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Usefulness of whole PTH assay in patients with renal osteodystrophy —Correlation with bone scintigraphy

Hayato KAIDA,* Masatoshi ISHIBASHI,* Hidemi NISHIDA,** Kenkichi BABA,*
Yuji HIROMATSU,*** Seiya OKUDA** and Naofumi HAYABUCHI*

*Division of Nuclear Medicine, PET Center and Department of Radiology,
**Department of Nephrology and Dialysis Unit, and ***Department of Endocrinology and Metabolism,
Kurume University School of Medicine

Objective: Intact parathyroid hormone (PTH) assay has recently been reported to be effective in evaluating both 1-84 PTH (whole PTH) and inactive 7-84 PTH. Inactive 7-84 PTH is considered to be increased in hemodialysis patients and to prevent the effects of 1-84 PTH, and intact PTH is considered to overestimate the PTH activity in these patients. As such, a whole PTH assay has recently been developed. The purpose of this study was to examine the usefulness of a whole PTH assay using the bone to soft tissue (B/ST) ratio on bone scintigraphy. ***Method:*** Twenty-five hemodialysis patients were included in our study. In all patients, bone scintigraphy and a blood test [whole PTH, intact PTH, alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P)] were performed. Regions of interest (ROIs) were drawn around the cranium, lumbar vertebrae, left femoral neck, and soft tissue of the medial left thigh to obtain the B/ST ratio. ***Results:*** The B/ST ratio of the cranium and left femoral neck correlated with whole PTH and intact PTH. In particular, the B/ST ratio of the cranium correlated most significantly with the value of whole PTH. Whole PTH levels correlated with intact PTH levels ($r = 0.891$, $p < 0.0001$). ***Conclusion:*** Our data indicate that a whole PTH assay may be useful in evaluating PTH activity using the B/ST ratio. The B/ST ratio of the cranium may reflect the bone metabolism of hemodialysis patients.

Key words: ^{99m}Tc-hydroxy-methylene-disphosphonate (^{99m}Tc-HMDP), bone scintigraphy, whole parathyroid hormone (whole PTH), intact parathyroid hormone (intact PTH)

INTRODUCTION

THE MEASUREMENT of intact parathyroid hormone (intact PTH) has been employed both in diagnosing renal osteodystrophy (ROD) and evaluating the therapeutic effects of ROD. PTH is the major determinant of rates of bone remodeling and turnover in hemodialysis patients with end-stage renal disease; accurate assessments of plasma PTH levels are essential not only for estimating the bone metabolism of ROD but also for appropriately monitoring the treatment of secondary hyperparathyroidism (SHP).[1,2] It has been reported that the intact PTH assay may facilitate evaluation of the levels of both serum 1-84 PTH (whole PTH) and inactive 7-84 PTH.[3] Inactive 7-84 PTH fragments are considered to prevent the effects of whole PTH in both bone and kidney, and to induce bone resistance to PTH and adynamic bone disease.[4,5] Recently, an intact PTH assay has been reported to overestimate the activity of PTH.[6] As a result, a whole PTH assay specifically measuring 1-84 PTH was developed. Bone biopsy has been regarded as the best method for evaluating the bone metabolism of ROD; unfortunately, it is invasive and expensive, and as such is not routinely used.[2,7,8] Noninvasive methods to be used in place of bone biopsy have been devised for the past 20 years.[7,8] Bone scintigraphy has been regarded as a noninvasive method, and is considered to be more sensitive than radiography in the evaluation of ROD. In particular, one of the semi-quantitative

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For reprint contact: Hayato Kaida, M.D., Division of Nuclear Medicine, PET Center and Department of Radiology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830–0011, JAPAN.

E-mail: hayato@med.kurume-u.ac.jp

methods of bone scintigraphy, determination of the bone to soft tissue (B/ST) ratio, has been used to quantitatively evaluate the bone metabolism of SHP and to make differential diagnoses of systemic bone disease.[9,10] Furthermore, we have examined the relationship between the B/ST ratio and bone metabolic markers in hemodialysis patients.[11] Using the B/ST ratio, the usefulness of the whole PTH assay on the maintenance of hemodialysis patients was evaluated.

MATERIALS AND METHODS

The study population consisted of 25 patients on maintenance hemodialysis, 17 males and 8 females. The patient age at the time of the study ranged from 28–75 years (mean 52.2 years).

Patients originally suffered from chronic glomerulonephritis (n = 19), renal sclerosis (n = 3), lupus nephritis (n = 1), polycystic kidney (n = 1), and Alport syndrome (n = 1). The average duration of hemodialysis was 118.5 months, with three dialysis sessions per week. No other medical problems such as liver disease, diabetes mellitus, or malabsorption were known to exist. Vitamin D analogues and calcium supplements were gradually withdrawn a month prior to the study. None of the patients took steroids, estrogen, aluminum-containing phosphate binders, bisphosphonate, anticonvulsants, or medication known to interact with calcium, vitamin D_3 or osteocalcin levels.

All patients performed normal outdoor activities and were on an unrestricted diet with the exception of protein and fluids. The patients who had either extraosseous uptake or ectopic calcification on the bone scintigraphy were excluded in the present study. Informed consent for participation in the present study was obtained from the patients or their guardians as part of the protocol approved by the Institutional Clinical Subpanel on Human Studies at our university hospital.

Bone scintigraphy

^{99m}Tc-hydroxymethylene-diphosphonate (^{99m}Tc-HMDP) (555 MBq, Nihon Medi-Physics Co. Ltd., Nishinomiya, Japan) was injected intravenously. In all patients, bone scintigraphy was obtained about 3 h after intravenous injection. Whole body images were recorded with the gamma camera (E.CAM, Siemens Medical Systems, Inc.; scan speed 15 cm/min, matrix 256 × 1024). The whole body field was used to digitally record anterior and posterior views (256 × 1024) on a dedicated computer system (Toshiba 5500 A/PI, Tokyo, Japan). Energy discrimination was provided by a 10% window centered on the 140 keV of Tc-99m.

Quantification of bone scintigraphy

Skeletal uptakes of Tc-99m HMDP were analyzed on a data processing system using the method reported by Fogelman et al.[12,13] In posterior views of whole-body scintigraphy, ROIs were set over the selected bony regions (Fig. 1). The B/ST ratio was measured by drawing ROIs around the cranium, lumbar vertebrae and left femoral neck, and medial parts of the soft tissue areas of the left thigh. The means of the ROIs were calculated in all patients.

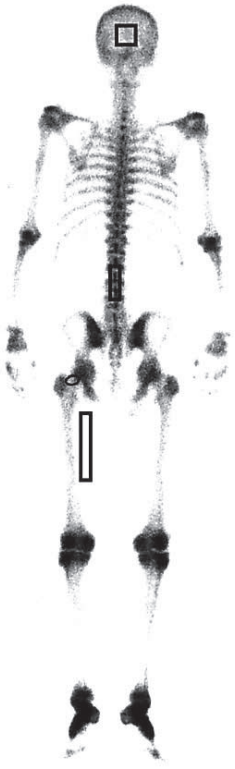

Fig. 1 The regions of interest (ROIs) were drawn around the cranium, lumbar vertebrae, left femoral neck, and soft tissue of the medial left thigh to calculate the bone to soft tissue ratio (B/ST ratio) on the bone scintigraphy.

Table 1 The result of B/ST ratios in 25 hemodialysis patients

	mean ± SD
craniuim	3.75 ± 1.93
femoral neck	5.49 ± 2.40
lumbar vertebrae	10.19 ± 4.73

Note; B/ST ratio = Bone to Soft Tissue Ratio
Data were expressed as mean ± SD

Laboratory data

The serum PTH concentrations in each patient were determined for all patients using a radioimmunoassay measuring intact PTH and whole PTH. Immunoreactive intact PTH was measured in all patients using the Allegro intact PTH kit (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Intact PTH concentrations ranged from 45.0 to 1300 pg/m*l* [559.44 ± 332.27 (mean ± SD)

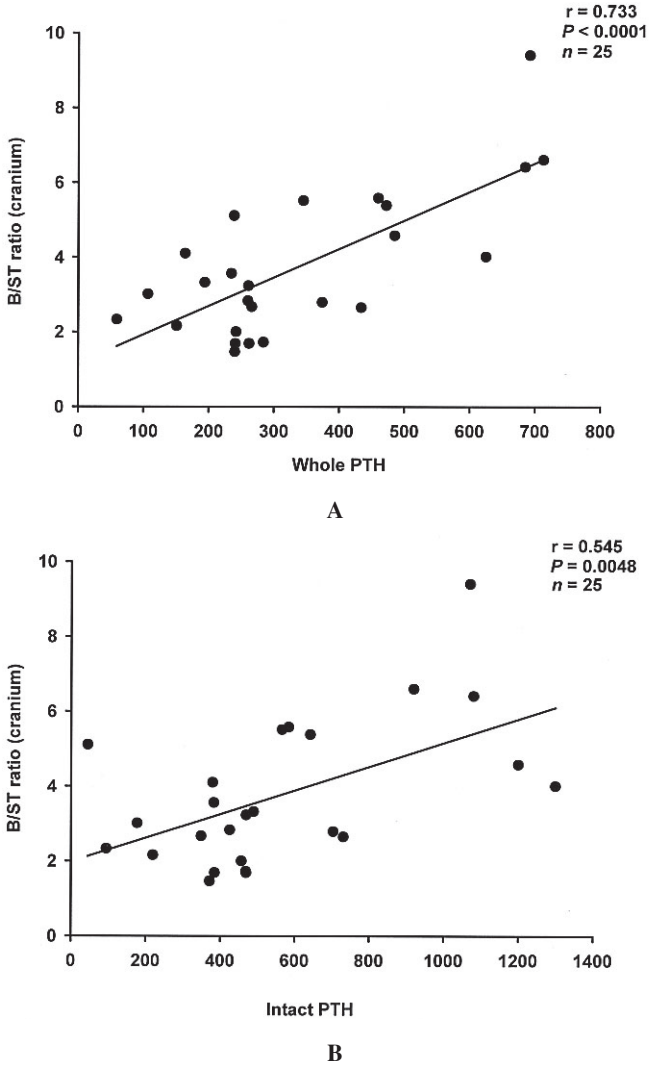

Fig. 2 The correlation between the bone to soft tissue ratio (B/ST ratio) of the cranium and whole parathyroid hormone (whole PTH) (r = 0.733, p < 0.0001) (A), and intact parathyroid hormone (intact PTH) (r = 0.545, p = 0.0048) (B).

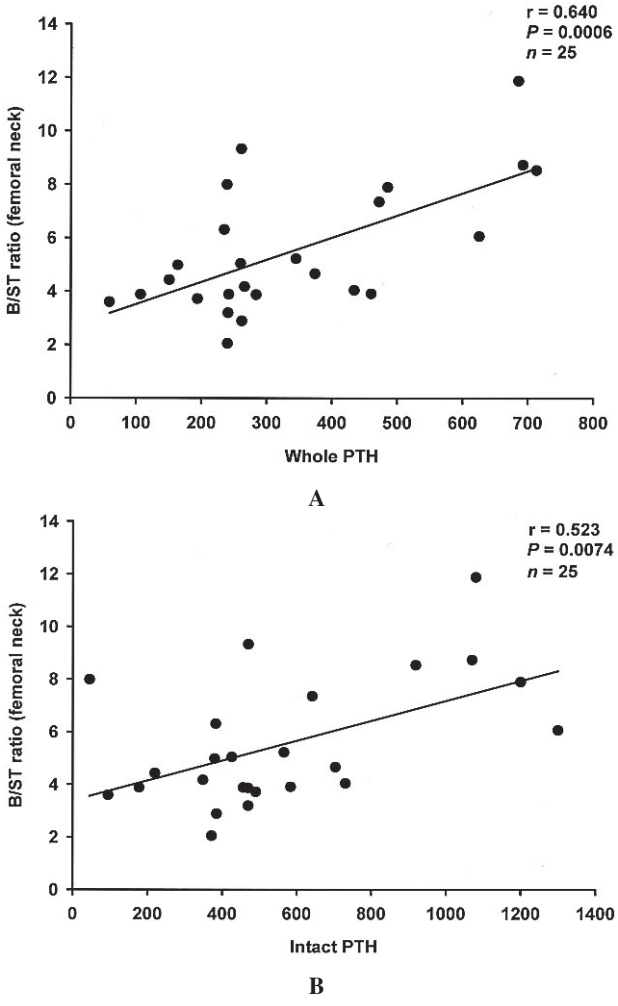

Fig. 3 The correlation between the bone to soft tissue ratio (B/ST ratio) of left femoral neck and whole parathyroid hormone (whole PTH) (r = 0.640, p = 0.0006) (A), and intact parathyroid hormone (intact PTH) (r = 0.523, p = 0.0074) (B).

pg/m*l*; normal range, 10.0–65.0 pg/m*l*]. Immunoreactive whole PTH was measured in all patients using a whole PTH two-site assay (Scantibodies Laboratories, Santee, CA, USA). Whole PTH concentrations ranged from 59.2 to 713 (339.60 ± 185.43; normal range, 5.0–35.0 pg/m*l*).[21] The serum concentrations of calcium [σ-cresolphthaleincomplexone (OCPC), Iyatron Co., Tokyo, Japan] (Ca) and phosphorus (Enzyme assay, Kyowa Co., Tokyo, Japan) (P) were also measured. Serum calcium and phosphorus ranged, respectively, from 5.30 to 12.2 mg/m*l* (9.66 ± 1.61 mg/m*l*; normal range, 8.5–10.5 mg/m*l*) and from 1.61 to 8.89 mg/m*l* (5.60 ± 1.58 mg/m*l*; normal range, 2.5–4.5 mg/m*l*). Serum total alkaline phosphatase (ALP) was measured by an automated method and was found to range from 119 to 1550 U/*l* (363.24 ± 299.09 U/*l*; normal range, 115.0–359.0 U/*l*).

Statistical analysis

All results are expressed as the mean ± SD. Statistical analyses were performed using linear correlation analysis (Statview; Abacus Concepts Inc., Berkeley, CA, USA). A probability level of less than 0.05 was considered significant.

RESULTS

Table 1 shows the mean values of the B/ST ratio of 25 hemodialysis patients at each bony region. The correlations between the B/ST ratio of each region and whole PTH or intact PTH were evaluated, with the following results: cranium B/ST ratio and whole PTH, r = 0.733 (p < 0.0001) (Fig. 2A) or intact PTH, r = 0.545 (p = 0.0048) (Fig. 2B); left femoral neck B/ST ratio and whole PTH, r = 0.640 (p = 0.0006) (Fig. 3A) or intact PTH, r = 0.523 (p = 0.0074) (Fig. 3B); lumbar vertebrae B/ST ratio and whole PTH, r = 0.440 (p = 0.028) (Fig. 4A) or intact PTH,

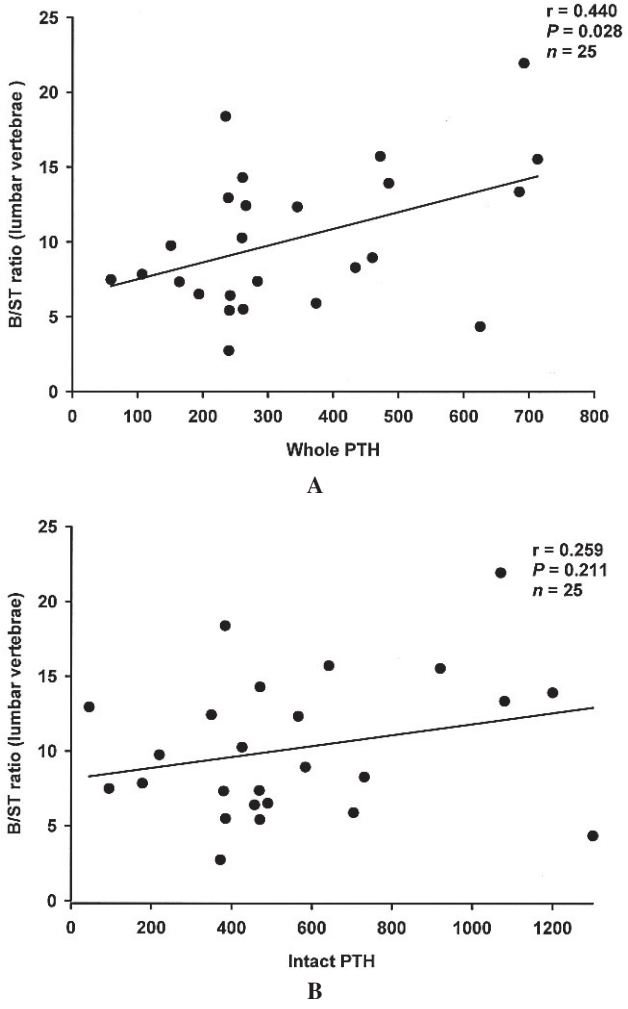

Fig. 4 The correlation between the bone to soft tissue ratio (B/ST ratio) of lumbar vertebrae and whole parathyroid hormone (whole PTH) (r = 0.440, p = 0.028) (A), and intact parathyroid hormone (intact PTH) (r = 0.259, p = 0.211) (B).

r = 0.259 (p = 0.211) (Fig. 4B); whole PTH and intact PTH, r = 0.891 (p < 0.0001). The values of whole PTH correlated very strongly with those of intact PTH (r = 0.891) (Fig. 5). The B/ST ratio of both the cranium and left femoral neck region correlated significantly with the values of whole and intact PTH. The values of whole PTH correlated more strongly with the B/ST ratio of both the cranium left femoral neck than with those of intact PTH. In particular, the B/ST ratio of the cranium correlated most significantly with the values of whole PTH. The correlation coefficient between the B/ST ratio of the lumbar vertebrae and the values of whole PTH was low. The B/ST ratio of lumbar vertebrae did not correlate significantly with the values of intact PTH.

DISCUSSION

Most researchers have described that the B/ST ratio might

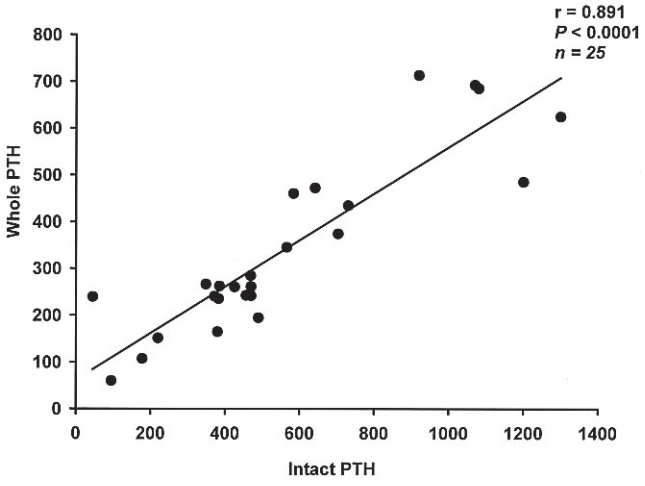

Fig. 5 The correlation between whole parathyroid hormone (whole PTH) and intact parathyroid hormone (intact PTH) (r = 0.891, p < 0.0001).

be useful in making a differential diagnosis of systemic bone disease, and in investigating the therapeutic effects on osteoporosis.[9,10,12–17] Most reports have regarded the usefulness of diagnostically differentiating ROD from other metabolic bone diseases. The clinical impact of the whole PTH assay has been investigated using bone biopsy. To our knowledge, the whole PTH assay has never been reported to be more useful in evaluating the PTH activity of hemodialysis patients than an intact PTH assay using noninvasive and semi-quantitative method (B/ST ratio). The ROIs were manually drawn around the selected area—the cranium, lumbar vertebrae, left femoral neck and soft tissue of the medial left femoral region—because the ratio of cortical bone to trabecular bone in the body was different and because the lumbar vertebrae (L2-4), femoral neck, and soft tissue of the thigh have been used to draw the ROIs in the past literature.[9,17] The major component of the cranium is cortical bone, and the ratio of cortical bone to trabecular bone is 95% to 5%.[18] The major component of lumbar vertebrae is trabecular bone, and the ratio of cortical bone to trabecular bone is 34% to 66%.[18] In the femoral neck, the ratio of cortical bone to trabecular bone is 75% to 25%.[24] Our data suggest that we could grasp the bone metabolism of ROD using the ROIs that were drawn over the bony regions on the strength of the difference in the ratio of cortical bone to trabecular bone.

With regard to the relationship between whole and intact PTH, the values of whole PTH correlated more strongly with those of intact PTH (r = 0.891). Our data were consistent with those of Coen et al.[4] The correlation between the B/ST ratio of the cranium with the values of both whole and intact PTH is likely due to the cortical bone of the cranium being more destroyed by excessive PTH secretions than any other bony region. Excessive PTH secretion affects cortical bone rather than trabecular bone.[19,20] As mentioned above, the cranium has much

more cortical bone than any other bony region. Because the cranium has the most cortical bone of all, it is thought that excessive PTH secretion might have the strongest influence on it. Regarding the lumbar vertebrae, the reason why the correlation coefficient between the B/ST ratio and the values of whole or intact PTH was low is that excessive PTH secretion has less of an influence on the lumbar vertebrae than any other bony region because the lumbar vertebrae contain much more trabecular bone than cortical bone. The values of whole PTH correlated more strongly with the B/ST ratio of both the cranium and left femoral neck than that of intact PTH. In chronic renal failure, it has been reported that the levels of inactive 7-84 PTH secreted by the parathyroid gland are increased and that 40–50% of intact PTH is composed of inactive PTH.[21] Also, it has been reported that the value of whole PTH is from 30–60% lower than that of intact PTH when the activity of PTH is measured using a whole PTH assay in hemodialysis patients.[22] Based on these findings, it has been reported that the activity of PTH might be overestimated in hemodialysis patients and that a whole PTH assay could estimate the activity of PTH more precisely in hemodialysis patients than an intact PTH assay.[3,22] Yamashita et al. have reported that a whole PTH assay may be a more useful adjunct to parathyroidectomy in both SHP and primary hyperparathyroidism.[23] As it is thought that a whole PTH assay might reflect the activity of PTH more precisely than an intact PTH assay, the finding that whole PTH correlates more strongly with the B/ST ratio than intact PTH may suggest the utility of the whole PTH assay in evaluating PTH in hemodialysis patient. Also, the results showing that the B/ST ratio of the cranium correlates more strongly with the values of both intact and whole PTH than with any other bony region indicate that the B/ST ratio of the cranium might be useful in estimating the bone metabolism of hemodialysis patients.

The practical applications of whole PTH in a clinical setting have begun to be evaluated, and we consider that the usefulness of whole PTH should be investigated with respect to research regarding the parathyroid gland in the field of nuclear medicine techniques. Studies of the parathyroid gland in the field of nuclear medicine have been estimated by an intact PTH assay.[25] Provided that the whole PTH assay is used, we believe that this assay in combination with parathyroid scintigraphy will enable us to more accurately diagnose SHP, and the obtained data may influence both the treatment and prognosis of SHP.

CONCLUSION

The whole PTH assay was proven to reflect PTH activity more precisely than intact PTH assay using noninvasive methods; more specifically, the semi-quantitative methods of bone scintigraphy, and the B/ST ratio of the cranium appears to accurately reflect the bone metabolism of hemodialysis patients.

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