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Original Article

Relationship Between Serum Intact Parathyroid Hormone Concentrations and Bone Remodeling in Type I Osteoporosis: Evidence that Skeletal Sensitivity is Increased

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Abstract. To define the role of parathyroid gland function in the pathophysiology of bone loss in type I (postmenopausal) osteoporosis, we measured serum intact parathyroid hormone (PTH) concentration by immunoradiometric assay (IRMA) and by multisite immunochemiluminometric assay (ICMA) in 63 postmenopausal osteoporotic women (PMOp) with vertebral compression fractures and in 75 age-comparable postmenopausal normal women (PMNl). Also, tetracycline-based histomorphometric indices in cancellous bone were assessed in iliac biopsy samples from 61 PMOp and 28 PMNl women. Serum PTH concentrations by IRMA were similar in PMOp and PMNl (medians, 3.92 and 3.77 pmol/l; NS) but were significantly lower in PMOp by the more sensitive ICMA (medians, 2.82 and 3.14 pmol/l; $P<0.01$). By multiple linear regression analysis, serum PTH was directly related ($P<0.001$) to activation frequency, bone resorption rate, bone formation rate, and the calculated rate of bone loss. For each unit (pmol/l) increase in serum PTH by ICMA, activation frequency increased by 1.3%/year more ($P=0.01$), bone resorption rate increased by 3.9%/year more ($P=0.003$), and the rate of cancellous bone loss was 2.8% greater ($P=0.0003$) in the PMOp women compared with the PMNl women. Concentrations of serum estradiol, but not serum estrone, had a weak opposing effect to PTH, especially for bone formation rate. These data suggest that in PMOp the bone has increased sensitivity to the biologic effects of PTH. This may represent one of the fundamental pathophysiologic defects in PMOp and, in the setting of estrogen deficiency, may explain, in part, their greater rate of bone loss.

Keywords: Parathyroid hormone (PTH); Osteoporosis; Bone resorption; Bone formation

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Introduction

Definition of the relationship between parathyroid gland function and bone turnover in type I (postmenopausal) osteoporosis is critical for a full understanding of the pathogenesis of this condition. The bone loss in osteoporosis is the result of an increase in bone resorption relative to bone formation. Because parathyroid hormone (PTH) is the major systemic regulator of bone resorption, bone loss in osteoporosis could be the result of increased PTH secretion or increased sensitivity of bone to PTH. That PTH has a role in the pathogenesis of osteoporosis is supported by the observation that parathyroidectomy prevents experimental osteoporosis induced by low-calcium diet or by immobilization [1,2]. Furthermore, after total parathyroidectomy, lumbar spine bone mineral density (BMD) is increased in postmenopausal women compared with age-matched normal controls [3]. However, if bone loss results from factors that act directly on bone, independently of PTH, decreased serum PTH concentrations would be expected.

However, data concerning circulating PTH concen-

trations in osteoporosis have been conflicting. Our group has found decreased mean concentration of serum immunoreactive PTH (iPTH) as assessed by two radioimmunoassays (RIAs) and normal concentration with a third assay in women with type I osteoporosis [4–6]. Other workers have reported that serum iPTH concentrations were increased [7–9] or normal [10]. Measurements of urinary cyclic AMP excretion [11,12] and renal tubular excretion of phosphate [6], indices of PTH biologic activity, in women with type I osteoporosis have given results that are consistent with suppressed PTH secretion. Thus, whether parathyroid gland function is increased, decreased, or unchanged in type I osteoporosis remains controversial.

Two recent methodologic developments prompted us to reconsider this question. First, sensitive and specific immunometric assays for intact PTH that use two or more antibodies – with one set directed against epitopes in the COOH-terminal region of the PTH molecule and a second set directed against NH_2-terminal epitopes – are now available. Thus, unlike most earlier RIAs that used competition RIAs that detect multiple fragments of PTH as well as intact PTH, these assay systems detect only the biologically active, intact molecule and do not detect the biologically inactive COOH-terminal fragments which represent more than 90% of the circulating immunoreactive forms [13,14]. Moreover, because such assays use an excess of each antibody, binding of the ligand is increased and sensitivity is increased. Second, a bone histomorphometric method has been developed that, for the first time, measures resorption rates and remodeling balance of cancellous bone in iliac crest biopsy samples as well as rates of bone formation [15]. With this technique, resorption rate in an iliac biopsy sample correlates as well with whole skeletal resorption rate assessed by calcium kinetics as did bone formation rate measured by conventional tetracycline-based histomorphometry [16].

These techniques have allowed us to define the level of parathyroid gland function in type I osteoporosis and to relate it to indices of bone remodeling. We have also assessed differences in serum estrogen concentrations. These data have allowed us to test the validity of several competing pathophysiologic models.

Methods

Experimental Subjects

Sixty-three postmenopausal women (designated PMOp), ages 50 to 74 years (mean±SD, 65±5 years) with moderate to severe osteoporosis, were studied. The inclusion criteria were either (1) lumbar spine BMD below the fracture threshold of 1.0 g/cm^2, as measured by dual-photon absorptiometry and one or more vertebral crush fractures, or at least three anterior wedge fractures, or both, or (2) BMD<0.85 g/cm^2 and at least one vertebral fracture. A wedge fracture was defined as a reduction in anterior vertebral height by 15% to 25% of posterior height, and a crush fracture was defined as a reduction in anterior or mid-vertebral height by >25% of posterior height or reduction of the entire vertebral height by >25% of the heights of adjacent vertebrae. All had normal renal function (serum creatinine ≤ 1.2 mg/dl; glomerular filtration rate within the age- and sex-adjusted normal range). Other than osteoporosis, none had any condition known to affect calcium metabolism. None had taken calcium (>500 mg/day) or vitamin D supplements for at least 3 months prior to the study or estrogen for at least 6 months prior to the study. None had ever been treated with sodium fluoride or diphosphonate drugs.

The 75 postmenopausal normal controls (PMNl), ages 50 to 79 years (mean±SD, 65±6 years), were in good health, had normal renal function, and were not taking drugs known to affect bone or calcium metabolism. None had had a Colles' or hip fracture, and none had evidence of vertebral compression deformities on radiographs of the lumbar spine. In 28 of these women, ages 52 to 74 years (mean±SD, 65±4 years), transiliac biopsies were performed for histomorphometry.

The study was approved by the Mayo Institutional Review Board, and informed consent was obtained.

Assay of Intact PTH in Serum

Serum specimens were obtained between 0800 and 1000 h after an overnight fast. Intact PTH was measured both by the Allegro intact PTH immunoradiometric assay (IRMA) kit (Nichols Institute, San Juan Capistrano, CA) [13] and by a multisite immunochemiluminometric assay (ICMA) developed in the Mayo Clinic Endocrine Laboratories [17].

Briefly, the IRMA uses two affinity-purified polyclonal goat antibodies: one is directed against synthetic human PTH (39–84) fragments immobilized on plastic beads, and the other is an ^{125}I-labeled anti-human PTH(1–34) for detection of the intact PTH-anti-PTH (39–84)-plastic bead complex. In our laboratory, the detection limit (+2.6 SD of the zero pool) was 0.84 pmol/l (8 pg/ml). The intra-assay and interassay coefficients of variation were 9.6% and 11.4%, respectively, at 4.3 pmol/l (41 pg/ml).

The ICMA is a solid-phase 'sandwich' assay that is similar to the one developed by Brown et al. [14]. It utilizes two immobilized affinity-purified polyclonal antibodies and a third liquid-phase chemiluminescent-labeled antibody. The solid-phase antibodies were raised in goats against conjugated synthetic fragments hPTH (1–44) and hPTH (44–68). A mixture consisting of 1 μg of each of these antibodies is bound covalently to polystyrene beads (Co-BindM, Micromembranes, Inc., Newark, NJ). The labeled antibody, an affinity-purified sheep anti-hPTH (1–34) labeled with acridinium esters, was purchased commercially (Ciba Corning, Medfield, MA). After incubation of 200 μl of specimen or standard in duplicate with labeled antibody overnight at 20 °C, the antibody-coated beads are added and the

mixture is incubated for 3 hours at 20 °C on a horizontal rotator. After three washing steps, luminescent activity is initiated by the injection of alkaline peroxidase and is measured on an MLA-2 luminometer (Ciba Corning, Medfield, MA). The assay was standardized with hPTH (1–84) (Peninsular Laboratories, Inc., Belmont, CA). Recovery of added hPTH (1–84) was 95% to 100%. The detection limit for the assay was 0.08 pmol/l (0.8 pg/ml). The intra-assay coefficient of variation was 3.5% to 5.3% and the interassay coefficient of variation was 10.7% at 2.1 pmol/l (20 pg/ml). Results from the ICMA correlate well (r = 0.81) with those from an adenyl cyclase bioassay using osteoblast-like (ROS 17/2.8) cells [17].

Bone Histomorphometry

Intact transiliac bone biopsy specimens (7.5 mm in diameter) were obtained from 61 of the PMOp and from 28 of the PMNl under local anesthesia at 3 days after completion of double labeling with demeclocycline hydrochloride (150 mg administered four times daily for 3 days with a labeling interval of 14 days). Bone specimens were fixed, dehydrated in progressive concentrations of alcohol (70% to 100%), and embedded in a composite of methyl and glycol methacrylates. Four pairs of consecutive 5-μm sections were obtained at 100-μm intervals by using a Reichert–Jung microtome (Reichert Scientific Instruments, Buffalo, NY). The first section of each pair was stained with Goldner–Masson stain and was used to measure the relative proportions of forming, resorbing, and inactive surfaces under direct light microscopy. Erosion depth and wall thickness were measured under polarized light. The second section, left unstained, was used for fluorescence microscopy and measurement of bone volume and total surfaces. Histomorphometry was carried out with a computerized semiautomated system (Bioquant IV, R and M Biometrics, Inc., Nashville, TN) that uses a microscope, digitizing tablet, and computer software, modified to perform all calculations and to merge data from multiple sections for each specimen.

Twenty 0.41-mm^2 fields from each slide were examined (>33 mm^2 for total sample area). Bone formation rate at the tissue level (BFR/BV), the amount of bone formed per unit time per unit bone volume, was calculated from the mineral apposition rate, the extent of mineralizing surface (calculated from the sum of the double-labeled surfaces and half the single-labeled surfaces), and the ratio of cancellous bone surface to cancellous bone volume as described [15,18]. Bone resorption rate at the tissue level (BRs.R/BV), the amount of bone resorbed per unit time per unit bone volume, was calculated from resorption depth determined by direct lamellar counting, the ratio of active formation surfaces to resorption surfaces and tetracycline-based formation data [15]. The only assumptions made in this method are: (a) there is complete temporal coupling, i.e., that every resorption phase is followed by a formation phase; and (b) steady-state conditions apply.

Cancellous bone balance, the fractional volume of cancellous bone lost per year (Dt.BV/BV), was computed from the difference between volumes of cancellous bone formed (BFR/BV) and resorbed (BRs.R/BV) over time. The activation frequency (Acf) of new bone mineral units (BMUs') is a function of the mean time between the initiation of two successive remodeling cycles at the same point on the surface and is calculated as the reciprocal, the sum of the erosion period, formation period (FP), and quiescent period, the last being the product of the FP times the ratio of quiescent surface to osteoid surface. The nomenclature and symbols recommended by the Bone Histomorphometry Nomenclature Committee of the American Society of Bone and Mineral Research have been used [19] with additional symbols for indices of bone resorption as previously described [15].

Assays of Estrogen in Serum

Serum estrone and estradiol concentrations were measured by extraction with freshly opened anhydrous diethyl ether and chromatography of the extracts over microcelite columns by the method of Devane et al. [20]. The assay sensitivity was 2 pg/tube for both estrone and estradiol. The intra- and interassay coefficients of variation were less than 10% for both assays.

Statistical Methods

Because the distributions of values of serum PTH, estrogen concentrations, and histomorphometric indices were not gaussian, differences between the groups were tested by the Wilcoxon rank-sum test and relationships between variables were determined by rank correlation techniques. The effects of serum PTH, adjusting for estrogen concentrations, on the histologic indices of bone remodeling in the osteoporotic and normal subjects, were compared by multiple linear regression methods [21]. Similar regression methods were used to assess the relationship of PTH levels to disease status, estrogen concentration, and indices of bone turnover. In each multiple regression analysis, all possible interactions among independent variables were assessed and all model assumptions verified. All statistical tests were two-tailed and procedures in the Statistical Analysis System (SAS) were used for statistical computations.

Results

Serum intact PTH concentrations measured by IRMA and ICMA were highly correlated (r=0.85; P<0.001) (Fig. 1). The distributions of concentrations of serum PTH values in PMNl and PMOp are shown in Fig. 2.

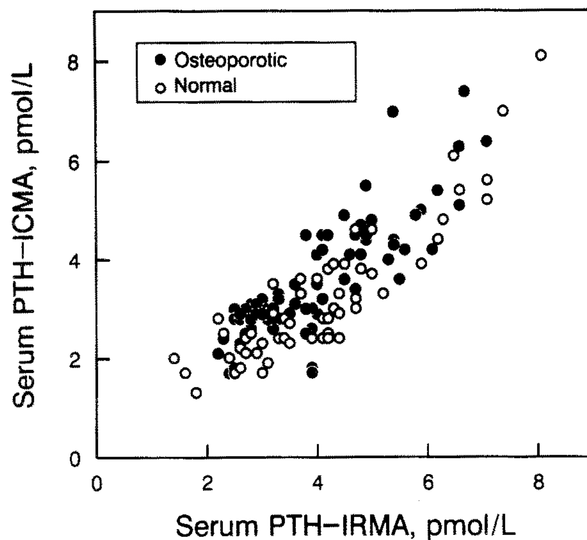

Fig. 1. Results of assays of concentrations of serum intact PTH in 124 PMOp (*filled circles*) and PMNl (*open circles*) by two methods (IRMA assay and ICMA assay). r=0.85.

The concentrations of serum PTH in PMOp and PMNl were not significantly different (medians, 3.92 and 3.77 pmol/l, respectively), when measured by the IRMA. By contrast, they were significantly lower in PMOp than in PMNl (medians, 2.82 and 3.14 pmol/l; P<0.01) when measured by the ICMA.

As previously reported [15], the median [range] for BRs.R/BV was significantly higher among PMOp than among PMNl (27.9%/year [2.3 to 96.3] and 13.9%/year [1.4 to 40.8]; P<0.05) and bone balance (Dt.BV/BV) was significantly more negative (−5.27%/year [−47.23 to 17.09] and −0.09%/year [−11.64 to 15.45]; P<0.05). There was an increase in Acf of borderline significance in PMOp (8.80 [0.88 to 46.32] and 5.88 [0.52 to 22.98] no. day × 10^{-4}; P=0.06). By contrast, BFR/BV was similar in the two groups (20.3%/year [2.2 to 73.3] for PMOp and 14.4%/year [1.4 to 52.3] for PMNl; P=0.20).

Serum PTH concentrations by both assays correlated significantly with histologic indices of bone resorption and bone formation in PMOp but not in PMNl (Table 1). The correlations were slightly higher for indices relating to bone resorption.

Table 1. Correlations between intact PTH concentrations and histologic indices

Index	r by group and assay			
	IRMA		ICMA	
	PMOp	PMNl	PMOp	PMNl
BRs.R/BV	0.41*	0.35	0.50*	0.24
Acf	0.43*	0.44†	0.48*	0.24
BFR/BV	0.35*	0.35	0.44*	0.18
Dt.BV	−0.33**	−0.06	−0.39**	−0.17

For differences between PMOp and PMNl: *P<0.001; †P<0.05; **P<0.01.

Serum estradiol concentrations were significantly lower in PMOp than in PMNl (medians, 29.4 pmol/l and 38.6 pmol/l; P<0.001) (Fig. 3) whereas serum estrone concentrations were significantly higher in PMOp (medians, 26.0 pmol/l and 19.0 pmol/l; P<0.01). Neither serum estradiol nor serum estrone concentration correlated significantly with any of the histologic indices.

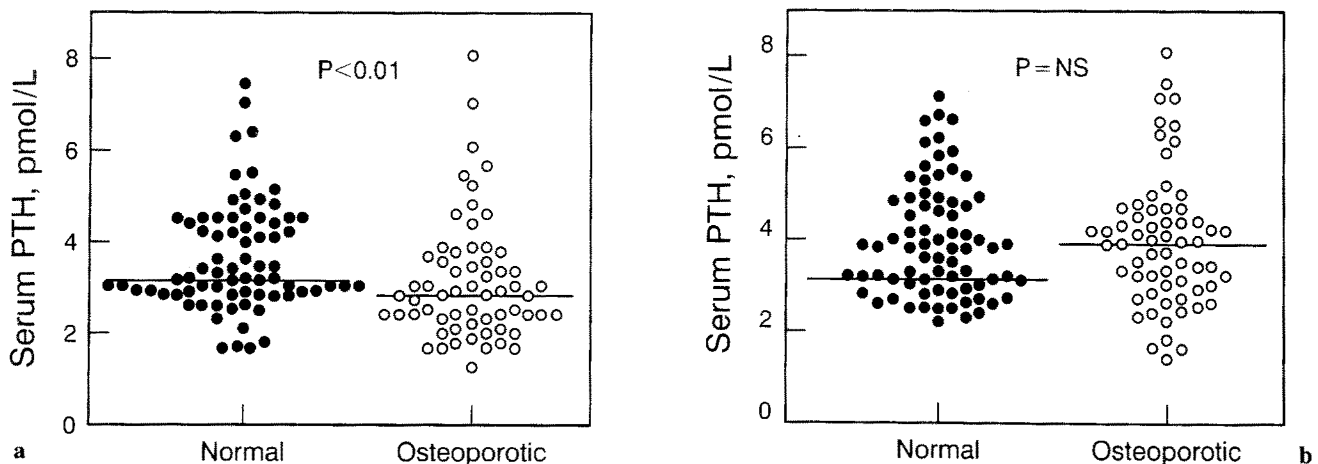

Fig. 2. Distribution of concentrations of serum PTH values in PMNl (*filled circles*) and PMOp (*open circles*) by ICMA (**a**) and IRMA (**b**). Median horizontal lines in PMOp did not differ significantly from median in PMNl IRMA but was significantly (P<0.01) lower by ICMA.

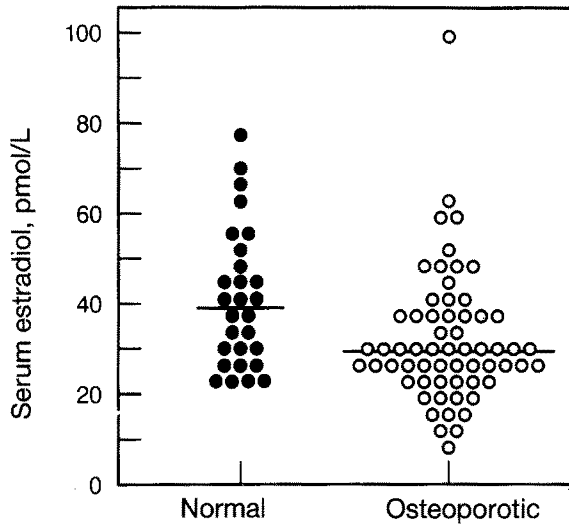

Fig. 3. Distribution of serum estradiol concentrations in PMNl (*open circles*) and PMOp (*filled circles*). Mean concentrations are lower ($P<0.01$) in PMOp.

Table 2 gives the results of multiple regression analyses using major histomorphometric indices of bone remodeling as dependent variables. The primary goal of this analysis was to quantify the effect of serum PTH on each index while adjusting for any significant effects of serum estrogen and disease state (osteoporosis or no osteoporosis). These data showed significant associations of serum PTH with all four histologic indices. Adjustments were made for the effect of the concentration of serum estradiol which were significant for BFR/BV and were marginally significant for BRs.R/BV; both effects were in the opposite direction of the effect of serum PTH. There were no significant associations with the concentration of serum estrone. The associations between serum PTH and BRs.R/BV, Acf, and Dt.BV/BV were significantly different between disease states. In each of these associations, the change in the dependent variable in response to change in serum PTH was greater in the PMOp women than in the PMNl women. The models predict that for each increase of serum PTH by the ICMA of 1 pmol/l in the PMOp women there will be an increase of 9.4%±1.7%/year in BRs.R/BV, an increase of 3.3%±0.7%/year in Acf, an increase of 5.1%±1.2%/year in BFR/BV, and a decrease of 4.0%±1.0%/year in Dt.BV/BV. The data in individual subjects for the association between serum PTH by the ICMA and each of the indices are shown in Figs. 4–7.

Multiple regression analyses using concentration of serum PTH as the dependent variable for each histomorphometric index of bone remodeling, adjusting for serum estrogen and disease state if significant, are given in Table 3. The primary goal of the analysis was to elucidate the mechanism of the increased sensitivity to PTH. Each of the models gave nearly equivalent results.

Table 2. Multiple regression models using histomorphometric indices as dependent variable and serum PTH as independent variable, adjusting for differences in serum estrogen and in disease state

	ICMA			IRMA		
	β(SE β)	*P*	R^2	β(SE β)	*P*	R^2
Acf						
Model:	—	<0.0001	0.24	—	<0.0001	0.22
Intercept	1.26 (2.25)	—	—	−0.006 (2.57)	—	—
Serum PTH						
In PMOp	3.27 (0.67)	<0.0001	—	2.85 (0.61)	<0.0001	—
In PMNl	1.96 (0.84)	0.0097	—	2.06 (0.75)	0.0028	—
Δ	1.31 (0.50)	0.0108	—	0.78 (0.43)	0.0731	—
BRs.R/BV						
Model:	—	<0.0001	0.31	—	—	0.26
Intercept	10.29 (6.36)	—	—	9.42 (7.13)	—	—
Serum estradiol	0.95 (0.49)	0.06	—	−0.94 (0.52)	0.08	—
Serum PTH						
In PMOp	9.41 (1.67)	<0.0001	—	7.48 (1.57)	<0.0001	—
In PMNl	5.54 (2.09)	0.004	—	5.08 (1.93)	0.004	—
Δ	3.86 (1.26)	0.0029	—	2.40 (1.13)	0.0357	—
BFR/BV						
Model:	—	<0.0001	0.20	—	0.0002	0.18
Intercept	13.00 (4.48)	—	—	11.48 (4.88)	—	—
Serum estradiol	−0.88 (0.34)	0.0111	—	−0.85 (0.34)	0.0147	—
Serum PTH	5.10 (1.17)	<0.0001	—	4.40 (1.07)	<0.0001	—
Dt.BV/BV						
Model:	—	<0.0001	0.23	—	<0.0001	0.19
Intercept	3.35 (3.29)	—	—	2.83 (3.79)	—	—
Serum PTH						
In PMOp	−3.97 (0.98)	<0.0001	—	−2.98 (0.90)	0.0013	—
In PMNl	−1.17 (1.23)	0.170	—	−0.86 (1.10)	0.1331	—
Δ	2.80 (0.73)	0.0003	—	2.12 (0.64)	0.0013	—

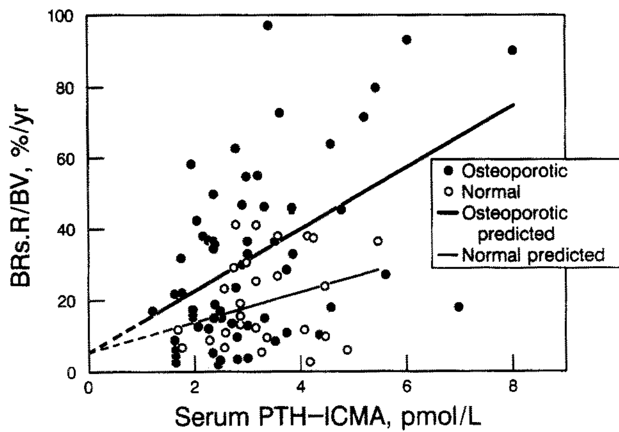

Fig. 4. Regression of BRs.R/BV on serum PTH by ICMA in PMNl (*thin line*) and PMOp (*thick line*). (R^2=0.31, P<0.0001).

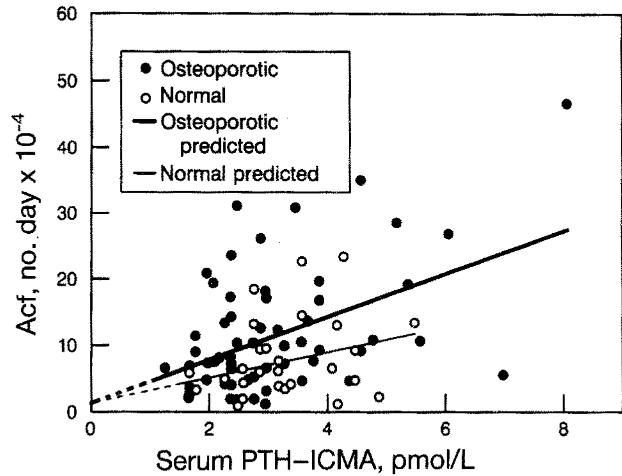

Fig. 5. Regression of Acf on serum PTH by ICMA in PMNl (*thin line*) and PMOp (*thick line*). (R^2=0.24, P<0.0001).

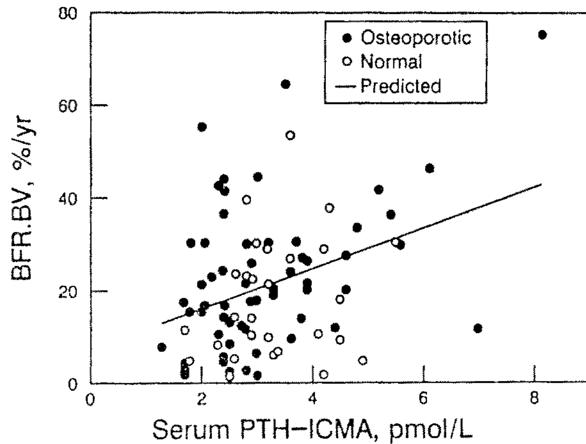

Fig. 6. Regression of BFR/BV (R^2=0.20, P<0.0001).

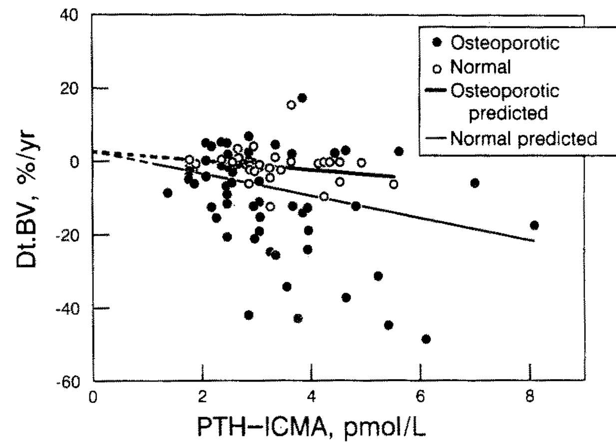

Fig. 7. Regression of Dt.BV/BV on serum PTH by ICMA in PMNl (*thin line*) and PMOp (*thick line*). (R^2=0.23, P<0.0001).

Table 3. Multiple regression models using serum PTH as dependent variable and bone histomorphometric indices as independent variable, adjusting for differences in serum estrogen and in disease state

	ICMA			IRMA		
	β(SE β)	P	R^2	β(SE β)	P	R^2
Model:	—	<0.0001	0.25	—	<0.0001	0.26
Intercept	1.81 (0.32)	—	—	2.45 (0.35)	—	—
Serum estradiol	0.079 (0.027)	0.0047	—	0.084 (0.030)	0.0056	—
Acf	0.062 (0.013)	<0.0001	—	0.071 (0.015)	<0.0001	—
Model:	—	<0.0001	0.27	—	<0.0001	—
Intercept	1.65 (0.32)	—	—	2.35 (0.36)	—	—
Serum estradiol	0.088 (0.027)	0.0015	—	0.093 (0.030)	0.0026	—
BRs.R/BV	0.026 (0.005)	<0.0001	—	0.027 (0.005)	<0.0001	—
Model:	—	<0.0001	0.23	—	<0.0001	0.21
Intercept	1.61 (0.35)	—	—	2.30 (0.39)	—	—
Serum estradiol	0.089 (0.028)	0.0018	—	0.095 (0.031)	0.0030	—
BFR/BV	0.036 (0.008)	<0.0001	—	0.037 (0.009)	<0.0001	—
Model:	—	0.0004	0.17	—	0.0008	0.15
Intercept	2.28 (0.31)	—	—	3.00 (0.33)	—	—
Serum estradiol	0.076 (0.029)	0.0094	—	0.080 (0.032)	0.0130	—
Dt.BV/BV	−0.033 (0.010)	0.0012	—	−0.034 (0.011)	0.0022	—

In all instances, the histomorphometric indices and the concentration of serum estradiol, but not serum estrone, were significantly and independently related to the concentration of serum PTH as assessed by either ICMA or IRMA. These associations were not influenced by the disease state.

Discussion

Previous attempts to evaluate parathyroid function in osteoporosis have produced conflicting results. One possible reason for this is the heterogeneity of the circulating immunoreactive forms of PTH. Glandular secretion of inactive COOH-terminal fragments increases under conditions of decreased PTH secretion [22], and these fragments have a longer half-life than intact PTH and thus accumulate in plasma [23]. Increases in the COOH-terminal fragment of PTH result in increases in total PTH immunoreactivity in assays with mid-molecule or COOH-terminal specificities [24], and, with these assays, investigators [4,10] have been unable to detect differences between osteoporotic and normal subjects. By contrast, the antisera that have 'whole-molecule' or NH_2-terminal specificity, suppressed parathyroid gland function in women with type I osteoporosis was demonstrated [6]. Although interpreted otherwise, suppression of parathyroid gland function is consistent with data showing that increases in serum PTH in response to phosphate administration were blunted in type I osteoporotic women [25]. Age-related increases in parathyroid gland function [6] as well as retention of immunoreactive fragments due to decreased renal function in some subjects could contribute to the increased iPTH levels found in some studies [7–9].

We attempted to resolve this controversy by using two new immunometric assays for PTH with greatly enhanced specificity and sensitivity. They detect only the intact hormone and not the biologically inert fragments [13,14]. The increased sensitivity allows detection of picomolar concentrations of the hormone and the assay of subnormal concentrations accurately.

Using these immunometric assays, we found that serum PTH concentrations were normal in PMOp (type I osteoporotic women) by IRMA, but were significantly decreased by ICMA. The reason for this discrepancy is unclear and deserves further study. The use of chemiluminescent aryl acridinium esters as high specific activity tracers enhances the sensitivity compared with radiometric assays using radioiodine tracers [26] and is responsible for the tenfold greater sensitivity of the ICMA. Furthermore, the different configurations of the antibodies directed against different epitopes in the two assays, together with the increased sensitivity of the ICMA, may have contributed to the different results.

Based on the finding of impaired calcium absorption in osteoporosis [5,27,28], there are three theoretic models for the pathophysiology of bone loss in type I osteoporosis. One model is that a primary decrease in calcium absorption due to an intrinsic gut defect or impaired vitamin D metabolism leads to secondary hyperparathyroidism and to increased bone loss [29,30]. In the second model, estrogen deficiency or some process independent of PTH [31] leads to a primary increase in bone loss that increases release of calcium into the circulation and inhibits PTH secretion; this secondarily decreases calcium absorption [5]. In this model, PTH plays no direct role in pathogenesis of bone loss. In the third model, increased sensitivity of bone to PTH leads to increased bone loss [32,33]. In this model, the increased rate of bone loss inhibits PTH secretion; however, because of increased sensitivity of bone to PTH, lower serum PTH concentrations are able to maintain higher bone turnover and higher rates of bone loss. The validity of these three models can be evaluated by examining the relationship of serum PTH concentration to the level of bone turnover. In the first model, the serum PTH concentration would be increased and there would be a positive relationship between it and bone turnover. In the second model, the serum PTH concentration would be decreased and there would be a negative relationship between it and bone turnover. In the third model, the serum PTH concentration would also be decreased but there would be a positive relationship between it and bone turnover.

Data obtained by immunometric assays for intact PTH show clearly that mean serum PTH concentration is not increased and may be decreased. Thus, the second or the third model, rather than the first model, appears to apply for the large majority of type I osteoporotic women although we cannot exclude the possibility of a subset with the characteristics of the first model. The finding of a positive correlation between serum PTH concentration and indices of remodeling and rates of cancellous bone loss strongly supports the third model over the second model.

As assessed by multiple linear regression analysis, serum PTH was strongly and significantly related to all four histomorphometric indices. Serum estradiol had a weak, opposing effect, especially for bone formation rate. The slope of the regression of serum PTH on histomorphometric indices of bone remodelling differed significantly between osteoporotic and normal women in a direction associated with increased bone turnover and increased bone loss. For each unit (pmol/l) increase in serum PTH by ICMA, activation frequency increased by 1.3%/year more (P=0.01), bone resorption rate increased by 3.9%/year more (P=0.003), and the rate of cancellous bone loss was 2.8% greater (P=0.0003) in the PMOp women compared with the PMNl women. Similar, but somewhat smaller, relationships were found for serum PTH by the IRMA.

Thus, the data are consistent with increased skeletal sensitivity to circulating PTH in an environment of estrogen deficiency accounting for at least part of the bone loss in type I osteoporosis, a hypothesis originally suggested by Heaney [32]. However, this hypothesis is not supported by data from another study by our group [34] in which bovine PTH (1–34) was infused at 400 U/

day over 3 days into postmenopausal normal and osteoporotic women and the effect on bone resorption was assessed by measurement of serum calcium concentration and urinary hydroxyproline excretion. Although both responses were greater in the osteoporotic than in the normal women, the increases did not achieve statistical significance. There are several reasons why increased bone sensitivity to PTH may not have been demonstrated in that study. First, the use of pharmacologic dosages of bovine PTH may have produced maximal responses in each group which could have masked differences that may have been present within the physiologic range. Second, although the osteoporotic patients had significantly lower bone mass, identical dosages of PTH were given to each group. Thus, the skeletal response may have been limited by the relatively lower number of bone remodeling units that could be activated by PTH in this group. Finally, the lack of sensitivity of the indices of bone resorption — changes in serum calcium concentration and urinary hydroxyproline excretion — may have underestimated the true biologic response. This study needs to be repeated with physiologic dosages of PTH adjusted to total bone mineral content and with more sensitive and specific indices of bone resorption, such as urinary excretion of pyridinium cross-links [35].

We also examined the relationship between serum estrogen concentrations and bone turnover in the normal and osteoporotic postmenopausal women. Two abnormalities were found. First, there was a small, but significant, decrease in the serum estradiol concentration and a small, but insignificant, increase in the serum estrone concentration. Because estradiol is at least threefold more potent than estrone, the net biologic effect probably was a decrease in estrogenic activity in the osteoporotic women. This is consistent with results of some [36,37] studies but not others [38–42]. This variability among studies suggests that a greater degree of estrogen deficiency is not a major etiologic factor for most women with type I osteoporosis, although it may be present in a variable subset. Second, the statistical model showed that serum estradiol had a weak effect on bone remodeling that was independent of and opposite to the effect of serum PTH for bone formation rate and, to a lesser degree, bone resorption rate. The inverse relationship between serum estrogen concentration and bone formation rate is consistent with the finding of estrogen receptors on human bone cells of the osteoblast lineage [43] and the finding that estradiol decreases proliferation of UMR-106 cells, a rat osteogenic sarcoma cell line [44].

In summary, in the presence of an increase in the resorption rate of cancellous bone, parathyroid gland function is not increased in type I osteoporosis and may be decreased. The positive relationship between serum PTH concentration and indices of bone remodeling is consistent with increased sensitivity of bone to PTH action. The opposing effect of serum estradiol concentration on the relationship between serum PTH and bone remodeling is consistent with a role for residual postmenopausal estrogen production in maintaining bone mass after menopause. Some postmenopausal women may have lower serum estrogen concentrations, which may contribute to the development of osteoporosis.

Increased sensitivity of bone to PTH may be one of the fundamental pathophysiologic defects in women with type I osteoporosis. This increased sensitivity may explain the greater susceptibiity of osteoporotic patients to low dietary calcium intake and the beneficial effect of calcium and vitamin D supplements in doses large enough to decrease PTH secretion in their treatment [45]. Although this defect may require estrogen deficiency to become manifest, it may explain, in part, the propensity of some but not all postmenopausal women to have osteoporosis, although all are estrogen deficient. Studies should now be made to determine the cellular and molecular causes of the enhanced response of bone cells to PTH in PMOp women.

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