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Assessment of therapeutic effect in patients with secondary hyperparathyroidism using bone scintigraphy

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Objective: The semi-quantitative method of bone scintigraphy [bone to soft tissue (B/ST) ratio] has been used in diagnosing and evaluating systemic metabolic bone diseases. The aim of this study is to evaluate of the therapeutic effect of secondary hyperparathyroidism (SHP). ***Methods:*** The subjects were ten hemodialysis patients with SHP. Seven patients underwent parathyroidectomy (PTX), and 22-Oxacalcitoriol (derivative of 1,25-dihydroxyvitamin D_3) (OCT) was given to three patients. Bone scintigraphy and blood tests [intact parathyroid hormone (PTH), alkaline phosphatase (ALP), calcium (Ca), phosphorus (P), bone alkaline phosphatase (BALP), and deoxypridinoline (DPYD)] were performed before and after treatment. Regions of interest were drown around cranium, lumbar vertebrae, femoral neck and soft tissue of left medial thigh to calculate the B/ST ratio. ***Result:*** The B/ST ratios of cranium, lumbar vertebrae, and femoral neck were reduced significantly after PTX (cranium, $p = 0.0079$, lumbar vertebrae, $p = 0.0282$, femoral neck, $p = 0.0252$). Intact PTH, ALP, Ca, P, BALP and DPYD levels were reduced significantly after PTX (intact PTH, $p = 0.003$, Ca, $p = 0.0005$, P, $p = 0.0393$, ALP, $p = 0.0051$, DPYD, $p = 0.0232$, BALP, $p = 0.0324$). After OCT administration, the B/ST ratio of each bony region showed tendency to diminish, although not significantly. Intact PTH levels were reduced significantly, although ALP, BALP, and DPYD levels were not. Ca and P levels were increased significantly because of the medicinal action of OCT. ***Conclusion:*** The B/ST ratio of cranium may be non-invasive method and have potential in evaluating the therapeutic effect of SHP.

Key words: ^{99m}Tc-hydroxy-methylene-disphosphonate (^{99m}Tc-HMDP), bone scintigraphy, secondary hyperparathyroidism (SHP), parathyroidectomy (PTX), 22-Oxacalcitoriol (OCT)

INTRODUCTION

SECONDARY HYPERPARATHYROIDISM (SHP) is one of the most serious complications occurring in maintenance hemodialysis patients. The causes of SHP are considered to be related to a barrier to vitamin D production in kidney, a decrease in both vitamin D receptor and Ca receptor, hyperphosphatemia, an increase in intact parathyroid hormone (PTH) levels, and bone resistance to PTH.[1–3] In the field of internal medicine therapy of SHP, oral and intravenous active vitamin D (calicitoriol) replacement therapy and calcium replacement therapy have been performed.[1,2] In many cases, these therapies can suppress bone turnover and PTH levels, but hyperphosphatemia and hypercalcemia occur.[3–5] As such, the use of vitamin D therapy has largely been suspended.[4] To overcome this obstruction, 22-Oxacalcitoriol (OCT) (Chugai Pharmaceutical, Tokyo, Japan), vitamin D analogue, has recently been developed. OCT has been reported to result in a lesser incidence of hypercalcemia, hyperphosphatemia, and adynamic bone disease than that occurring with calcitoriol, and to suppress PTH secretion.[3,5] In the case of

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resistance to internal medicine therapy and intact PTH levels in excess of 500 pg/m*l*, parathyroidectomy (PTX) has been performed.[1,2] PTX improves the clinical symptoms of advanced SHP (itching, irritability, and cough) and bone turnover.[2] Unfortunately, if PTX is not performed at the optimal time, skeletal deformity, vessel calcification, and marked reduction in bone are irreversible.[2] In these circumstances, it is important to estimate the bone metabolism as well as the overall prognosis of SHP in its early stage. In evaluating the bone metabolism of hemodialysis patients, bone biopsy has been considered to be the gold standard in clarifying the extent of bone turnover[6]: This method, however, is invasive and too expensive to be performed routinely.[7,8] Non-invasive and alternative methods have been evaluated over the last 20 years[7,8] and the use of bone metabolic markers has been identified as a means of evaluating bone metabolism. Bone metabolic markers have been reported to correlate well with bone histological parameters,[8] and have been widely used to estimate both bone turnover and the therapeutic effects of renal osteodystrophy (ROD) in a clinical setting. In evaluating the diagnostic imaging ability of ROD, bone scintigraphy, dual x-ray absorptiometry (DXA), and bone X-ray have been carried out. Unfortunately, bone mineral density measured by DXA and computed tomography (CT) have been considered to be the result of chronic morphological bone change, and these devices do not always accurately reflect the current degree of bone turnover.[10] In normal human beings, there are large variations in bone mineral density, and low levels of bone mineral density are not always indicative of rapid bone loss.[10] Currently, no clinically accepted technique can determine prospectively which patients with SHP will lose bone and who would benefit from surgery. Based on the evaluation of ROD, bone scintigraphy has been thought to be a more sensitive method than morphological imaging, and semi-quantitative parameters, namely, the bone to soft tissue (B/ST) ratio, have been used to make the differential diagnosis of systemic metabolic bone diseases.[9,11,15] We have investigated bone biochemical markers and B/ST ratio.[13] In the present study, we evaluated the therapeutic effects of SHP, while determining both bone metabolic markers and the B/ST ratio, so-called, semi-quantitative method using bone scintigraphy before and after OCT and PTX.

MATERIALS AND METHODS

This study focused on ten hemodialysis patients, six males and four females. The age at the time of the study ranged from 25 to 71 years (mean 51.3 years). The causative diseases were chronic glomerulonephritis and malignant hypertension as well as hepatitis B-type related nephritis. The average duration of the hemodialysis was 159.5 months, with three dialysis sessions per week. No other medical problems such as liver disease, diabetes mellitus, or malabsorption were known to exist. None of the patients took steroids, estrogen, aluminum-containing phosphate binders, coumarins, anticonvulsants or any medications known to interact with the 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. Informed consent for participation in the present study was obtained from patients or their guardians as part of the protocol approved by the Institutional Clinical Subpanel on Human Studies at our university hospital.

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

Bone scintigraphy

The patients were administered 555 MBq of ^{99m}Tc-hydroxy-methylene-disphosphonate (HMDP) (Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan) after hemodialysis. Whole-body images were acquired approximately 3 hours after radiotracer injection and recorded with a 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 5500A/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 with the data-processing system using the method reported by Fogelman et al.[9,12] Regions of interest (ROIs) were manually drawn over selected areas; cranium, lumbar vertebrae (the center part of the lumbar vertebrae 3), left femoral neck, and soft tissue of the left medial femoral region (Fig. 1). Based on average counts obtained by the ROIs, the B/ST ratio was calculated with respect to the areas of cranium, lumbar vertebrae, and femoral neck respectively. Two nuclear medicine physicians measured the B/ST ratio twice, and confirmed the reappearance of B/ST ratio.

Laboratory data

The serum PTH concentrations were determined for all patients using a radioimmunoassay that measured intact PTH. Immunoreactive intact PTH was measured in all patients using the Allegro intact PTH kit (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The serum concentrations of calcium [σ-cresolphthalein-complexone (OCPC), Iyatron Co., Tokyo, Japan] (Ca) and phosphorus (Enzyme assay, Kyowa Co., Tokyo, Japan) (P) were also measured. Intact PTH concentrations ranged from 372 to 980 pg/m*l* (mean ± SD 568.3 ± 185.3 pg/m*l*; normal range, 10.0–65.0 pg/m*l*). Serum calcium and phosphorus ranged, respectively, from 7.31 to 12.09 mg/m*l* (10.46 ± 1.44 mg/m*l*; normal range, 8.5–10.5 mg/m*l*) and from 3.64 to 8.04 mg/m*l* (6.04 ± 1.44 mg/m*l*; normal range 2.5–4.5 mg/m*l*), respectively. Serum total alkaline phosphatase (ALP) was measured by an automated method, with levels ranging from 100.0 to 787.0 U/*l* (353.60 ± 201.55 U/*l*; normal range 115.0–359.0 U/*l*). Serum bone alkaline phosphatase (BALP) was measured using a radioimmunometric assay (ALKPHASE-B, Metra Biosystems, Inc., Mountain View, CA, USA), with levels ranging from 16.1 to 108.0 U/*l* (49.11 ± 33.41 U/*l*; normal range, 9.6–35.4 U/*l*). Serum deoxyprydinoline (DPYD) was measured by high-performance liquid chromatography (SRL, Inc., Tokyo, Japan), with levels ranging from 7.0 to 69.0 pmol/m*l* (26.20 ± 20.20 pmol/m*l*; normal range, <7.0 pmol/m*l*).

Parathyroidectomy (PTX)

Seven hemodialysis patients underwent PTX. The surgical method involved total parathyroidectomy and parathyroid autotransplantation. PTX was performed when intact PTH levels exceeded 500 pg/m*l*, and when resistance to internal treatment such as oral active vitamin D pulse therapy or intravenous active vitamin D pulse therapy appeared. Calcium replacement therapy using agents such as calcium salts was performed to prevent adynamic bone disease after PTX.

OCT (22-Oxacalcitoriol)

1,25-Dihydroxy-22-oxavitamin D_3 {22-Oxacalcitoriol (OCT), generic name: maxacalcitoriol} (Chugai Pharmaceutical Co., Ltd, Tokyo, Japan) is a derivative of 1,25-dihydroxyvitaminD_3 (calcitoriol). OCT was given to three hemodialysis patients, and administered three times per week at the end of hemodialysis. OCT administration was initiated when intact PTH levels exceeded 300 pg/m*l* and

Table 1 The B/ST ratio and the result of paired t-test before and after OCT

	before	after	p value
Cranium	6.30 ± 4.87	4.30 ± 3.07	ns
Femoral Neck	6.80 ± 3.98	4.87 ± 2.34	ns
Lumbar Vertebrae	16.19 ± 12.51	11.43 ± 9.57	ns

Note; B/ST ratio = bone to soft tissue ratio
Data were expressed as mean ± SD

Table 2 Serum biochemical markers and the result of paired t-test before and after OCT

	before	after	p value
Intact PTH	490.67 ± 130.24	231.00 ± 151.99	0.0084
ALP	240.00 ± 163.70	129.33 ± 47.35	0.2413
Ca	9.27 ± 1.88	10.95 ± 1.29	0.00395
P	6.12 ± 1.82	6.75 ± 1.82	0.6264
DPYD	18.00 ± 13.45	6.33 ± 3.51	0.208
BALP	31.40 ± 23.37	16.10 ± 4.65	0.2752

Note; Intact PTH = Intact Parathyroid Hormone, ALP = Alkaline Phosphatase, Ca = Calcium, P = Phosphorus, BALP = Bone Alkaline Phosphatase, DPYD = Deoxypyridinoline
Data were expressed as mean ± SD

Table 3 The B/ST ratio and the result of paired t-test before and after PTX

	before	after	p value
Cranium	4.21 ± 1.28	2.50 ± 0.61	0.0079
Femoral Neck	5.23 ± 2.19	3.93 ± 1.47	0.0252
Lumbar Vertebrae	7.36 ± 1.84	5.65 ± 1.53	0.0282

Note; B/ST ratio = bone to soft tissue ratio
Data were expressed as mean ± SD

Table 4 Serum biochemical markers and the result of paired t-test before and after PTX

	before	after	p value
Intact PTH	657.14 ± 234.15	102.71 ± 93.59	0.003
ALP	402.29 ± 206.83	298.29 ± 156.97	0.0051
Ca	10.96 ± 0.96	8.72 ± 0.97	0.0005
P	6.00 ± 1.57	4.70 ± 1.21	0.0393
DPYD	29.71 ± 22.45	8.29 ± 4.72	0.0232
BALP	56.70 ± 35.62	24.46 ± 6.49	0.0324

Note; Intact PTH = Intact Parathyroid Hormone, ALP = Alkaline Phosphatase, Ca = Calcium, P = Phosphorus, BALP = Bone Alkaline Phosphatase, DPYD = Deoxypyridinoline
Data were expressed as mean ± SD

resistance to oral active vitamin D pulse therapy appeared.[13] The initial dose of OCT was 10 μg when intact PTH levels exceeded 500 pg/m*l*, and 5 μg when intact PTH was at lower levels. The mean duration of administration was approximately 1 year. When calcium levels exceeded 11.5 mg/m*l* or intact PTH levels decreased to 150 mg/m*l* or less, OCT administration was stopped altogether or the dosage was altered.[14] The maximum dose was 20 μg.

Justification of the therapeutic value

OCT: In a week before administration of OCT, both bone scintigraphy after hemodialysis and blood tests evaluating intact PTH, ALP, Ca, DPYD, and BALP were carried out. When intact PTH levels were between 150 and 250 pg/m*l*, OCT was considered to be appropriate treatment for SHP, and bone scintigraphy was performed.

PTX: In a week before PTX, both bone scintigraphy after hemodialysis and blood tests were performed, as described above. After 6 months of PTX, bloods test in tandem with bone scintigraphy were carried out to evaluate the therapeutic effects of PTX.

Statistical analysis

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

RESULTS

In the OCT group, the B/ST ratio of no skeletal region showed a tendency to diminish significantly (cranium, $p = 0.19$; lumbar vertebrae, $p = 0.14$; femoral neck, $p = 0.19$) (Table 1). Intact PTH levels decreased significantly, while ALP, BALP, and DPYD levels did not (intact PTH, $p = 0.0084$; ALP, $p = 0.2413$; BALP, $p = 0.2752$; DPYD, $p = 0.208$). Calcium levels increased significantly, while phosphorus levels did not (Ca, $p = 0.00395$; P, $p = 0.6264$) (Table 2). In the PTX group, the B/ST ratio of each skeletal region showed a tendency to decrease significantly (cranium, $p = 0.0079$; lumbar vertebrae; $p = 0.0282$; femoral neck, $p = 0.0252$) (Table 3). Intact PTH, ALP, Ca, BALP, P, and DPYD levels as well as the B/ST ratio were reduced significantly after PTX (intact PTH, $p = 0.003$; Ca, $p = 0.0005$; P, $p = 0.0393$; ALP, $p = 0.0051$; DPYD, $p = 0.0232$; BALP, $p = 0.0324$) (Table 4).

DISCUSSION

Numerous researchers have described the usefulness of the semi-quantitative method of bone scintigraphy, the so-called B/ST ratio, with regard to diagnosing systemic metabolic bone disease, including SHP.[9,11,12,15,24–26] The ROIs were manually drawn around cranium, lumbar vertebrae, left femoral neck, and soft tissue of the medial left femoral region, because we made note of the difference in the ratio of cortical bone to trabecular bone in each bony region, and lumbar vertebrae (L2–4), femoral neck, and soft tissue of the thigh have been used to measure the B/ST ratio in the past literature. In cranium, the ratio of cortical bone to trabecular bone was 95% to 5%, and cranium has much more cortical bone than trabecular bone.[16] In lumbar vertebrae, the ratio of cortical bone to trabecular bone is 34% to 66%, and lumbar vertebrae have much more trabecular bone than cortical bone.[16] In femoral neck, the ratio of cortical bone to trabecular bone is 75% to 25%.[27] By means of drawing ROIs around the selected area, the difference in the ratio of cortical bone to trabecular bone enabled us to grasp the bone turnover before and after treatment of SHP for each bony region. With respect to bone metabolic markers, BALP and DPYD were measured before and after treatment of SHP. BALP has been reported to be the best method for evaluating bone formation of patients with chronic renal failure.[17] It has also been reported that BALP levels are a useful diagnostic marker for differentiating ROD.[8,18] DPYD has been reported to be useful as a specific biochemical marker of resorption in hemodialysis patients, as DPYD is present only in bone and dentin.[19] It has also been reported that serum pyridinolines are promising markers of bone resorption in patients with chronic renal failure.[17,19] In the PTX group, the B/ST ratio of cranium, femoral neck, and lumbar vertebrae were decreased significantly, particularly in cranium. On ROD, it has been reported that PTH affects cortical bone much more than trabecular bone,[20,21] and that cortical bone takes longer to recover than trabecular bone after PTX.[2] We thought that cranium may be affected by excessive PTH secretion more strongly because of having so much more cortical bone. Regarding bone metabolic markers, we found intact PTH, Ca, P, BALP, and DPYD levels to be decreased significantly after PTX, which was consistent with previous reports.[2,7,22]

In the OCT group, the B/ST ratio of each skeletal region showed a decreasing tendency, although not significantly. Intact PTH levels were significantly decreased; DPYD, BALP, and ALP were also decreased, though not significantly. OCT has been reported to suppress PTH and bone turnover of SHP.[5] Our result indicating a significant decrease in intact PTH levels is consistent with this report. The levels of bone metabolic markers have also reported to decrease after OCT administration.[14] Our result indicating decreased DPYD, BALP, and ALP levels is in agreement with this report. After OCT administration, Ca and P levels were increased, as OCT is a vitamin D analogue and has been reported to cause hypercalcemia and hyperphosphatemia less frequently than calcitoriol.[5,23] In short, the increases in Ca and P levels were likely due to the medicinal action of OCT. OCT suppresses bone resorption; as such, OCT can also suppress bone turnover, and the resulting improvements in ostitis fibrosa have

been proven by bone biopsy.[5,23] The results indicating that the B/ST ratio of cranium, lumbar vertebrae, and femoral neck show a tendency to decrease suggest that the bone turnover of SHP can be suppressed by OCT to the same extent as by PTX. This result reveals that OCT may be a promising treatment in the field of internal medicine therapy of SHP. If we examine many cases hereafter, we think that B/ST ratio of each bony region will show a decreasing tendency significantly in OCT groups. In this research we have investigated only three cases regarding OCT, because there were some cases in which OCT was discontinued due to hypercalcemia and hyperphosphatemia, and there were much more cases of PTX than those of OCT.

The significant decrease in the B/ST of cranium after PTX suggests that this parameter may allow us to evaluate the therapeutic effects of SHP. Unlike lumbar vertebrae and femoral neck, cranium is not affected by bone remodeling followed by loading and bone degeneration and it has much more cortical bone. We believe that the B/ST ratio will enable us to grasp the current bone metabolism of cortical bone in SHP more precisely, and reflect the therapeutic effects of SHP. To our knowledge, the B/ST ratio of cranium has not been reported to be useful in estimating the therapeutic effect of SHP, nor has the ratio of cortical bone to trabecular bone. Bone biopsy has been reported to confirm the improvement of SHP after PTX and OCT administration.[22] Using bone metabolic markers, we can judge the therapeutic effect of SHP. Unfortunately, it is difficult to estimate the bone metabolism of local bony regions and based on differences in the bony composition. Bone scintigraphy is a non-invasive method and accurately reflects current bone metabolism and ectopic calcification due to SHP systematically. It can be also used to estimate bone metabolism based on differences in the bony composition. Although B/ST ratio has been reported to be limited with respect to making a diagnosis of systemic metabolic bone diseases,[9] we believe that the B/ST ratio, which can reflect current bone metabolism, may be useful in evaluating the therapeutic effects of SHP.

At present, it is thought that PTX should be performed at an optimal time during the therapeutic course for SHP. One of the most important things to decide the prognosis of SHP is to realize the bone metabolism of cortical bone. Using the B/ST ratio, we are convinced that we can comprehend the therapeutic effect of SHP more accurately, which may contribute to deciding the treatment planning and improving the prognosis.

CONCLUSION

Our results indicate that the B/ST ratio reflects the bone metabolism of SHP and that the B/ST ratio of cranium may be very useful in evaluating the therapeutic effects of SHP.

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