studies of bone mass change. J Bone Miner Res. 9:1515–1523.
39. **Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM.** 1988 Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism. J Clin Endocrinol Metab. 67:1294–1298.