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A clinical assessment of the relationship between bone scintigraphy and serum biochemical markers in hemodialysis patients

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Background: Renal osteodystrophy is a metabolic bone disease and a common complication of end-stage chronic renal failure and maintenance dialysis treatment. In this study, we examined the correlation between quantifying bone scintigraphy and serum biochemical markers in hemodialysis patients. ***Methods:*** Bone scintigraphy with technetium-99m-hydroxy-methylene-diphosphonate (^{99m}Tc-HMDP) was performed on 28 patients on maintenance hemodialysis. Bone scintigraphy was performed using a standard protocol and was quantified by setting regions of interest (ROIs) over selected regions. The bone-to-soft-tissue ratio (B/ST ratio) at each region was calculated in all patients. The B/ST ratios were then compared with serum biochemical markers. ***Results:*** The B/ST ratio for the skull correlated well with serum bone-specific alkaline phosphatase (BAP) ($r = 0.735$, $p < 0.001$), serum deoxypyridinoline (DPD) ($r = 0.806$, $p < 0.001$) and intact parathyroid hormone (intact PTH) ($r = 0.701$, $p < 0.001$). The B/ST ratio for the lumbar spine correlated with intact PTH ($r = 0.387$, $p < 0.05$) but not with serum BAP or serum DPD. The B/ST ratio for the femoral neck correlated with serum DPD ($r = 0.431$, $p < 0.05$) and intact PTH ($r = 0.449$, $p < 0.05$) but not with serum BAP. ***Conclusions:*** Our data suggest that quantitative bone scintigraphy is a sensitive and useful method for evaluating bone metabolism in hemodialysis patients. The B/ST ratio for the skull may reflect changes of bone metabolism in hemodialysis patients.

Key words: technetium-99m-hydroxy-methylene-diphosphonate, bone-specific alkaline phosphatase, deoxypyridinoline, bone-to-soft-tissue ratio, renal osteodystrophy

INTRODUCTION

CHRONIC RENAL FAILURE produces changes in bone metabolism that affect bone structure and bone turnover. Renal osteodystrophy (ROD) is a complication of chronic renal failure that is often associated with metabolic bone disorders. It has been observed that most patients with end-stage renal failure during chronic maintenance dialytic therapy have abnormal bone histology.[1,2] Bone biopsies, bone scintigraphy, biochemical markers, and bone films have been used to assess metabolic bone disorders and bone turnover.[3,4] Bone turnover is usually assessed by histomorphometric analysis of bone biopsies, which is probably the most reliable method available at present. Bone biopsy remains the gold standard for a diagnosis of ROD,[5] but it is an invasive method that cannot be routinely used.

In this context, the need for non-invasive diagnostic techniques has long been recognized. Bone scintigraphy has been acknowledged as a sensitive method for early detection and assessment of metabolic bone disease.[6] The skeletal uptake index of bone-seeking radiopharmaceuticals, expressed as the bone-to-soft-tissue ratios (B/ST ratios) of tracer, has been proposed as a non-invasive and effective method for measurement of bone turnover.[7] Several other non-invasive methods have been developed for detecting ROD in dialysis patients. In addition to intact parathyroid hormone (intact PTH), the levels of which can be determined by highly precise

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radioimmunometric assay, several enzymes and matrix proteins synthesized from osteoblasts and protein fragments released after bone matrix breakdown have been proposed in recent years as serum biochemical markers of bone formation and resorption rates.[8] Serum bone-specific alkaline phosphatase (BAP) appears to be essential for the process of mineralization and bone formation; it provides useful information regarding the rate of bone turnover in hemodialysis patients.[9] During bone resorption, bone collagen is degraded, resulting in the release of several collagen crosslinks into the blood. Deoxypyridinoline (DPD) is involved in intramolecular and intermolecular crosslinking and is specific to bone degradation. It has been found that serum levels of DPD are significantly increased in hemodialysis patients, making it a specific serum marker of bone resorption in hemodialysis patients.[10,11]

There is still a paucity of studies focusing on the assessment and correlation of bone turnover using serum biochemical markers and quantitative analysis of bone scintigraphy. Based on these serum biochemical markers, we have studied the diagnostic value of the B/ST ratios using bone scintigraphy in non-invasive evaluations of the changes of bone metabolism in hemodialysis patients.

MATERIALS AND METHODS

Technetium-99m-hydroxy-methylene-diphosphonate (^{99m}Tc-HMDP) quantitative analysis of bone scintigraphy was performed on 28 patients (14 men, 14 women; age range, 22–67 y; mean age, 46.6 y) receiving maintenance dialysis treatment. All patients were anuric. The original disease was chronic glomerulonephritis in all patients. The average duration of hemodialysis was 72 months, with three dialysis sessions per week. All patients were treated with phosphate binders. None of the patients had received other drugs known to affect bone metabolism. None of the patients had undergone parathyroidectomy. None of the patients had clinical or biochemical evidence of liver disease.

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

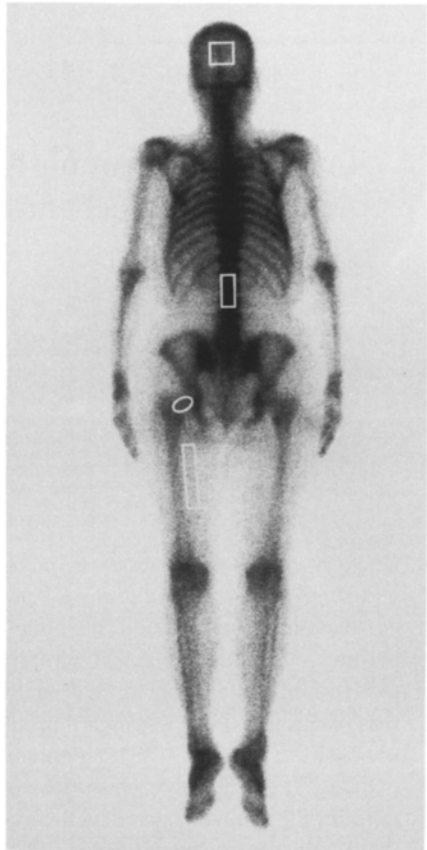

Fig. 1 ROIs in the skull, lumbar spine, femoral neck and medial parts of the soft tissue areas of the thigh were set on posterior projection.

Quantification of bone scintigraphy

Skeletal and soft tissue uptakes of ^{99m}Tc-HMDP were analyzed on a data processing system using the modified method reported by Rosenthall et al.[12] On whole-body posterior views, regions of interest (ROIs) were set over selected regions (Fig. 1). The B/ST ratios were measured by drawing ROIs around the skull, lumbar spine, femoral neck and medial parts of the soft tissue areas of the thigh. The means of the ROIs of all patients were calculated by a computer system.

Laboratory data

Predialysis blood sampling was performed. The serum PTH concentration in each patient was 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 (s-cresolphthalein complexone (OCPC); Iyatron Co., Tokyo, Japan) and phosphate (enzyme assay; Kyowa Co., Tokyo, Japan) were also measured. Intact PTH concentrations ranged from 21.0 to 1100.0 pg/m*l* (mean, 432.6 ± 323.3 pg/m*l*;

Table 1 Clinical data and the B/ST ratios in dialysis patients

Patient no.	Sex	Age (y)	Total dialysis duration (mos.)	Intact PTH (pg/m*l*)	Ca (mg/d*l*)	P (mg/d*l*)	Serum DPD (pmol/m*l*)	Serum BAP (U/*l*)	B/ST ratios		
									H/S	F/S	L/S
1	F	54	162	170.0	9.9	5.0	18.0	36.1	2.51	2.25	5.03
2	F	61	10	85.0	10.0	4.1	15.0	17.9	2.68	2.18	7.65
3	F	34	129	140.0	9.0	4.4	11.0	29.6	2.23	7.67	15.93
4	M	66	161	980.0	9.5	6.6	36.0	98.2	5.58	3.90	8.94
5	F	54	6	870.0	8.6	5.8	12.0	53.6	4.65	5.43	11.16
6	F	29	51	21.0	9.8	5.8	13.0	19.2	1.34	3.19	5.33
7	F	38	111	320.0	8.1	6.1	13.0	27.3	3.02	3.72	12.07
8	M	25	10	130.0	8.6	6.3	8.0	13.8	1.52	2.98	10.25
9	F	66	113	210.0	8.3	5.3	13.0	76.0	3.56	4.00	7.16
10	F	32	19	100.0	10.2	5.1	7.0	16.5	2.54	3.05	10.63
11	F	64	11	770.0	8.0	5.3	28.0	111.0	5.14	2.92	7.53
12	M	22	162	830.0	6.8	8.5	19.0	39.7	3.46	6.10	14.40
13	M	40	153	380.0	9.2	4.2	13.0	46.7	1.85	3.45	10.19
14	M	34	11	420.0	8.5	8.7	9.0	20.9	2.17	4.70	9.76
15	M	44	160	1100.0	10.5	6.4	25.0	68.6	5.45	4.47	10.69
16	M	67	50	530.0	11.1	3.6	15.0	32.9	3.00	3.22	5.82
17	F	48	5	29.0	10.9	5.5	6.0	19.7	2.95	3.62	6.33
18	F	40	115	400.0	8.9	3.9	24.0	64.6	3.76	0.61	2.56
19	F	45	10	23.0	10.4	6.8	5.0	10.9	1.63	2.81	5.10
20	F	52	136	420.0	7.9	14.0	18.0	23.6	4.21	2.24	6.37
21	M	63	2	520.0	7.4	5.4	18.0	37.3	2.01	4.96	9.65
22	M	41	12	510.0	9.2	3.6	8.0	55.6	2.87	0.85	9.71
23	M	35	133	940.0	10.3	6.2	30.0	32.9	5.74	7.09	13.09
24	M	49	8	680.0	10.6	8.0	49.0	108.0	8.62	9.55	11.87
25	F	56	17	59.0	9.9	5.7	4.0	13.3	2.22	4.34	8.38
26	M	41	1	720.0	9.4	5.5	16.0	51.7	7.18	6.26	15.47
27	M	46	116	372.0	12.2	5.2	6.0	12.7	1.36	2.36	2.88
28	M	61	142	385.0	10.4	6.7	5.0	18.0	1.56	2.78	5.64

B/ST ratios = Bone-to-soft-tissue ratios; H/S = B/ST ratio for the skull; F/S = B/ST ratio for the femoral neck; L/S = B/ST ratio for the lumbar spine; intact PTH = intact parathyroid hormone; Ca = total serum calcium; P = serum inorganic phosphate; DPD = deoxypyridinoline; BAP = bone-specific alkaline phosphatase.

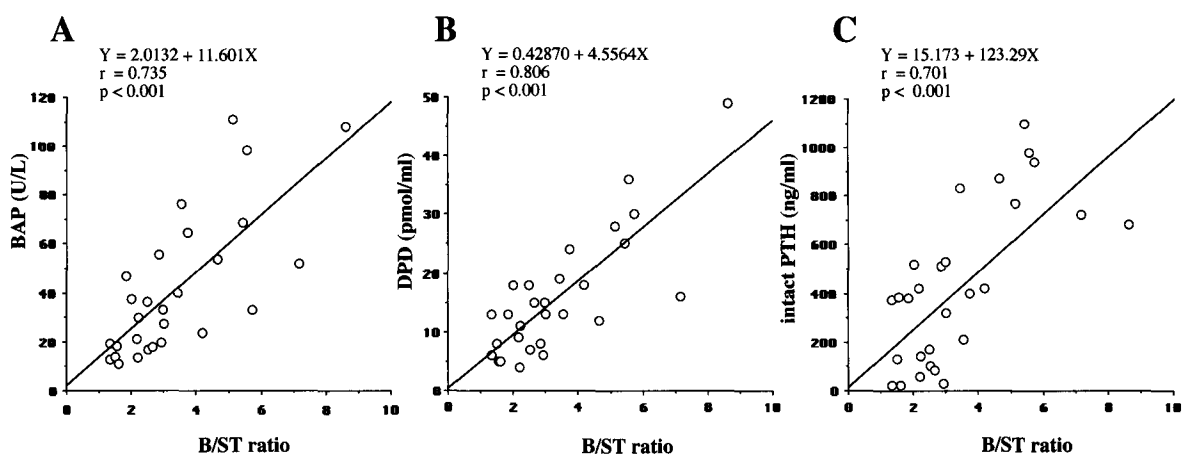

Fig. 2 (A) Relationship between the bone-to-soft-tissue (B/ST) ratio for the skull and serum bone-specific alkaline phosphatase (BAP). Regression equation: $y = 2.0132 + 11.601x$ with y, BAP activity concentration (U/*l*) (and x, the B/ST ratio for the skull) ($r = 0.735$, $p < 0.001$, $n = 28$). (B) Relationship between the B/ST ratio for the skull and serum deoxypyridinoline (DPD). Regression equation: $y = 0.42870 + 4.5564x$ with y, DPD activity concentration (pmol/m*l*) (and x, the B/ST ratio for the skull) ($r = 0.806$, $p < 0.001$, $n = 28$). (C) Relationship between the B/ST ratio for the skull and intact parathyroid hormone (intact PTH). Regression equation: $y = 15.173 + 123.29x$ with y, intact PTH activity concentration (pg/m*l*) (and x, the B/ST ratio for the skull) ($r = 0.701$, $p < 0.001$, $n = 28$).

Table 2 Correlations between the B/ST ratios and serum biochemical markers

	B/ST ratios		
	Skull	Lumbar spine	Femoral neck
Serum BAP			
r	0.735	0.153	0.254
p	< 0.001	0.440	0.194
Serum DPD			
r	0.806	0.208	0.431
p	< 0.001	0.291	0.016
Intact PTH			
r	0.701	0.387	0.449
p	< 0.001	0.041	0.015

B/ST ratios = Bone-to-soft-tissue ratios; BAP = bone-specific alkaline phosphatase; DPD = deoxypyridinoline; Intact PTH = intact parathyroid hormone.

normal range = 10.0–65.0 pg/m*l*). Serum calcium and phosphate levels ranged, respectively, from 6.8 to 12.2 mg/m*l* (mean, 9.4 ± 1.2 mg/m*l*; normal range = 8.5–10.5 mg/m*l*) and from 3.6 to 14.0 mg/m*l* (mean, 6.0 ± 2.0 mg/m*l*; normal range = 2.5–4.5 mg/m*l*). Serum BAP was measured by radioimmunometric assay (ALKPHASE-B; Metra Biosystems, Inc., Mountain View, CA, USA) and ranged from 10.9 to 111.0 U/*l* (mean, 41.3 ± 29.0 U/*l*; normal range = 9.6–35.4 U/*l*). Serum DPD was measured by high-performance liquid chromatography (HPLC) and ranged from 4.0 to 49.0 pmol/m*l* (mean, 15.9 ± 10.4 pmol/m*l*; normal range, <7.0 pmol/m*l*).

Statistics and analysis

Values are expressed as the mean ± SD. Correlation was assessed by linear regression analysis and the Pearson's correlation coefficient (Statview; Abacus Concepts Inc., Berkeley, CA, USA). The significance of the magnitude of correlation coefficients was determined using the B/ST ratios and serum biochemical markers. A probability of less than 0.05 was considered significant.

RESULTS

The relevant clinical data and the B/ST ratios are summarized in Table 1. The B/ST ratio (mean ± SD) was 3.39 ± 1.84 in the skull, 8.91 ± 3.52 in the lumbar spine and 3.95 ± 2.00 in the femoral neck. There were good correlations between the B/ST ratio for the skull and serum BAP ($r = 0.735$, $p < 0.001$; Fig. 2A), the B/ST ratio for the skull and serum DPD ($r = 0.806$, $p < 0.001$; Fig. 2B) and the B/ST ratio for the skull and intact PTH ($r = 0.701$, $p < 0.001$; Fig. 2C). The B/ST ratio for the lumbar spine correlated with intact PTH ($r = 0.387$, $p < 0.05$) but not with serum BAP or serum DPD. The B/ST ratio for the femoral neck correlated with serum DPD ($r = 0.431$, $p < 0.05$) and intact PTH ($r = 0.449$, $p < 0.05$) but not with serum BAP. Their correlations are summarized in Table 2. We were unable to demonstrate a statistically significant correlation of the B/ST ratios with serum calcium, serum phosphate, age or duration of hemodialysis treatment.

DISCUSSION

Renal osteodystrophy describes the spectrum of disorders of mineral and skeletal metabolism associated with chronic renal dysfunction. The mechanisms involved in the development of renal osteodystrophy are complex and are induced by numerous factors.[1] Bones showing an increased uptake of radiopharmaceuticals include the skull, mandible, sternum, shoulders, vertebrae and distal thirds of the long bones.[4,13] Abnormal bone scintigraphy reflects abnormalities in collagen metabolism and increased bone turnover.[10] Such conditions can be related to secondary hyperparathyroidism, which is frequently observed in uremic patients.

The quantitative methods of bone scintigraphy have been proposed for the evaluation of metabolic bone disorders. Measurement of the B/ST ratios has been proposed by Wiegmann et al.,[14] Rosenthall et al.,[12] Fogelman et al.[15] and Lien et al.[7] The B/ST ratio indexes are of limited value in the investigation of metabolic bone disease in the opinion of Fogelman et al., but it has been proposed as a useful index by Lien et al. Individual regions of interest (ROIs) were delineated at different sites in their studies. There is no report about suitable sites of ROIs in previous studies. There has been no previous report regarding the B/ST ratios for the skull by using the quantitative analysis of bone scintigraphy, although symmetrical increase activity has been known in the skull in hemodialysis patients.[13] In this study, ROIs were delineated at three skeletal sites: the skull, the lumbar spine and the femoral neck. ROIs of soft-tissue mass were delineated at the medial parts of the thigh as previously described.[12] We estimated the degree of accumulation of ^{99m}Tc-HMDP by using the B/ST ratios reflecting the bone metabolism of dialysis patients. ^{99m}Tc-labeled diphosphonate is related mainly to sites of newly forming bone, with the largest uptake occurring on immature amorphous calcium phosphate at the mineralization front.[16] It is well recognized that accumulation of ^{99m}Tc-labeled diphosphonate reflect conditions of the accelerated bone turnover. The B/ST ratio was 3.39 ± 1.84 in the skull, 8.91 ± 3.52 in the lumbar spine and 3.95 ± 2.00 in the femoral neck. The largest B/ST ratio was found at the lumbar spine, though patients that had degenerative change of the lumbar spine were excluded in this study. Degrees of accumulation of ^{99m}Tc-labeled diphosphonate were not influenced by its degenerative change.

The remodeling (bone turnover) process is coupled with osteoblasts and osteoclasts in normal bone.[1] ROD may result in abnormal bone turnover, coupling (bone formation and resorption) and mineralization. Bone turn-

over is mainly influenced by serum PTH, which induces bone formation by osteoblasts and bone resorption by osteoclasts.[17] With advancing renal dysfunction, skeletal PTH resistance occurs.[4] Observations of serum biochemical markers are useful in anuric patients. Serum BAP provides useful information regarding bone turnover in hemodialysis patients, and the sensitivity of serum BAP is higher than that of intact PTH.[8] Serum pyridinoline provides valuable information regarding the rate of bone remodeling and showed a significantly closer correlation with bone histomorphometoric parameters than did intact PTH.[10] In the present study, we used serum BAP as an index of bone formation and used serum DPD as an index of bone resorption.

The B/ST ratios were then compared with these biochemical markers of bone turnover. To our knowledge, no previous studies have used this approach. We found that in the skull, the B/ST ratio correlated closely with serum biochemical markers (serum BAP, serum DPD). We believe that this finding is a new and original observation. The skull is a site rich in cortical bone, whereas the lumbar spine and femoral neck are not.[18] Schober et al. demonstrated that a reduction in mineralized cortical bone in dialysis patients with clinically significant renal osteodystrophy correlated with generalized thinning of the cortical bone.[19] The abnormalities in bone metabolism affect the skull in particular.[20] The skull which contains mostly cortical bone may be predominantly influenced by metabolic bone disorders in hemodialysis patients.

Bone formation and skeletal mineralization were influenced by serum BAP.[9] A close relationship between the accumulation of ^{99m}Tc-labeled diphosphonate and serum BAP was observed, and radiotracer uptake is influenced by osteoblast activity.[21] The B/ST ratio for the skull may be an indicator of osteoblast activity. Moreover, bone resorption is usually coupled with bone formation.[1] In recent years, measurement of serum DPD has been made possible by the HPLC method, and the usefulness of this method has already been demonstrated.[22] It is often said that serum DPD strongly reflects bone resorption.[23] During bone resorption, degradation of bone collagen is influenced by specific osteoclast-related enzymes.[1] The present study determined for the first time that serum DPD and the B/ST ratio for the skull are also highly correlated. The B/ST ratio for the skull may be not only an indicator of osteoblast activity but also an indicator of osteoclast activity in hemodialysis patients. Quantitative bone scintigraphy and serum biochemical markers may be useful in providing a dynamic assessment of bone turnover.

It is considered that the B/ST ratio for the skull may provide a new procedure and will be useful as an index of bone metabolism in hemodialysis patients. Although B/ST ratios are of limited value in the investigation of metabolic bone disorders,[15] the B/ST ratio for the skull may be useful for the clinical evaluation of ROD.

CONCLUSION

The B/ST ratio for the skull correlated closely with serum biochemical markers of bone turnover. Thus, consideration of the B/ST ratio along with quantitative analysis and bone scintigraphy may be useful for estimating bone turnover, and may be available for the longitudinal follow-up of hemodialysis patients.

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