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Technical and Clinical Characterization of the Bio-PTH (1–84) Immunochemiluminometric Assay and Comparison with a Second-Generation Assay for Parathyroid Hormone

Masaaki Inaba,[1*] Kiyoshi Nakatsuka,[1] Yasuo Imanishi,[1] Masakazu Watanabe,[2] Yuji Mamiya,[2] Eiji Ishimura,[1] and Yoshiki Nishizawa[1]

Background: **The Bio-Intact parathyroid hormone (1–84) assay (Bio-PTH), a newly developed two-site immunochemiluminometric assay, measures exclusively PTH (1–84) in contrast to second-generation "intact PTH" (I-PTH) assays. We investigated the technical performance and clinical significance of this new assay.**
Methods: **PTH was measured simultaneously by the Bio-PTH assay and Allegro intact PTH IRMA in sera from Japanese patients with calcium disorders.**
Results: **Measured Bio-PTH in serum was unaffected by six freeze-thaw cycles and was stable at 4 °C for 7 days and during storage at −20 or −80 °C over 28 days. The calibration curve was linear to 1800 ng/L. The detection limit was 3.9 ng/L. The intra- and interassay imprecision was <2.8% and 3.5%, respectively, for analyte concentrations spanning the range of the calibration curve. Bio-PTH was unaffected by a 1000-fold excess of PTH (7–84), although I-PTH reacted equally with PTH (7–84) and PTH (1–84). Bio-PTH was correlated with I-PTH in healthy individuals (r = 0.953; P <0.0001; n = 26) and in the full population without renal dysfunction (r = 0.994; P <0.0001; n = 62). In 72 volunteers, mean (SD) Bio-PTH was 22.2 (7.1) ng/L, or 62% of the mean I-PTH [36.1 (22.3) ng/L]. This ratio was 51% in hemodialysis patients (n = 177). Mean Bio-PTH was high in patients with primary hyperparathyroidism [121 (85) ng/L; n = 18] and hemodialysis patients [102 (104) ng/L; n = 177], low in idiopathic hypoparathyroidism [5.5 (2.8) ng/L; n = 4], and within 2 SD of the mean for healthy controls in Paget disease of the bone [34 (15) ng/L; n = 9] and bone metastasis [24 (12) ng/L; n = 8].**
Conclusion: **The Bio-PTH assay is sensitive and precise and produces expected results for patients with the studied disorders of calcium metabolism.**

Evidence indicates that the second-generation intact parathyroid hormone (I-PTH) assay detects not only PTH (1–84) but also large N-truncated fragments, mostly PTH (7–84) *(1, 2)*. It is reported that PTH (7–84) acts antagonistic to PTH (1–84) and that, therefore, the second-generation I-PTH assay probably could not estimate parathyroid function *(2)*. N-Terminal truncated fragments persist in the circulation for much longer than PTH (1–84) because of their exclusive excretion into urine *(3)*. Furthermore, increased serum calcium or 1,25-dihydroxyvitamin D concentrations stimulate the release of N-truncated PTH fragments compared with PTH (1–84) from the parathyroid gland *(4, 5)*. With deterioration of renal function and an increase in serum calcium, it is possible that serum PTH measured by the second-generation I-PTH assay may lead to overestimation of parathyroid function. Therefore, a new assay that specifically identifies intact PTH (1–84) is desirable.

The Bio-Intact PTH (1–84) assay (Nichols Institute) has recently been developed to specifically measure the intact PTH (1–84) molecule but not PTH fragments lacking one or several of the N-terminal amino acid residues of PTH (1–84) *(6, 7)*. Briefly, the Bio-PTH assay is a two-site immunochemiluminometric assay that uses a biotinylated capture antibody recognizing the (39–84) region and an acridinium-labeled antibody that binds PTH (1–84) with-

[1] Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.
[2] SRL Inc., Tokyo, Japan.
*Address correspondence to this author at: Department of Metabolism, Endocrinology and Molecular Medicine, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka 545-8585, Japan. Fax 81-6-6645-3808; e-mail inaba-m@med.osaka-cu.ac.jp.
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out cross-reactivity with any of the N-terminally truncated PTH fragments.

We investigated the analytical performance of the Bio-PTH assay in serum obtained from Japanese patients with various metabolic bone diseases and assessed the potential clinical usefulness of this assay for estimating parathyroid function.

Patients and Methods

SAMPLE COLLECTION

Blood drawn after an overnight fast was kept on ice for no more than 1 h before centrifugation at 1200*g* for 5 min. The serum samples were stored at −80 °C until being assayed. Before the Bio-PTH assay was performed, the frozen samples were thawed and assayed immediately. Dilution studies were performed on sera from healthy controls and primary hyperparathyroidism. Informed consent was obtained from all study participants. All of the measurements were performed in the same assay run to avoid the interassay variance otherwise indicated.

BIO-PTH AND SECOND-GENERATION ALLEGRO I-PTH ASSAYS

Serum active PTH (1–84) was measured by the Bio-PTH assay, which is a two-site chemiluminometric assay, as described previously *(6, 7)*. Briefly, the Bio-PTH assay uses an acridinium ester-labeled goat anti-PTH antibody that binds to the N-terminal amino acids of the human PTH molecule and a biotinylated capture antibody recognizing the (39–84) region *(6, 7)*. The sandwich complex was bound to streptavidin-coated magnetic particles, incubated, and then washed. The particles were then quantified in the luminometer. Serum I-PTH, which was found to react not only with biologically active PTH (1–84) but also with large C-terminal fragments, which are present in sera from healthy controls and, in particular, uremic patients *(1, 6–8)*, was measured by a second-generation Allegro I-PTH IRMA (Nichols Institute) *(9, 10)*.

INTRAASSAY AND INTERASSAY VARIANCES OF BIO-PTH AND I-PTH ASSAYS

We evaluated the analytical performance by determining the intra- and interassay imprecision of the Bio-PTH and I-PTH assays. We assessed intraassay imprecision by measuring four serum samples with different concentrations of PTH in 10 replicates each and interassay precision with the same samples over a 10-day period.

STABILITY OF PTH IMMUNOREACTIVITY MEASURED BY BIO-PTH ASSAY

To investigate the stability of PTH in samples during storage, we stored three serum pools with different PTH concentrations at 25, 4, −20, and −80 °C for 1, 2, 3, 6, 7, and 14 days before measuring for the PTH concentrations by Bio-PTH assay.

FREEZE/THAW EXPERIMENTS AND INTERFERENCE

Two serum samples with different PTH concentrations, as measured by the Bio-PTH assay, were repeatedly frozen at −20 °C and thawed in a water bath at 15 °C. The number of freeze-thaw cycles for any one sample was up to six. Serum samples with I-PTH concentrations of 23.4 ng/L were measured simultaneously with the Bio-PTH and I-PTH assays with and without the addition of PTH (7–84) at final concentrations of 75, 700, 2000, and 7500 ng/L to investigate the interference of PTH (7–84) with each assay.

DETERMINATION OF SERUM PTH BY BIO-PTH AND I-PTH ASSAYS IN HEALTHY INDIVIDUALS AND PATIENTS WITH METABOLIC BONE DISEASES

To investigate the correlation between results obtained with the Bio-PTH and I-PTH assays, sera obtained from healthy individuals (n = 26) and from patients with various metabolic bone diseases (n = 36) were analyzed simultaneously for serum Bio-PTH and I-PTH. Serum samples obtained from 72 healthy controls and 216 patients [primary hyperparathyroidism (n = 18), idiopathic hypoparathyroidism (n = 4), Paget disease of the bone (n = 9), metastatic bone disease (n = 8), uremic patients on hemodialysis (n = 177)] were measured in the Bio-PTH assay to determine values for healthy controls and the changes produced by various metabolic bone diseases.

STATISTICAL ANALYSIS

Data were analyzed by use of the StatView 5.0 J program (Abacus Concepts, Inc.) on a computer running the Windows operating system. All results are shown as the mean (SD) unless otherwise indicated. Data on the stability of the Bio-PTH immunoreactivity are expressed as the means of duplicate measurements. Correlation coefficients were calculated by simple regression analysis, and the differences in means between two groups were analyzed by the Student *t*-test. P values <0.05 were considered statistically significant.

Results

PRECISION OF BIO-PTH ASSAY COMPARED WITH THE ALLEGRO I-PTH ASSAY

A typical Bio-PTH calibration curve is shown in Fig. 1. The assay was linear up to 1800 ng/L. The lower detection limit was 3.9 ng/L for the Bio-PTH assay with each concentration measured in 10 replicates, which was the lowest Bio-PTH value significantly greater than zero (Fig. 1, inset). The intraassay CV (10 determinations per sample) for the Bio-PTH assay was 1.6–2.7% over the range of the calibration curve (20–1200 ng/L), and the interassay CV was 1.8–3.5% (10 determinations per sample; Table 1). The intra- and interassay CV for the I-PTH assay were 3.4–4.1% over the range of 20–1100 ng/L and 1.0–3.5% over the range of the calibration curve, respectively. The lower detection limit for the I-PTH assay was 2.8 ng/L (data not shown).

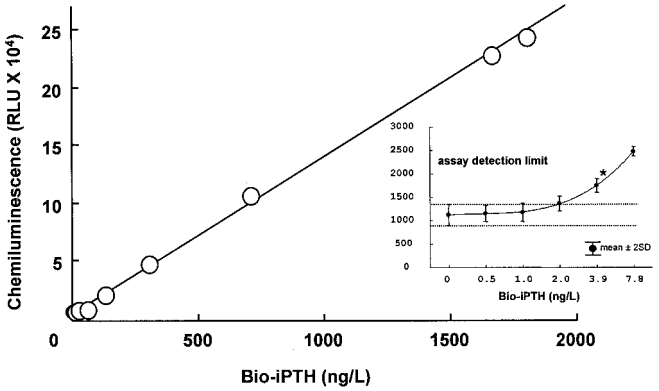

Fig. 1. Representative calibration curve for the Bio-PTH assay.

Data are the means of duplicate measurement. (*Inset*), assay detection limit is 3.9 ng/L, which was the lowest measurable Bio-PTH value distinguishable from zero. It was determined by measuring the assay zero calibrator 10 times in the same analytical run and the value corresponding to 2 SD above the mean of the zero calibrator. *RLU*, relative light units.

STABILITY OF BIO-PTH IMMUNOREACTIVITIES IN SERUM DURING STORAGE

The stability of PTH, as measured by the Bio-PTH assay, in serum at various temperatures is shown in Fig. 2. The serum PTH concentrations measured by the Bio-PTH assay did not decrease significantly in samples stored at −20 or −80 °C for 14 days. However, in samples stored at 25 and 4 °C, the values measured by the Bio-PTH assay decreased significantly. In addition, the same samples, with Bio-PTH values of 53 and 173 ng/L, that were used in the experiments illustrated in Fig. 2 were subjected to repeated freezing–thawing for up to six cycles before being analyzed by the Bio-PTH assay (Fig. 3). The values obtained with the Bio-PTH assay were not affected by up to six freezing–thawing cycles.

LINEARITY AND INTERFERENCES

To examine whether the assays were influenced by some substances in serum, serum samples with high concentrations of PTH, as measured by Bio-PTH assay, were diluted 1:2, 1:4, 1:8, 1:16, and 1:32 with the assay Sample Diluent before being analyzed. The assay was linear within the measurement range up to 1800 ng/L (Fig. 4).

Interference from PTH (7–84) was tested in serum from a healthy individual. As shown in Table 2, when PTH (7–84) was added to the serum at final concentrations of 75 and 700 ng/L, the PTH concentrations measured by the I-PTH assay increased significantly, from 12 to 84 and 717 ng/L, respectively, whereas those measured by the Bio-PTH assay did not change appreciably, from 6.9 to 6.1 and 6.7 ng/L, respectively. As the final concentration of PTH (7–84) increased to 2000 and 7500 ng/L, the concentration measured by the I-PTH assay increased to >1800 ng/L, whereas the concentrations measured by the Bio-PTH increased slightly, to 8.5 and 8.8 ng/L, respectively. To further assess the possible interference by hemolysis,

Table 1. Intra- and interassay precision of the Bio-PTH and Allegro I-PTH assays.

	Intraassay[a] (n = 10)			Interassay[b] (n = 10)		
Assay	Mean, ng/L	SD, ng/L	CV, %	Mean, ng/L	SD, ng/L	CV, %
Bio-PTH	20	0.34	1.6	20	0.72	3.5
	149	2.87	1.9	146	2.56	1.8
	493	13.4	2.7	495	10.2	2.1
	1212	22.5	1.9	1159	25.2	2.2
Allegro I-PTH	22	0.80	3.6	22	0.78	3.5
	144	5.94	4.1	143	4.81	3.4
	468	16.0	3.4	475	4.93	1.0
	1034	35.5	3.4	1027	34.5	3.4

[a] Intraassay CV for Bio-PTH assay were determined by measuring 10 replicates of four serum samples with different serum PTH concentrations in the same assay.

[b] Interassay CV were determined by measuring the same samples daily over a 10-day period.

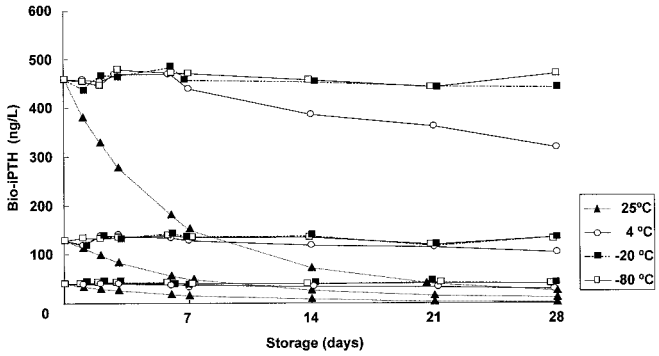

Fig. 2. Stability of immunoreactivities in three sera with different PTH concentrations during storage, as measured by the Bio-PTH assay.

Serum samples from three individuals with different PTH concentrations, as measured by Bio-PTH assay, were assayed before and at the indicated days after storage at 25, 4, −20, or −80 °C.

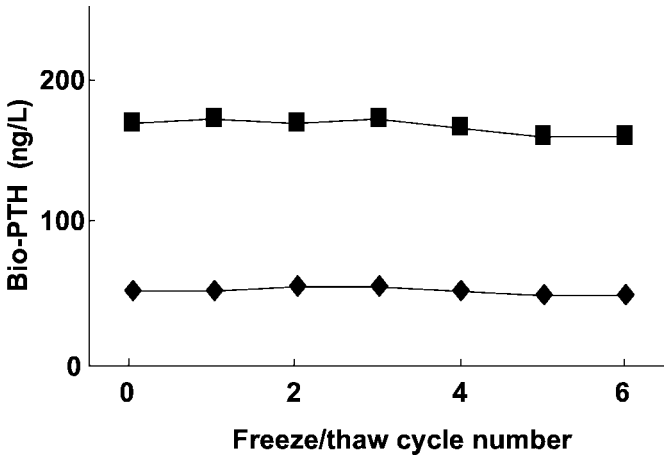

Fig. 3. Stability of immunoreactivity in three sera with different PTH concentrations after repeated cycles of freezing–thawing, as measured by the Bio-PTH assay.

Serum samples from two individuals with different serum PTH concentrations, as measured by the Bio-PTH assay, were subjected to repeated freezing–thawing at the indicated times before measurement. One cycle of freezing–thawing consisted of freezing at −80 °C and thawing in a water bath at 15 °C.

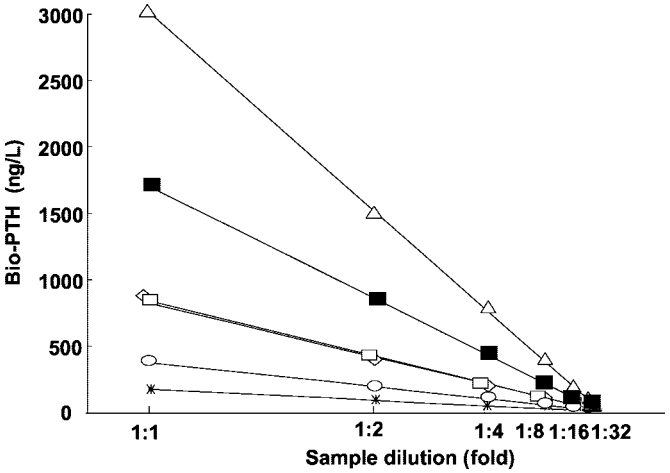

Fig. 4. Linear dilution curves for six sera with different PTH concentrations, as measured by the Bio-PTH assay.

Dilutions: 1:1, undiluted sample; 1:2, 1 part serum plus 1 part diluent; 1:4, 1 part serum plus 3 parts diluent; 1:8, 1 part serum plus 7 parts diluent; 1:16, 1 part serum plus 15 parts diluent; 1:32, 1 part serum plus 31 parts diluent.

serum lipids, or bilirubin, we diluted the three sera used for the experiment illustrated in Fig. 2, with different PTH concentrations as measured by the Bio-PTH assay, in plasma containing lysed blood cells, high concentrations of lipids, or bilirubin. Serum values measured by the Bio-PTH assay were essentially unaffected by hemoglobin up to 4.85 g/L, serum lipids up to 3.2 g/L, or bilirubin C and F up to 204 and 191 g/L, respectively (data not shown).

CORRELATION BETWEEN SERUM BIO-PTH AND I-PTH VALUES

To study the correlation between the PTH concentrations measured by the Bio-PTH and I-PTH assays, we assayed 62 serum samples at the same time in the Bio-PTH and I-PTH assays. As shown in Fig. 5, we observed a significant and positive correlation between serum Bio-PTH and I-PTH values in healthy individuals [slope, 0.638 (95% confidence interval, 0.553–0.723); y-intercept, 0.479 (95% confidence interval, −2.518 to 3.457); $S_{y|x}$ 0.282; r = 0.953; P <0.0001; n = 26] or in the healthy individuals and patients with metabolic bone diseases [slope, 0.575 (95% confidence interval, 0.559–0.591); y-intercept, 1.836 (95% confidence interval, −2.025 to 5.697); $S_{y|x}$ = 0.151; r = 0.994; P <0.0001; n = 62].

Table 2. Interference of PTH (7–84) in the Bio-PTH and I-PTH assays.[a]

Final concentration of PTH (7–84), ng/L	Bio-PTH assay		I-PTH assay	
	Bio-PTH, ng/L	Cross-reactivity, %	I-PTH, ng/L	Cross-reactivity, %
0	6.9		12.3	
75	6.1	−1.1	83.9	95.5
700	6.7	0.0	717	100.7
2000	8.5	0.1	>1800	
7500	8.8	0.0	>1800	

[a] PTH was measured in duplicate with each assay. Serum with I-PTH of 23.4 ng/L was measured simultaneously with the Bio-PTH and I-PTH assays with and without the addition of an equal volume of PTH (7–84) at the final concentrations of 0–7500 ng/L.

SERUM BIO-PTH IN PATIENTS WITH METABOLIC BONE DISEASES

Mean (SD) serum Bio-PTH was 22.2 (7.1) ng/L in healthy controls (n = 72). The results of Bio-PTH assay indicated high serum Bio-PTH concentrations in patients with primary hyperparathyroidism and hemodialysis patients, low values in those with idiopathic hypoparathyroidism, and values within 2 SD of the mean for healthy controls in those with Paget disease of the bone and metastatic bone disease (Fig. 6). Mean (SD) serum Bio-PTH was as follows: 120.5 (84.8) ng/L in primary hyperparathyroidism (n = 18), 102.4 (104.2) ng/L in hemodialysis patients (n = 177), 5.5 (2.8) ng/L in idiopathic hypoparathyroidism (n = 4), 34.1 (15.2) ng/L in Paget disease of the bone (n = 9), and 23.8 (11.5) ng/L in metastatic bone disease (n = 8). Sixteen of 18 (89%) patients with primary hyperparathyroidism and 120 of 177 (68%) hemodialysis patients had Bio-PTH concentrations >2 SD above the mean of the healthy controls (36.4 ng/L). The numbers of patients with serum Bio-PTH within 2 SD of the mean of the healthy controls were 2 of 18 patients with primary hyperparathyroidism, 1 of 4 patients with idiopathic hypoparathyroidism, 9 of 9 patients with Paget disease of bone, and 7 of 8 patients with metastatic bone disease. Three of four patients with idiopathic hypoparathyroidism and one of eight patients with metastatic bone disease who developed humoral hypercalcemia of malignancy had Bio-PTH concentrations more than 2 SD below the mean for the healthy controls (8.0 ng/L). Of interest, the Bio-PTH/I-PTH ratio was 0.51 (0.34) in uremic patients on hemodialysis, significantly lower than the value [0.64 (0.10)] in healthy controls.

Discussion

The results of the present study indicate that clinical application of a PTH (1–84)-specific Bio-PTH assay is acceptable under routine clinical laboratory conditions from either an analytical or a clinical perspective. Inter- and intraassay variances are very small throughout the ranges usually used under routine conditions, including those used in the study of various metabolic bone diseases (Table 1 and Fig. 5), indicating that the likelihood of clinically significant error in this assay is small. As shown in Table 1, the intra- and interassay CV were better than those of the second-generation I-PTH assay. In addition, the assay was linear throughout the ranges investigated routinely, with an acceptable assay detection limit (Fig. 1). Moreover, all sera obtained from patients with metabolic bone diseases showed linear dilution in the Bio-PTH assay (Fig. 4). Together with the data indicating that the values obtained with the Bio-PTH assay are not affected

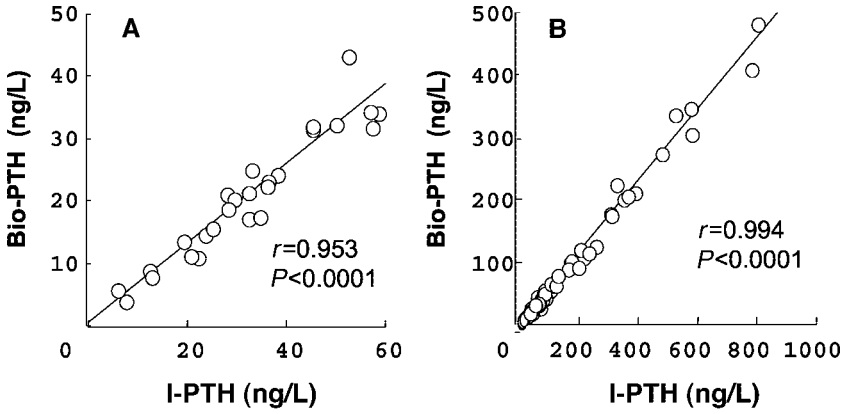

Fig. 5. Correlation between serum Bio-PTH and I-PTH in healthy controls (*A*) and healthy controls plus patients with various metabolic bone diseases (*B*).

Blood samples from 26 healthy controls and 36 patients with metabolic bone diseases without renal impairment were assayed. Serum PTH was measured with the Bio-PTH and I-PTH assays simultaneously to investigate the correlation between two PTH assays.

by high concentrations of hemoglobin, lipids, or bilirubin, the possibility of the presence of substances in serum that interfere with the Bio-PTH assay is small. Furthermore, the serum values obtained with the Bio-PTH assay were not affected by the addition of PTH (7–84) (Table 2), a major form of N-truncated PTH fragments in serum *(1, 11, 12)*. The authors of another report have indicated that serum values obtained with the Bio-PTH assay also are not affected by the addition of PTH (2–34), (3–34), (4–34), or (5–34) peptides to the test samples *(6)*. Furthermore, the immunoreactivity measured by the Bio-PTH assay is stable enough to allow easy handling of clinical samples (Figs. 2 and 3). Although the immunoreactivity measured by the Bio-PTH assay in human serum decreased significantly after 24 h of incubation at 25 °C, it was stable at 4 °C at least for up to 24 h (Fig. 2). When stored at −20 and −80 °C, the immunoreactivity in serum measured by the Bio-PTH assay remained unchanged up to 28 days (Fig. 2). Lastly, six repeated cycles of freezing–thawing did not affect serum concentrations as measured by the Bio-PTH assay (Fig. 3). Taken collectively, these data indicate that the Bio-PTH assay could provide an assay that allows easy handling of clinical samples.

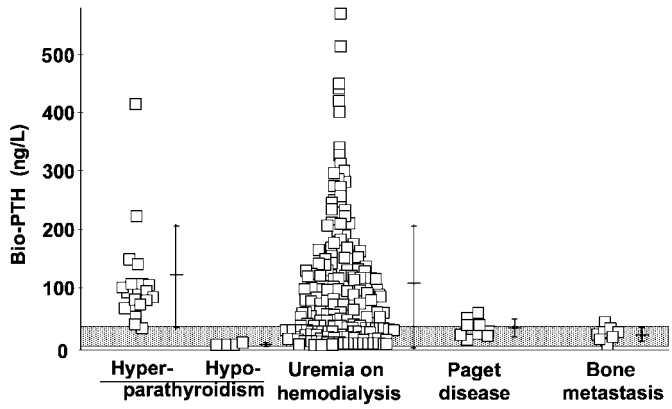

Fig. 6. Serum PTH in patients with various metabolic bone diseases, as measured with the Bio-PTH assay.

Serum PTH was measured in patients with primary hyperparathyroidism (n = 18), idiopathic hypoparathyroidism (n = 4), uremia on hemodialysis (n = 177), Paget disease of bone (n = 9), and metastatic bone disease (n = 8). *Shaded area* indicates values obtained for healthy controls. The *horizontal lines* indicate the means and the *error bars* indicate the SD for each group.

The validity of Bio-PTH assay was supported by (*a*) a good correlation with the I-PTH assay in sera obtained from healthy controls and patients with various metabolic bone diseases (Fig. 5), and (*b*) its good reflection of parathyroid activity in various metabolic bone diseases (Fig. 6). In the patients with increased parathyroid function resulting from primary hyperparathyroidism, almost 90% had serum Bio-PTH concentrations exceeding 2 SD of the mean for the healthy controls. In contrast, serum Bio-PTH concentrations in 75% of the patients with idiopathic hypoparathyroidism were more than 2 SD below the mean for the healthy controls. Although 2 of 18 patients with primary hyperparathyroidism and 1 of 4 patients with idiopathic hypoparathyroidism had serum Bio-PTH concentrations within 2 SD of the mean for the healthy controls, those concentrations were abnormally high in the former group and low in the latter group of patients for their serum calcium concentrations. Among eight patients with metastatic bone disease, only one, who developed humoral hypercalcemia of malignancy, had serum Bio-PTH concentrations more than 2 SD below the mean for the healthy controls. These data clearly indicated that serum concentrations measured by the Bio-PTH assay provide a valuable indicator to estimate parathyroid function.

The second-generation I-PTH assay is now known to react similarly with both the PTH (1–84) molecule and the PTH (7–84) molecule (Table 2). It has been reported that PTH (7–84) may contribute to the occurrence of skeletal resistance to PTH in hemodialysis patients because of its reported antagonistic action to PTH (1–84) *(2, 13)*; we therefore suggest that serum PTH concentrations determined by I-PTH assay might indicate the sum of the agonistic and antagonistic actions of PTH. Mean concentrations measured by the Bio-PTH and I-PTH assays in healthy controls (n = 72) were 22.2 (7.1) and 36.1 (22.3) ng/L, indicating that the non-(1–84) molecular forms account for ~40% of circulating PTH immunoreactivity. Because N-truncated non-(1–84) PTH fragments persist in

the circulation for much longer than PTH (1–84) because of their exclusive excretion into urine *(3)*, serum PTH concentrations affected by renal impairment attributable to accumulation of non-(1–84)-PTH fragments should be greater in the I-PTH assay than in the Bio-PTH assay. In agreement with this hypothesis, the serum Bio-PTH/I-PTH ratio was decreased significantly in hemodialysis patients compared with healthy controls. In healthy individuals, the proportion of non-(1–84) PTH fragments in all PTH molecules increases with hypercalcemia and decreases with hypocalcemia *(14, 15)*. In support of this, we found that serum calcium is an independent factor negatively associated with the serum Bio-PTH/I-PTH ratio in hemodialysis patients, suggesting that an increase in serum calcium might suppress the Bio-PTH/I-PTH ratio (manuscript submitted for publication). Taken collectively, these results suggest that PTH values obtained with the second-generation I-PTH assay are complicated by the presence of inactive PTH fragments, which could be modulated by serum calcium and renal dysfunction. Therefore, the results obtained with the second-generation I-PTH assay may not accurately reflect parathyroid function, particularly in those with renal dysfunction and calcium disorders.

In conclusion, we suggest that the serum Bio-PTH assay is more suitable than the second-generation I-PTH assay for estimating parathyroid function.

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