

Effects of Hormone Replacement Therapy on Bone Mineral Density in Postmenopausal Women With Primary Hyperparathyroidism

Four-Year Follow-up and Comparison With Healthy Postmenopausal Women

Brandon J. Orr-Walker, MBChB; Margaret C. Evans, BSc; Judy M. Clearwater; Anne Horne, MBChB; Andrew B. Grey, MBChB; Ian R. Reid, MD

Background: Long-term treatment of patients with asymptomatic primary hyperparathyroidism remains controversial, but the presence of osteoporosis is regarded as an indication for parathyroidectomy. Hormone replacement therapy (HRT) is a possible alternative therapy in osteopenic postmenopausal women with the disorder, and results of short-term studies suggest a beneficial effect on bone mass comparable to that achieved by parathyroidectomy. Longer-term data are required to further assess the efficacy of this treatment in chronic stable primary hyperparathyroidism.

Methods: We report the results of the extension from 2 to 4 years of a randomized, placebo-controlled trial of HRT in postmenopausal women with primary hyperparathyroidism. Of 23 postmenopausal women with primary hyperparathyroidism, 11 received active HRT with conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 5 mg/d, and 12 received placebo. Bone mineral density was measured throughout the skeleton at 6-month intervals using dual-energy x-ray absorptiometry in these women and in 50 normocalcemic age-matched control subjects. None of the 23 patients withdrew during the extension period.

Results: Changes in bone mineral density were more positive in those taking HRT than placebo, with the between-group differences at 4 years being 4.6% in the total body, 7.5% in the lumbar spine, 7.4% in the femoral neck, 8.2% in the femoral trochanter, 6.8% in the legs, and 7.0% in the forearm ($P < .01$). At skeletal sites composed predominantly of cortical bone, there was a progressive divergence of the 2 groups. Biochemical markers of bone turnover remained lower throughout the study in women taking HRT. When rates of bone loss were compared between the placebo group and healthy women of comparable age, bone loss tended to be more marked throughout the skeleton in women with hyperparathyroidism, but only in the total body and its legs subregion was this difference significant.

Conclusions: Hormone replacement therapy is efficacious in the long-term management of osteopenia in postmenopausal women with primary hyperparathyroidism and thus represents an important new therapeutic option for asymptomatic patients who do not have other indications for surgery. Bone loss seems to be accelerated in untreated primary hyperparathyroidism.

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P RIMARY hyperparathyroidism is a common condition affecting up to 3% of postmenopausal women.¹ Automated biochemical testing has resulted in a quadrupling of the apparent incidence of this disorder² and has led to the recognition that many of these individuals are asymptomatic. Thus, the optimal management of mild hyperparathyroidism is unclear. Results of prospective studies³⁻⁵ have suggested that the natural history of asymptomatic primary hyperparathyroidism is benign in most individuals so that conservative management without surgery is an option. However "asymptomatic" does not necessarily imply uncomplicated. Osteoporosis might be more common in patients with primary hyperparathyroidism,⁶ particularly

in postmenopausal women, the group in whom the diagnosis is most frequently made.

Osteoporosis has been put forward as an indication for parathyroidectomy, and surgery results in increases in bone mineral density (BMD).⁷⁻⁹ However, hormone replacement therapy (HRT) also substantially increases BMD in postmenopausal women with primary hyperparathyroidism, as Grey et al¹⁰ demonstrated in a recent randomized controlled trial. To our knowledge, there are no randomized controlled studies comparing surgery with HRT, but observational studies^{8,9} suggest that the changes in BMD in the first 1 to 2 years after either of these interventions are comparable. Before HRT can be accepted as a therapy for osteopenia in postmenopausal women

From the Department of Medicine, University of Auckland, Auckland, New Zealand.

PARTICIPANTS AND METHODS

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The 33 women (17 receiving active therapy and 16 receiving placebo) who completed the original 2-year randomized comparison of HRT with placebo were invited into a 2-year extension. Twenty-three (11 receiving active therapy and 12 receiving placebo) agreed and continued in the masked study. The decision to participate in the extension was made by patients without knowledge of their BMD data from years 1 and 2 of the study. All 23 patients entering the extension completed it.

Full details of the study protocol have been published previously.¹⁰ In each patient, hypercalcemia was detected incidentally on routine blood testing, and primary hyperparathyroidism was confirmed by the presence of a concomitant elevation of serum ionized calcium levels and intact parathyroid hormone levels. Any patient electing non-surgical management of hyperparathyroidism who was free of other diseases and medications that affect calcium metabolism was eligible for study entry.

Table 1 shows the baseline data for patients who entered the trial extension. Those electing to continue in the study were not significantly different from those withdrawing with respect to any of the variables shown. However, baseline BMD at several sites was lower in those randomized to HRT compared with those taking placebo in this cohort, suggesting that in some way there was a bias toward those with more severe osteoporosis in the HRT group deciding to remain in the study.

This article also reports BMD data from 50 healthy women of comparable age receiving placebo alone in studies of the prevention of postmenopausal bone loss. They were studied using the same densitometer and during the same period as patients with hyperparathyroidism. Their baseline characteristics (**Table 1**) were comparable to those of patients with hyperparathyroidism except with respect to body mass index and dietary calcium intake. The higher body weight of this cohort of women with hyperparathyroidism has been reported previously.¹¹ Baseline biochemistry results for controls show the expected differences from patients with hyperparathyroidism (**Table 2**).

PROTOCOL

At the beginning of the original study, patients were individually randomized by an independent researcher following a predetermined, documented strategy. The randomization was carried out without knowledge of the patient's clinical details. This individual then supervised the dispensing of the appropriate medication into bottles labeled with the patient's study number. Treatment codes could only be accessed by this individual, and this was permitted only after withdrawal of a patient from the study.

In the second 2 years of the study, patients continued their previously assigned treatment (either conjugated equine estrogen, 0.625 mg/d, and medroxyprogesterone acetate, 5 mg/d, or placebo). The women were seen every 6 months, at which time BMD (Lunar DPX-L, Madison, Wis), interim medical history (including a specific inquiry regarding fractures), and compliance with trial medication (assessed by tablet counts) were assessed. At study entry and at the final visit, all patients underwent lateral radiography of the thoracic and lumbar spine. Incident fractures were defined as reductions in anterior, middle, or posterior heights of the vertebral bodies that were 20% or greater and 4 mm or greater.

STATISTICAL ANALYSIS

Baseline data for the HRT and control groups were compared with those for the placebo group using the Student *t* test. The effects of HRT on bone loss in women with hyperparathyroidism were assessed by repeated-measures analysis of variance of the absolute changes in BMD from baseline for each patient. Because of the trend for baseline bone densities to be lower in the HRT group, this analysis included baseline BMD as a covariable, although this adjustment made little difference in the *P* values derived. By convention, data in the figures are shown as percentages of baseline values.

Rates of change in BMD during the entire study period were determined in patients with hyperparathyroidism assigned to placebo treatment and in the control group by linear regression of each patient's BMDs against time. The slopes of these regression lines were then compared between the groups, with and without adjustment for weight, using the general linear models procedure of SAS. All analyses were performed using SAS statistical software version 6.12 (SAS Institute Inc, Cary, NC), tests were 2-tailed, and $\alpha = .05$.

with hyperparathyroidism, its long-term efficacy requires documentation. This study reports an extension of our original randomized controlled trial to 4 years and compares the rates of bone loss in women with hyperparathyroidism receiving placebo with those in healthy postmenopausal women.

RESULTS

EFFECTS OF HRT

The effects of HRT on BMD in patients with primary hyperparathyroidism are shown in **Figures 1, 2, and 3**. At all sites there were significant benefits from the use of HRT, with the between-group differences at 4 years being 4.6% in the total body, 7.5% in the lumbar spine,

7.4% in the femoral neck, 8.2% in the femoral trochanter, 6.8% in the legs, and 7.0% in the forearm. In the predominantly cortical regions (forearm and legs), the 2 groups progressively diverged throughout the study, with bone loss at these sites during years 2 to 4 being significantly greater in the placebo group ($P < .01$). Elsewhere in the skeleton, the therapeutic dividend tended to plateau in the latter half of the study period, although it was clearly maintained.

During the 4 study years there were no incident vertebral fractures in either group. In the HRT group, 1 woman had a fractured humerus and 1 had a fractured fibula. In the placebo group, there was 1 fractured fibula. The rate of fractures was not different between groups. The incident fracture rate for the whole group was 3.2% per year (95% confidence interval, 0.7%-9.2%).

COMPARISON OF HEALTHY AND HYPERPARATHYROID WOMEN

Serum ionized calcium concentrations had been stable in years 1 and 2¹⁰ but declined slightly in year 4 in the HRT group (Table 2). There was a rise in parathyroid hormone concentrations in the placebo group, which did not occur in those taking HRT, and the latter patients showed a reduction in bone turnover markers (serum alkaline phosphatase level and urine hydroxyproline excretion). The reduction in fasting urine calcium excretion that was observed in years 1 and 2 in the HRT group was no longer apparent at 4 years. The serum 25-hydroxyvitamin D level tended to decline in both groups, but the serum creatinine level was stable.

Although minor vaginal bleeding and mastalgia were common at initiation of HRT in these women,¹⁰ only 1 woman had further bleeding between years 2 and 4 of the study, and this settled without changes to her treatment. Breast tenderness was reported during the trial extension in 1 woman receiving HRT and 3 receiving placebo.

Figure 4 shows mean rates of change in BMD in women with hyperparathyroidism compared with control women of similar ages. These data have been adjusted for differences in body weight, but essentially the same results emerge without this adjustment. Bone loss tended to be more marked throughout the skeleton in women with hyperparathyroidism, but only in the total body and its legs subregion was this significant ($P = .006$ and $P < .001$ for between-group comparisons of rates of bone loss with weight correction for the body and legs, respectively; $P = .01$ and $P = .002$ without weight correction).

COMMENT

The results of this study confirm that HRT has a significant beneficial effect on BMD throughout the skeleton in postmenopausal women with primary hyperparathyroidism. The early effects are comparable to those reported by others from shorter, observational studies,^{8,9} but the present data extend the earlier studies by demonstrating that the treatment dividend tends to increase over time, particularly in cortical bone. Thus, at the end of 4 years of therapy, patients receiving HRT have BMDs at most sites that are 7% to 8% higher than those of patients receiving placebo. Such differences would be expected to result in a substantial decrease in the risk of fracture. The low rate of fractures in all patients with hyperparathyroidism in the present study, however, has not permitted this question to be directly addressed here.

The size of the benefit resulting from HRT in the present study is at least as great as that reported after surgery in most series. Data describing changes in axial BMD after parathyroidectomy^{8,9,12-15} are limited with respect to the number of patients studied and the duration of follow-up. However, only one study has demonstrated treatment effects greater than those seen in the present study. Silverberg et al¹³ report increases of 12% in spine and hip

Table 1. Baseline Characteristics of Participants*

| Characteristic | HRT Group (n = 11) | Placebo Group (n = 12) | Control Group (n = 50) |
|---|--------------------|------------------------|------------------------|
| Age, y | 65.9 ± 9.1 | 67.0 ± 5.0 | 65.4 ± 3.5 |
| Years since menopause | 15.3 ± 8.2 | 16.5 ± 7.3 | 15.8 ± 6.3 |
| Dietary calcium intake, mg/d | 610 ± 333† | 464 ± 198† | 1030 ± 592 |
| Body mass index, kg/m ² | 29.6 ± 7.3† | 29.7 ± 5.9† | 25.6 ± 4.1 |
| Alcohol consumption, g/d | 2.9 ± 5.1 | 2.8 ± 4.4 | 2.3 ± 1.2 |
| Smokers, No. | 3 | 0 | 3 |
| Bone mineral density, g/cm ² | | | |
| Lumbar spine | 0.91 ± 0.11† | 1.08 ± 0.19 | 1.04 ± 0.13 |
| Femoral neck | 0.75 ± 0.11 | 0.82 ± 0.14 | 0.83 ± 0.12 |
| Trochanter | 0.70 ± 0.12 | 0.76 ± 0.16 | 0.75 ± 0.11 |
| Total body | 0.94 ± 0.09† | 1.03 ± 0.09 | 1.05 ± 0.07 |
| Legs | 0.93 ± 0.12† | 1.05 ± 0.12 | 1.08 ± 0.09 |
| Middle forearm | 0.50 ± 0.07 | 0.52 ± 0.10 | 0.57 ± 0.06 |

*Data are given as mean ± SD except where indicated otherwise. HRT indicates hormone replacement therapy.

†Significant difference from the control group.

Table 2. Biochemical Indices at Baseline and 4 Years*

| Variable | Placebo Group | | HRT Group | | Control Group (Baseline) |
|-------------------------------|---------------|-------------|-------------|--------------|--------------------------|
| | Baseline | 4 y | Baseline | 4 y | |
| Ionized calcium, mmol/L† | 1.42 ± 0.02 | 1.42 ± 0.03 | 1.38 ± 0.02 | 1.32 ± 0.02‡ | 1.25 ± 0.01§ |
| Phosphate, mmol/L | 0.99 ± 0.03 | 0.93 ± 0.04 | 1.09 ± 0.05 | 0.99 ± 0.04 | 1.21 ± 0.13§ |
| Parathyroid hormone, pmol/L | 7.8 ± 0.9 | 11.4 ± 1.5‡ | 8.1 ± 1.0 | 9.4 ± 1.3 | 3.0 ± 0.20§ |
| 25(OH)D, µg/L | 26 ± 3 | 19 ± 3‡ | 20 ± 2 | 14 ± 3‡ | 29 ± 2 |
| 1,25(OH) ₂ D, ng/L | 75 ± 12 | ... | 75 ± 9 | ... | 38 ± 2§ |
| Creatinine, µmol/L¶ | 91 ± 3 | 89 ± 4 | 85 ± 3 | 86 ± 5 | 83 ± 1 |
| Alkaline phosphatase, U/L | 109 ± 10 | 107 ± 8 | 106 ± 8 | 76 ± 6‡ | 73 ± 2§ |
| uHP/Cr, mmol/mol | 46 ± 6 | 37 ± 5 | 50 ± 8 | 29 ± 3‡ | 29 ± 3§ |
| uCa/Cr, mol/mol | 0.57 ± 0.16 | 0.44 ± 0.10 | 0.50 ± 0.10 | 0.48 ± 0.09 | 0.24 ± 0.02§ |

*Data are given as mean ± SEM. HRT indicates hormone replacement therapy; 25(OH)D, serum 25-hydroxyvitamin D; 1,25(OH)₂D, serum 1,25-dihydroxyvitamin D; uHP/Cr, fasting urine hydroxyproline-creatinine ratio; uCa/Cr, fasting urine calcium-creatinine ratio; and ellipses, variable not measured at that time point. All other indices were measured in serum. Methods have been described previously.¹⁰

†To convert ionized calcium from millimoles per liter to milliequivalents per liter, divide millimoles per liter by 0.50.

‡Significantly different from baseline, $P < .05$.

§Significantly different from the pooled hyperparathyroid group, $P < .005$.

||To convert phosphate from millimoles per liter to milligrams per deciliter, divide millimoles per liter by 0.323.

¶To convert creatinine from micromoles per liter to milligrams per deciliter, divide micromoles per liter by 88.4.

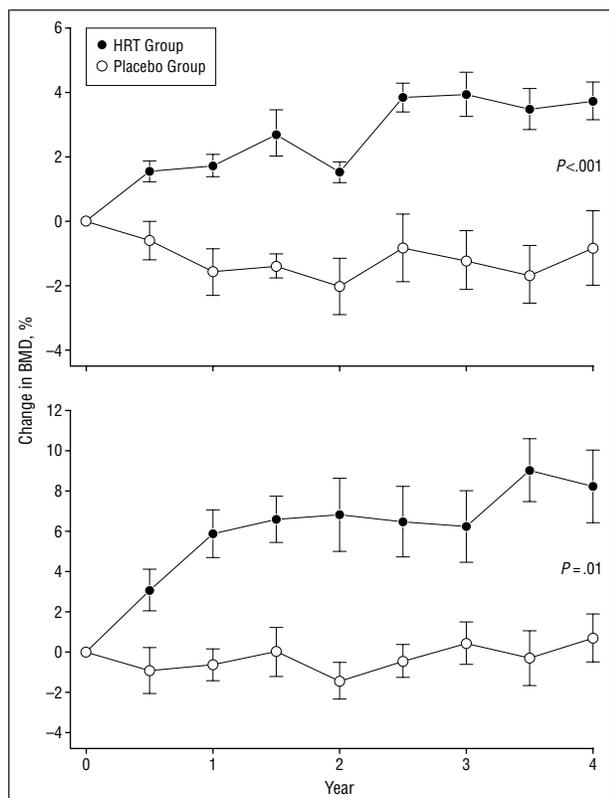


Figure 1. Mean \pm SE change in bone mineral density (BMD) of the total body (top) and lumbar spine (bottom) in postmenopausal women with primary hyperparathyroidism given hormone replacement therapy (HRT) or placebo for 4 years. Results are expressed as percentages of baseline values. Changes in BMD were significantly more positive in patients receiving HRT.

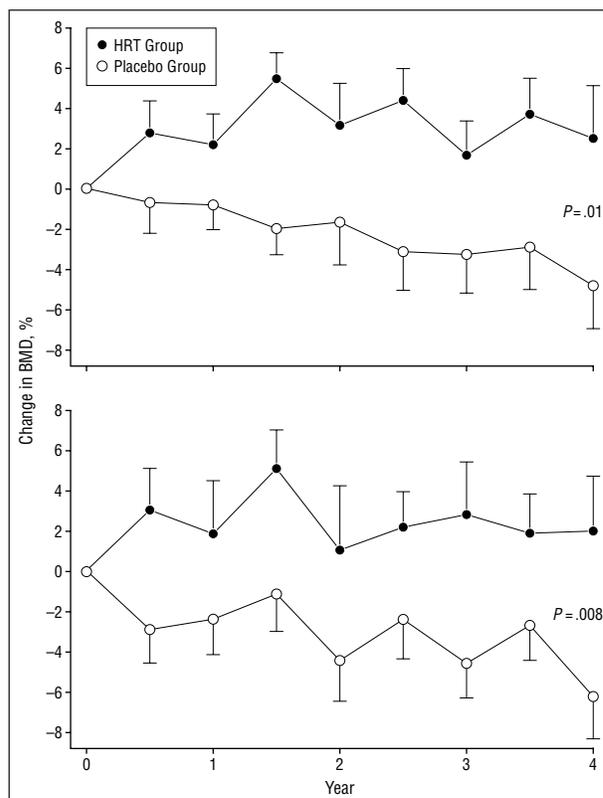


Figure 2. Mean \pm SE change in bone mineral density (BMD) of the femoral neck (top) and femoral trochanter (bottom) in postmenopausal women with primary hyperparathyroidism given HRT or placebo for 4 years. Results are expressed as percentages of baseline values. Changes in BMD were significantly more positive in patients receiving HRT.

BMD 4 years after surgery. These patients seem to have had more severe disease than those in the present study (based on their serum calcium concentrations), suggesting that they are not a strictly comparable cohort, and a different bone densitometer was used for the follow-up assessments from that on which the baseline values were measured. Cross-calibration of densitometers is clearly a potential source of error. Results of other studies^{4,16} suggest that forearm BMD is not substantially increased after successful parathyroidectomy, although the present data indicate that this might be because of the relatively high rate of ongoing loss at this site in untreated patients. Although the present study did not compare medical and surgical therapy, its results support those of 2 recent non-randomized studies^{8,9} in suggesting that HRT is at least as effective as surgery in managing osteopenia in postmenopausal women with primary hyperparathyroidism.

In contrast to studies of antiresorptive agents in healthy postmenopausal women, the magnitudes of the treatment effects in the present study were similar at predominantly cortical and trabecular sites. In part, this might reflect the shorter duration of many of those studies, during which the more gradual but progressive changes in cortical bone have yet to “catch up” with those in the trabecular compartment. This may be related to the slower turnover of cortical bone. Alternatively, this difference in response may be attributable to hyperparathyroidism. In support of this possibility are studies^{17,18} showing greater deficits in cortical bone in hyperparathyroidism, based on

densitometric and bone biopsy data. Bone remodeling kinetics in patients with primary hyperparathyroidism are different from those in healthy individuals, with smaller resorption volumes, shorter active resorption periods, and a higher frequency of remodeling cycles resulting in equivalent overall resorption rates.¹⁹ The effect of treatment on the remodeling transient might therefore differ from that found in euparathyroid individuals.

Bone loss tended to be more rapid in patients with hyperparathyroidism than in normocalcemic controls in the present study and was significantly accelerated in the total body and legs, both sites rich in cortical bone. This confirms results of an earlier study²⁰ in this cohort during 2 years of observation. Few comparable data are available. Results of studies of forearm BMD in primary hyperparathyroidism are conflicting, showing rates of bone loss from 0% to 5% per year (reviewed by Grey⁶). Only 2 other studies have prospectively assessed axial BMD in primary hyperparathyroidism. Guo et al⁹ reported that lumbar spine BMD declined at the same rate as in controls and that total body and femoral neck BMDs declined more rapidly. These findings are broadly consistent with our own. In contrast, Silverberg et al²¹ reported stability of BMD at the lumbar spine, femoral neck, and forearm during 7 years of observation. This cohort was heterogeneous (comprised of men and premenopausal and postmenopausal women), the study was uncontrolled, and there was a change in the bone densitometer used during the monitoring period. Thus, the pres-

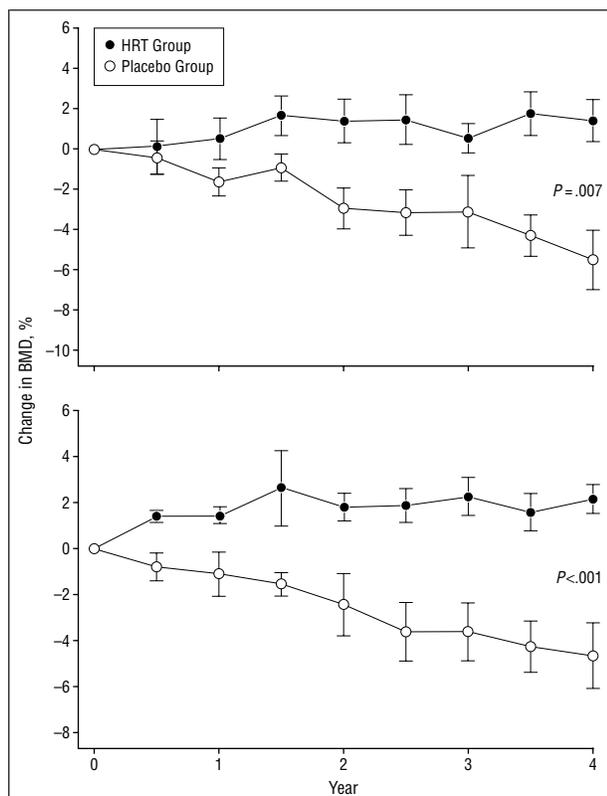


Figure 3. Mean \pm SE change in bone mineral density (BMD) of the proximal forearm (top) and legs (bottom) of the total body scans in postmenopausal women with primary hyperparathyroidism given HRT or placebo for 4 years. Results are expressed as percentages of baseline values. Changes in BMD were significantly more positive in patients receiving HRT.

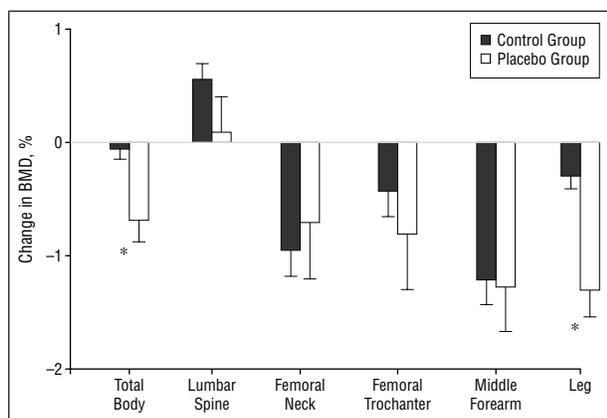


Figure 4. Rates of change in bone mineral density (BMD) in women with primary hyperparathyroidism receiving placebo compared with those in healthy women of comparable age. Data have been adjusted for body weight. Asterisk indicates a significant difference between groups, $P < .01$.

ent data and those of Guo et al⁹ are probably a more reliable assessment of the skeletal effects of primary hyperparathyroidism in postmenopausal women.

There is an apparent contradiction between the demonstrated increase in bone loss in the present study and a previous study¹¹ in which BMD assessed cross sectionally changed little in postmenopausal women with hyperparathyroidism. These findings might be reconciled by the observation that body weight is higher in postmenopausal women with this condition.^{11,15,22-24} Higher

body weight at the time of developing primary hyperparathyroidism would result in patients initially having a higher than normal BMD. Subsequently, higher rates of bone loss will result in normal absolute BMD some years later, although the weight-adjusted BMD will be reduced. Indeed, most studies reporting low BMDs in patients with this condition have presented weight-adjusted data. The scenario of a high baseline BMD with an increased rate of subsequent loss will give rise to a variety of findings in cross-sectional studies, depending on the disease duration at the time of sampling.

This scenario could also explain the variable fracture data that have been published. The present results suggest that the risk of vertebral and nonvertebral fractures is low in asymptomatic primary hyperparathyroidism. Other studies have indicated that the risk of fracture at the time of diagnosis is higher in primary hyperparathyroidism, but an ascertainment bias may have contributed to these findings, and some previous studies have included patients with more severe disease. Prospective data²⁵ from the Mayo Clinic initially indicated that incident fracture rates were not increased in patients with mild primary hyperparathyroidism, but results of a more recent study²⁶ from the same group contradict this. The largest study of fracture risk in primary hyperparathyroidism is that of Larsson et al.²⁷ During 23000 person-years of observation of women with primary hyperparathyroidism, the relative risk of hip fracture was 0.93. Thus, the data currently available are unable to definitively answer the important question of fracture risk in mild primary hyperparathyroidism.

The possible association of high body weight with hyperparathyroidism remains unexplained. These patients are overweight before the development of hypercalcemia,²⁸ suggesting that the obesity is not a consequence of hyperparathyroidism. There are now data^{29,30} suggesting that body weight is positively associated with serum parathyroid hormone concentrations in healthy individuals and that the low vitamin D levels seen in obesity do not account for this relationship. The mild secondary hyperparathyroidism associated with higher body weight possibly results in autonomous hyperparathyroidism in a few patients who have some other predisposition. If this hypothesis proves to be correct, then it has important implications for understanding some of the other possible associations of primary hyperparathyroidism, such as hypertension, insulin resistance, and increased cardiovascular mortality. Each of these might be contributed to by preexisting obesity, and, were this the case, would be unlikely to improve after parathyroidectomy.

Although many uncertainties remain with respect to the pathogenesis and skeletal effects of mild primary hyperparathyroidism, results of the present study confirm the efficacy of HRT in the long-term management of osteopenia in postmenopausal women with this condition. This provides an important new therapeutic option for asymptomatic patients who do not have other indications for surgery.

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