Bone Scintigraphy in Renal Osteodystrophy

P. de Graaf, I. M. Schicht, E. K. J. Pauwels, J. te Velde, and J. de Graeff

University Hospital, Leiden, The Netherlands

Bone scintigraphy with Tc-99m HEDP was performed in 30 patients on maintenance hemodialysis, and the results of quantitative analysis were compared with those of a normal group. To permit this comparison, elevated background activity due to the absence of renal radiotracer excretion was reduced by hemodialysis to levels found in the normals. Histologic proof of renal osteodystrophy had been obtained in all patients. The incidence of radiographic abnormalities was 46%, whereas abnormal scans were found in 25 patients (83%); skeletal lesions were also more pronounced and detected earlier. However, even when the scans appeared normal, the quantitative analysis showed increased skeletal activity in all patients. The total skeletal activity proved to be a good index of the severity of renal osteodystrophy and appeared dependent on both osteomalacia and hyperparathyroidism. These findings show that bone scintigraphy is a sensitive method to detect skeletal involvement in renal osteodystrophy.

J Nucl Med 19: 1289–1296, 1978

Typical bone changes in uremia, such as osteitis fibrosa, osteomalacia, and sometimes osteosclerosis (*1,2*), are commonly referred to as renal osteodystrophy. Two main pathogenic mechanisms have been identified: disordered vitamin D metabolism (*3*) and secondary hyperparathyroidism (*4,5*). Diagnosis is generally based on biochemical, histologic, and radiographic findings (*6*). Biochemical data provide information about the hyperparathyroid state (*7,8*) but are of limited diagnostic value. Microscopic bone studies allow more specific recognition of bone abnormalities than current radiographic methods, although the latter can be improved with magnification techniques (*9*).

Recently, abnormal bone scans in patients on maintenance hemodialysis have been reported (*11–14*). Qualitative studies showed increased skeletal activity, often before the radiographic changes (*11,12*). At present, the only quantitative data available concern bone-to-soft-tissue activity ratios in the distal femur, which were significantly increased in dialysis patients (*13,14*). This increase of skeletal activity in renal osteodystrophy has been attributed mainly to osteomalacia (*13–15*) or to hyperparathyroidism (*11*).

However, bone scintigraphy in uremic patients is complicated by delayed or absent renal radiotracer excretion, which may lead to increased skeletal uptake and elevated soft-tissue levels (*12,18*). In our experience, increased background radioactivity occurs in uremic patients and often results in a scan of inferior quality after 2–3 hr, except in those patients in whom skeletal uptake is markedly increased due to severe osteodystrophy. We attacked this problem by using hemodialysis to lower the activity of circulating radiotracer to normal levels before we collected quantitative data. This paper presents the results of such studies in normal controls and patients with histologically proven renal osteodystrophy.

Received Feb. 22, 1978; revision accepted July 12, 1978.

For reprints contact: P. de Graaf, Dept. of Nephrology, University Hospital, Leiden, The Netherlands.

MATERIALS AND METHODS

Thirty patients (21 males and nine females) on maintenance hemodialysis were studied. The median age was 37 yr (range 15–58 yr), the median dialysis duration 41 mo (range 4–101 mo). Creatinine clearance was below 5 ml/min in all patients; nine patients had been nephrectomized. Subtotal parathyroidectomy had been performed in five patients. All patients were treated with phosphate-binding antacids. Seven patients were on low doses of dihydrotachysterol (0.2 mg daily). Before scintigraphy, the relevant biochemical, radiographic, and histologic investigations were performed. Parathyroid hormone data were excluded from this study. A radiographic skeletal survey, performed without the use of magnification techniques, included the skull, chest, spine, hands, feet, and pelvic region. Findings were arbitrarily graded as: normal (0), mild (+), and markedly abnormal (++). Biopsy specimens of bone from the iliac crest were taken in all patients, embedded in methyl methacrylate and stained, as previously reported (*10*). Bone histologic findings were semiquantitatively scored and graded as normal (0), mild (1), moderate (2), and severe (3), for both osteitis fibrosa and osteomalacia. Bone remodelling was graded according to the bone surface area covered with active osteoblasts and osteoclasts. Osteoid excess was graded according to the width of the osteoid seam in relation to the presence of osteoblastic lining.

All patients and eight normal volunteers (median age 35 yr, range 22–51 yr) were given 10 mCi Tc-99m HEDP per 70 kg body weight. Peak circulating activity was found between ½ and 1½ min after i.v. administration. Serial blood samples (1 ml) were collected at regular intervals in both groups and counted after 5½ hr. In the patients, dialysis was started 15 min after administration of the radiotracer and continued for 4¾ hr. At the end of this period, circulating activity in all patients was less than 10% of the initial peak values, radioactive decay taken into account. An RP6 HP (acrylonitrile membrane) connected to a single-patient unit was used throughout. An example of the method used is shown in Fig. 1. Reproducibility, evaluated in two patients and two normals, was well within the statistical error.

Scintigraphy was performed after 6 hr with a large-field gamma camera provided with two scalers and controls to register counts in selected regions of interest. Images were obtained by standard positioning of all skeletal parts under the detector, as shown in Figs. 4, 5, and 6. Because a computer was not available, quantitative data were collected by registering count rates in both groups within standardized rectangular areas over the skeletal regions of interest mentioned below. Bladder activity, if present, was taken into account. The kilocounts (kC) of radioactivity registered in these regions were: head region, 200 kC; chest region, 300 kC; spine, 80 kC; pelvic region, 350 kC; hip region, 250 kC; thighs, 75 kC; knee region, 75 kC; lower legs, 50 kC; ankles and feet, 25 kC; and hands, 25 kC. The activity in the lower extremities was registered separately. Only spine and hand activities were not registered in all patients. The counting rate per selected region was measured, expressed as kC/sec and normalized to a dose of 10 mCi Tc-99m. When necessary, skeletal activity was corrected for radioactive decay and background activity. In both groups, the sum of the activity rates counted in the head region (noted as skull), chest region, pelvic and hip region, and lower extremities was taken as an index of the total skeletal activity. Although detailed quantitative skeletal information could not be obtained without a computer, and the quantitative data collected represent the radioactivity in the entire region of interest including soft-tissues, unavoidable inaccuracies were minimized by using standardized regions of interest in both groups and reducing soft-tissue activity in the patients by means of hemodialysis.

Qualitative scan findings were arbitrarily graded on a double-blind basis. The degree of abnormal skeletal uptake was assessed from the total of the nine selected regions (excluding that of the hands) showing increased activity. Zero or near-zero increases were graded as normal (0), an increase in less than six regions as mild (+), and in more than five regions as marked (++).

RESULTS

Table 1 shows the clinical, biochemical, radiographic, histologic, and scintigraphic findings. Histo-

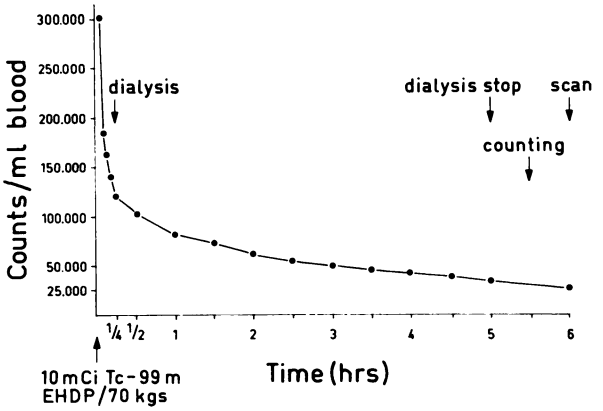

FIG. 1. Example of the standardized method used in patients and controls before scintigraphy.

TABLE 1. CLINICAL, BIOCHEMICAL, HISTOLOGIC, RADIOGRAPHIC, AND SCINTIGRAPHIC DATA

Patient No.	Sex & age (yr)	Total dialysis duration (mos.)	Px*	Ca* mmol/l	PO_4* mmol/l	A.P.* U/l B.	Bone histology O.F.*	Bone histology O.M.*	X-ray changes	Scan uptake	Total skeletal activity kC/sec*
Normal values:				2.25–2.65	0.8–1.45	<60					2.6–4.1
1	M 57	93	+	2.37	1.38	68	1	0	0	+	7.21
2	F 40	22	—	2.32	2.27	81	2	2	0	++	8.92
3	M 57	23	—	2.41	3.12	29	1	2	0	0	6.87
4	M 52	59	+	2.03	3.17	86	2	2	+	++	7.98
5	M 51	45	—	2.16	3.07	73	1	0	0	+	7.39
6	M 28	62	—	2.24	2.00	173	3	1	+	++	9.29
7	M 35	65	+	2.21	1.26	57	0	3	+	+	7.83
8	F 32	35	—	2.30	2.84	67	2	2	0	+	7.69
9	F 35	39	—	2.80	3.02	212	3	2	++	++	9.29
10	M 28	71	—	2.33	1.39	76	3	1	+	++	9.63
11	F 36	73	—	2.21	1.76	80	2	1	+	++	8.59
12	M 30	101	+	2.52	2.42	80	1	3	++	++	11.38
13	M 42	46	—	2.16	2.35	79	1	2	0	+	6.33
14	M 38	32	—	2.20	2.31	45	1	1	0	+	6.10
15	F 37	41	—	2.01	1.06	213	2	3	+	++	9.36
16	F 40	17	—	2.34	1.67	93	1	2	0	+	6.69
17	M 29	39	—	2.14	2.05	192	3	2	+	++	9.07
18	M 48	46	—	2.25	3.13	69	1	2	+	0	6.89
19	M 30	71	—	2.23	1.28	137	2	3	++	++	8.82
20	F 48	11	—	2.39	1.74	65	1	1	0	0	5.72
21	M 23	23	—	2.33	1.71	48	2	3	0	+	7.21
22	F 22	41	—	1.90	1.57	89	2	3	0	++	8.03
23	M 52	36	—	2.39	1.97	60	1	1	0	0	5.81
24	M 58	31	—	2.36	1.36	44	1	2	0	+	6.93
25	F 37	77	+	1.93	1.78	35	1	2	0	+	7.77
26	M 31	28	—	2.30	1.73	240	3	2	++	++	9.83
27	M 42	77	—	1.92	1.62	202	3	3	+	++	8.82
28	M 33	41	—	2.24	1.39	147	1	1	0	+	8.17
29	M 45	4	—	1.92	1.94	56	1	1	0	0	6.94
30	M 15	9	—	1.77	1.69	660	3	2	++	++	10.70

* Abbreviations used: Px = subtotal parathyroidectomy. Calcium and phosphorus = mean of five consecutive predialysis values. A.P. = alkaline phosphatate (U/l Bessey), value at time of scan. O.F. = osteitis fibrosa. O.M. = osteomalacia. kC/sec = kilo-counts/sec. Histologic, radiographic and scintigraphic grading: see Materials and Methods.

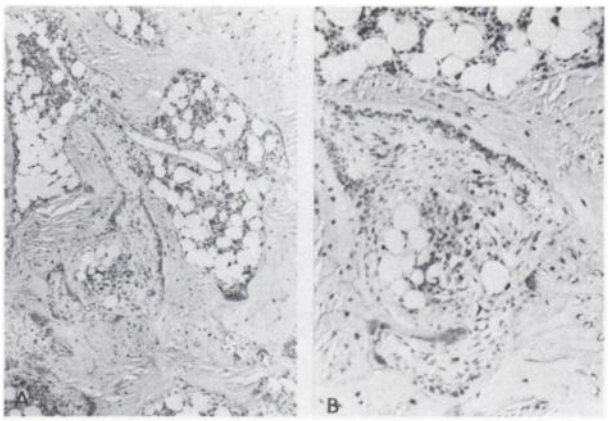

FIG. 2. (A) Part of a bone biopsy section, showing large part of bone surface covered with osteoblasts and osteoclasts. A similar amount of bone turnover was found in all microscopical fields. (B) Higher magnification shows that only part of bone surface is covered with osteoblast seams, remainder being covered with flattened endosteal cells (top). Example of osteitis fibrosa grade II. Methacrylate, 2 μm, Gallamine-Giemsa, ×100 (A) and ×450 (B). (50% photographic reduction)

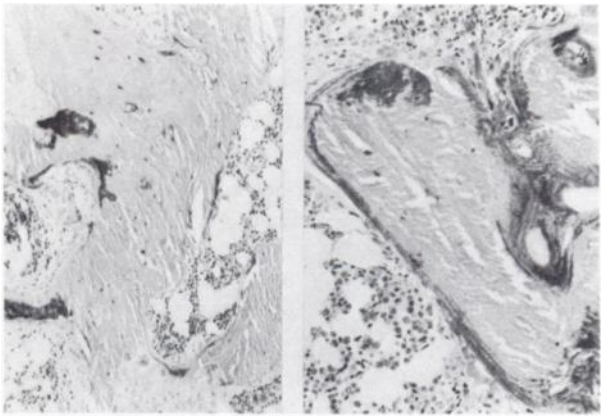

FIG. 3. Left: Example of osteomalacia, grade I. Part of bone biopsy section showing increased amounts of osteoid (black) associated with osteoblast seams. Whole bone surface in all microscopical fields was covered with osteoblasts and osteoclasts (osteitis fibrosa, grade III). Right: Osteomalacia, grade III. Note increased amounts of osteoid, not associated with increased bone turnover. Methacrylate, 2 μm, Goldner stain, ×100 (left) and ×450 (right). (33% photographic reduction)

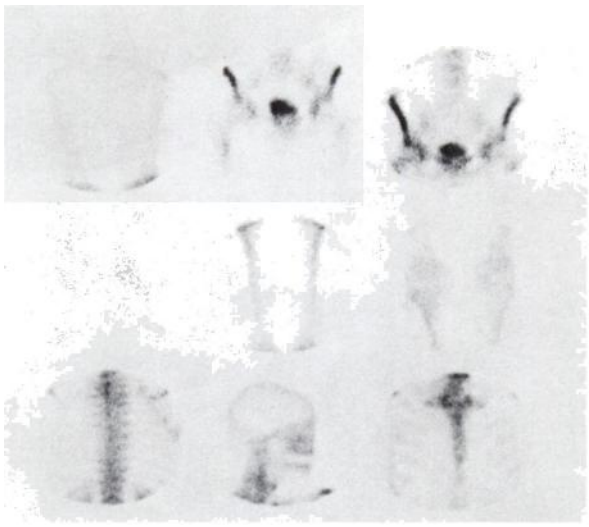

FIG. 4. Example of bone scan graded as normal.

logically increased bone remodelling and/or excess osteoid was found in all 30 patients. Twenty-seven of these patients (90%) showed a combination of osteitis fibrosa and osteomalacia. In Figs. 2 and 3 examples of the various grades of bone microstructure are shown. Serum alkaline phosphatase was elevated in 23 patients (76%) and correlated with the degree of osteitis fibrosa ($r = 0.71$, $p < 0.001$). Radiographic abnormalities were found in only 14 patients (46%) and were graded "marked" in only five.

Qualitative analysis revealed abnormal scans in 25 patients (83%), with a markedly diffuse and increased activity in 14 (47%). Only one false-negative scan was obtained. Examples of scans graded as normal, mild, and markedly abnormal are shown in Figs. 4, 5, and 6. The incidence of increased activity in the different skeletal regions of interest was: head region, 60% (skull, 50%; mandibles, 56%); chest region, 50%; spine, 50%; pelvic region, 46%; hip region, 60%; thighs, 60%; knees, 70%; lower legs, 50%; ankles, 56%; and hands, 46%.

Circulating activity in the two groups at the time of scanning was comparable: less than 10% of the initial activity recorded in both the patients and the controls. In the patients, circulating activity varied, depending on the dose administered and the degree of skeletal disease. Patients with severe osteodystrophy had high skeletal activity and lower levels of circulating activity than normals, and vice versa, which indicates that background activity did not play a large role in the skeletal activity registered. However, the observation that circulating activity in the patients with mild osteodystrophy was generally slightly higher than in the normals suggests that the excretion of the tracer under hemodialysis was less effective than the normal renal excretion.

Quantitative data obtained in both groups are shown in Figs. 7 and 8. The upper limit of the total skeletal activity in normals (Fig. 8) did not exceed 4.1 kC/sec (range 2.6–4.1, mean 3.07 kC/sec).

Increased activity was recorded in almost all skeletal regions of the patients investigated (Fig. 7), even when the scans appeared normal (Table 1). In the latter group, serum alkaline phosphatase levels were near normal, bone microstructure showed only mild

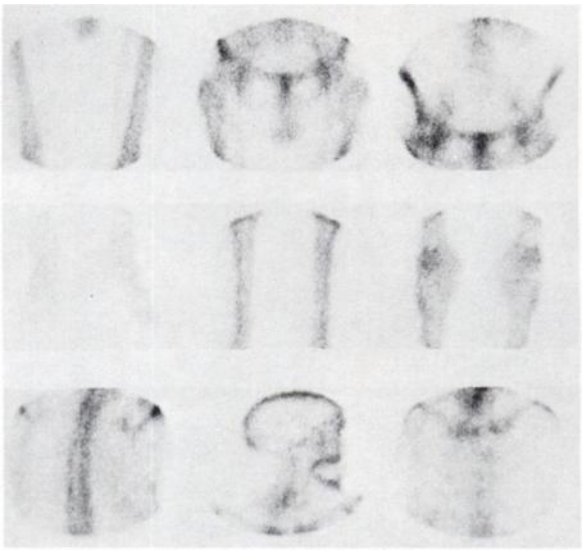

FIG. 5. Example of bone scan graded as mild (upper limit). Note activity in femoral arteries, suggestive of arterial calcification. Radiographs also showed calcified arteries.

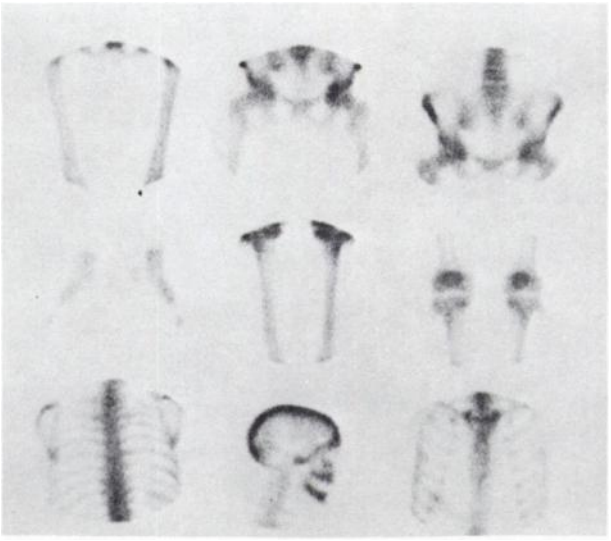

FIG. 6. Example of markedly abnormal bone scan, showing diffuse increased activity accumulation in all skeletal parts.

osteodystrophy, and the total skeletal activity was less than 7 kC/sec. Qualitatively abnormal skeletal uptake was observed only when the total skeletal activity exceeded 6 kC/sec (Fig. 9). Marked qualitative scan abnormalities were noted when the total skeletal activity exceeded 8 kC/sec. In this group marked osteodystrophy was confirmed with conventional diagnostic methods (Table 1). Radiographic abnormalities were seen when the total skeletal activity exceeded 7.5 kC/sec and were marked at levels above 8.5 kC/sec (Fig. 9). The highest skeletal activity was recorded in Patient 12, who had been on dialysis for almost 9 yr and had severe pulmonary calcification, visible on the scan and confirmed by open lung biopsy. Subtotal parathyroidectomy had been performed in this patient, but only two parathyroid glands were removed.

In the remaining four patients, all of whom had been parathyroidectomized before scintigraphy because of severe osteodystrophy, the total skeletal activity was less than 8 kC/sec. All these patients were on low doses of dihydrotachysterol. In the three other patients on dihydrotachysterol (without parathyroidectomy) no improvement was noted and their skeletal activity was above 8.5 kC/sec.

After scintigraphy, subtotal parathyroidectomy was performed in all but two of the patients with marked scintigraphic abnormalities and a total skeletal activity above 8.5 kC/sec. Additionally, one patient (No. 8) with a total skeletal activity of 7.7 kC/sec was parathyroidectomized. The exceptions concerned one patient (No. 30) who had a renal transplant and one (No. 26) who was inoperable. In all of the ten patients who were parathyroidectomized, significant parathyroid hyperplasia was found. The mean weight of the excised parathyroid tissue was 1450 mg (normal total parathyroid weight $\approx$120 mg). Subsequently, these patients could safely be treated with calcium and dihydrotachysterol. Five other patients had renal transplants (Nos. 13, 16, 21, 23, and 25) and the remaining 13 patients, who had less severe scintigraphic abnormalities, were treated with daily oral calcium and dihydrotachysterol.

In one patient (No. 9) scintigraphy was repeated 3 wk after parathyroidectomy. She was clearly in hypoparathyroid state, but identical quantitative results were obtained.

DISCUSSION

In all of the patients in the present study, bone biopsy specimens had provided histologic proof of renal osteodystrophy. Serum alkaline phosphatase was elevated in 76% of them, and radiographic changes were found in 46%. The low incidence of radiographic abnormalities illustrates the insensitivity of this technique with respect to skeletal lesion in renal osteodystrophy.

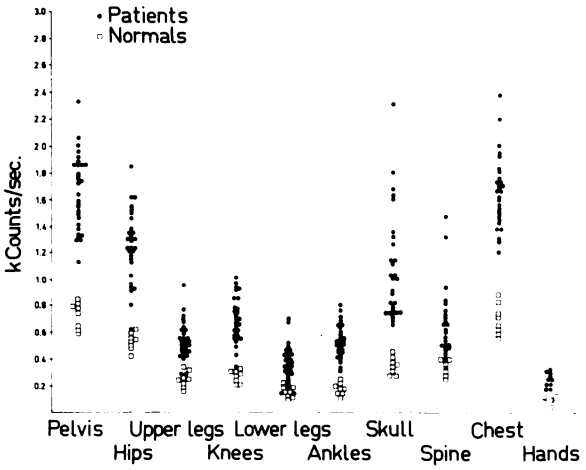

FIG. 7. Quantitative data obtained in selected regions of interest in both groups, expressed as kC/sec corrected for 10-mCi Tc-99m HEDP dose.

Abnormal bone images obtained with Tc-99m-labeled phosphate compounds have been reported in nonuremic hyperparathyroidism and osteomalacia (*13,19,20*), and recently in renal osteodystrophy (*11–14*). In the present study, qualitative scintigraphic analysis showed an incidence of abnormal scans of 83%, which supports the conclusion reached by Sy (*11*) and Ølgaard (*12*) that qualitative scin-

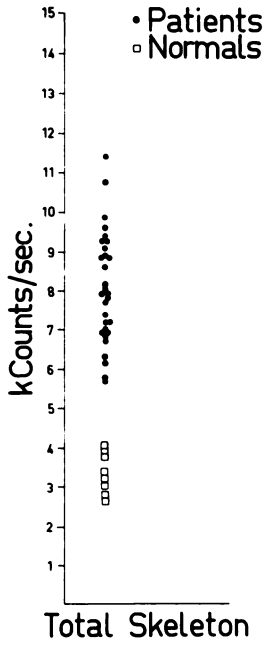

FIG. 8. Total skeletal activity, expressed as kC/sec corrected for 10-mCi Tc-99m HEDP dose.

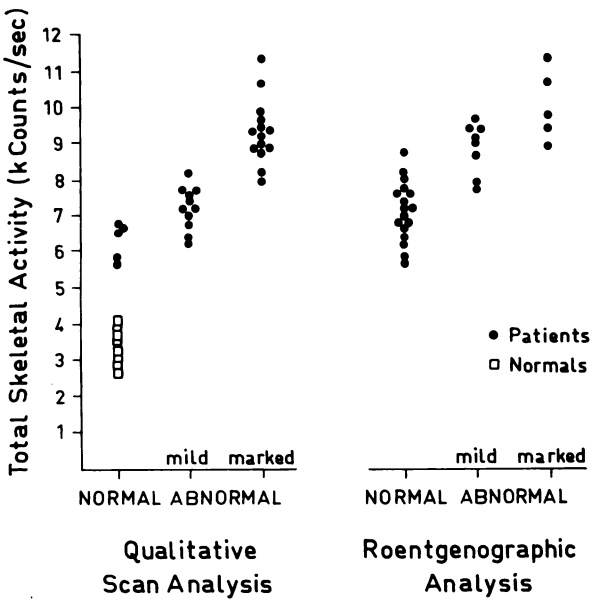

FIG. 9. Relationship between total skeletal activity, qualitative scan, and roentgenographic findings.

tigraphic analysis is superior to conventional radiographic methods.

Rosenthall, Kaye, and Wiegmann (*13,14*), who quantitated bone uptake, found a significant increase in the ratio between distal-femur bone and soft tissue in dialysed patients. In the present study, quantitative analysis showed increased skeletal uptake in all patients with histologic evidence of renal osteodystrophy. In contrast with the qualitative scan findings, a marked increase of skeletal activity, compared with normals, was registered in almost all skeletal regions of interest (Fig. 7). Furthermore, scintigraphy provided more information than bone microscopy, since the former indicates the extent and severity of osteodystrophy in the whole skeleton. The advantage of quantitative over qualitative scintigraphy and radiographic analysis is further illustrated in Fig. 9. In contrast with the x-ray findings, the total skeletal activity clearly separated patients from normals and appeared to be a reliable index of the degree of skeletal involvement. The scan findings therefore aided in the clinical management of the patients. Those with severe scintigraphic and histologic bone abnormalities and a total skeletal activity above 8.5 kC/sec were parathyroidectomized, and all of them clearly showed parathyroid hyperplasia. The remaining patients with less severe scintigraphic abnormalities were treated conservatively.

Because detailed skeletal information could not be obtained by our method without computerized analysis, some caution should be exercised in the interpretation of the results. However, our preliminary data do indicate that, in renal osteodystrophy, quantitative bone scintigraphy, when aided by computerized analysis, offers a potentially reliable technique for the early detection of skeletal involvement and the assessment of its severity. Since scintigraphy is a noninvasive technique and neither the radiation dose nor the cost exceeds that of a radiographic skeletal analysis, scintigraphy appears to be the method of choice for the routine detection and followup of renal osteodystrophy. Furthermore, the influence of background activity can be minimized by reducing circulating activity with hemodialysis. We cannot, however, completely exclude the possibility that some extra increase of skeletal uptake occurred due to less efficient tracer excretion under hemodialysis, thereby contributing to lower background levels in the scans.

Unfortunately, the scintigraphic findings do not permit differentiation between hyperparathyroidism and osteomalacia as the main cause of the bone abnormality, and abnormal scans should therefore be supplemented with bone microscopy. This is due to the nonspecificity of radiopharmaceutical bone uptake, which is a multifaceted process whose precise mechanism of action is still not fully understood (*21*). Evidence has been obtained that the binding of Tc-99m phosphate complexes occurs by ionic exchange at crystal surface areas (*22*), which are greatest in immature bone where osteoid is newly deposited. Increased local vascularity would facilitate this process (*23*). Furthermore, enzymatic receptor

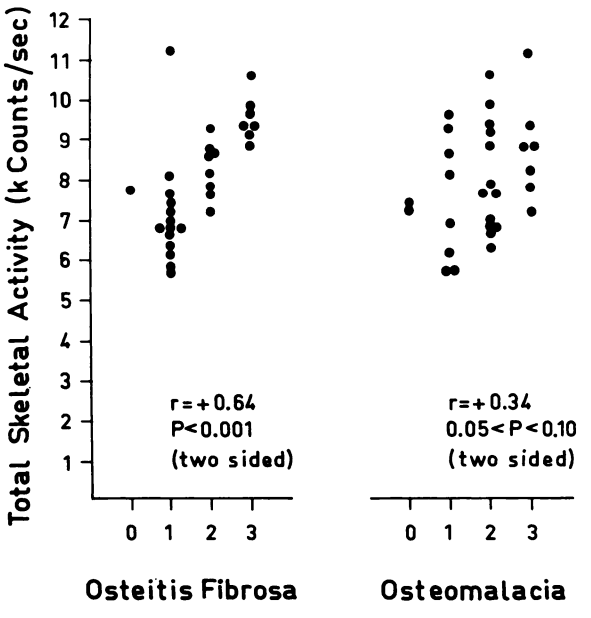

FIG. 10. Relationship between total skeletal activity and various grades of osteitis fibrosa and osteomalacia.

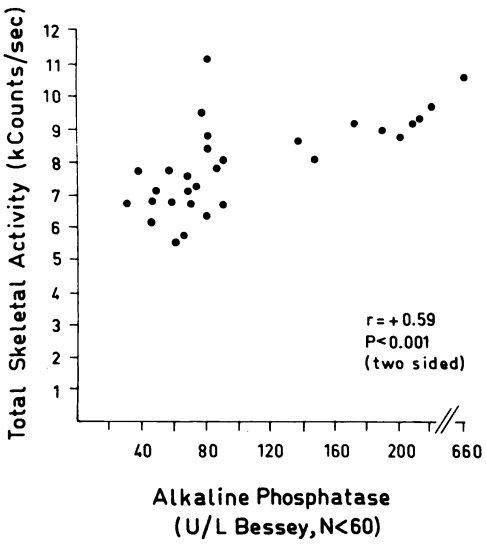

FIG. 11. Relationship between total skeletal activity and serum alkaline phosphatase.

binding has been demonstrated in vitro (*24*), and clinical and experimental evidence of radiopharmaceutical binding to immature collagen has been presented (*13–17*).

In renal osteodystrophy, Sy (*11*) related increased skeletal uptake mainly to the effects of hyperparathyroidism and found significant regression of skeletal activity after parathyroidectomy. Rosenthall, Kaye, and Wiegmann (*13–15*) attributed increased skeletal uptake to abnormal collagen metabolism, in particular to an increased amount of immature collagen, which they related mainly to osteomalacia. These authors found no relationship between bone uptake and hyperparathyroidism, and only a limited decrease of bone uptake was observed after parathyroidectomy (*13,14*).

In the present study, a relationship between skeletal activity and the histologic degree of osteomalacia was not evident (Fig. 10). However, autoradiographic studies have shown that the radionuclide does not bind directly to the osteoid tissue itself, but presumably to the immature collagenous matrix (*25,26*). These results therefore do not exclude osteomalacia as an important determinant in radionuclide bone uptake, as illustrated by several patients with high skeletal activity, marked osteomalacia, and minimal or no histologic signs of osteitis fibrosa (Table 1).

A significant correlation was found, however, between the total skeletal activity, serum alkaline phosphatase (Fig. 11), and osteitis fibrosa (Fig. 10); alkaline phosphatase also correlated significantly with the histologic degree of osteitis fibrosa. These results thus strongly suggest a relationship between skeletal uptake and hyperparathyroidism. Moreover, all parathyroidectomized patients with high skeletal activity had shown parathyroid hyperplasia at operation. In agreement with the findings of others (*13,14*), repeated quantitative analysis in one of our patients did not show a decrease of skeletal activity after parathyroidectomy. However, this decrease occurs eventually (*11,13,14*) and would not be expected soon after parathyroidectomy if radionuclide uptake in bone were dependent mainly on the amount of immature collagen. Thus, a direct parathyroid hormone effect is apparently not a predominant contributory factor in bone uptake of radiotracer, but our data and those of Sy (*11*) do suggest that hyperparathyroidism contributes to increased bone uptake.

In renal osteodystrophy, hyperparathyroidism and osteomalacia coexist. Hyperparathyroidism induces an increased rate of bone resorption and fibroblastic and osteoblastic activity, with a resulting increase in the formation and deposition of organic matrix. This ground substance will subsequently fail to mature and mineralize in the absence of biologically active vitamin D metabolites. Hence, the combination of hyperparathyroidism and vitamin D deficiency increases the rate of bone turnover and collagen metabolism, and results in an excess amount of immature collagen, high enzyme activity, and presumably increased surface areas for radionuclide bone binding.

It is suggested that such a combined state will facilitate radiotracer uptake and binding to bone and might explain the often exceptionally high skeletal uptake seen in renal osteodystrophy in this study.

ACKNOWLEDGMENTS

We are grateful to our volunteers and to the personnel of the Department of Nuclear Medicine for their cooperation. We also thank Mrs. Mary Mentink for preparing the manuscript.

This study was presented in part at the 1977 Annual Meeting of the Society of Nuclear Medicine, Chicago, IL, June 20–23.

REFERENCES

1. STANBURY SW: Bone disease in uremia. *Amer J Med* 44: 714–724, 1968

2. KAYE M, PRITCHARD JE, HALPENNY GW, et al: Bone disease in chronic renal failure with particular reference to osteosclerosis. *Medicine* (Baltimore) 39: 157–190, 1960

3. MAWER EB, BACKHOUSE J, TAYLOR CM, et al: Failure of formation of 1,25-dihydroxycholecalciferol in chronic renal insufficiency. *Lancet* 1: 626–628, 1973

4. BRICKER NS, SLATOPOLSKY E, REISS E, et al: Calcium, phosphorus and bone in renal disease and transplantation. *Arch Intern Med* 123: 543–553, 1969

5. KATZ AI, HAMPERS CL, MERRILL JP: Secondary hyperparathyroidism and renal osteodystrophy in chronic renal failure. Analysis of 195 patients, with observations on the effects of chronic dialysis, kidney transplantation and

subtotal parathyroidectomy. *Medicine* (Baltimore) 48: 333–374, 1969

6. EASTWOOD JB, BORDIER PHJ, DE WARDENER HE: Some biochemical, histological, radiological and clinical features of renal osteodystrophy. *Kidney Int* 4: 128–140, 1973

7. DUURSMA SA, VISSER WJ, DORHOUT MEES EJ, et al: Serum calcium, phosphate and alkaline phosphatase and morphometric bone examinations in 30 patients with renal insufficiency. *Calc Tiss Res* 16: 129–138, 1974

8. RITZ E, KREMPIEN B, MEHLS O, et al: Skeletal abnormalities in chronic renal insufficiency before and during maintenance hemodialysis. *Kidney Int* 4: 116–127, 1973

9. MEEMA HE, RABINOVICH S, MEEMA S, et al: Improved radiological diagnosis of azotemic osteodystrophy. *Radiology* 102: 1–10, 1972

10. TE VELDE J, BURKHARDT R, KLEIVERDA K, et al: Methylmethacrylate as an embedding medium in histopathology. *Histopathology* 1: 319–330, 1977

11. SY WM, MITTAL AK: Bone scan in chronic dialysis patients with evidence of secondary hyperparathyroidism and renal osteodystrophy. *Br J Radiol* 48: 878–884, 1975

12. ØLGAARD K, HEERFORDT J, MADSEN S: Scintigraphic skeletal changes in uremic patients on regular hemodialysis. *Nephron* 17: 325–334, 1976

13. ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate kinetics and imaging in metabolic bone disease. *J Nucl Med* 16: 33–39, 1975

14. WIEGMANN T, ROSENTHALL L, KAYE M: Technetium-99m-pyrophosphate bone scans in hyperparathyroidism. *J Nucl Med* 18: 231–235, 1977

15. ROSENTHALL L, KAYE M: Observations on the mechanism of Tc-99m-labeled phosphate complex uptake in metabolic bone disease. *Semin Nucl Med* 6: 59–67, 1976

16. WIEGMANN T, KIRSCH J, ROSENTHALL L, et al: The relationship between bone uptake of Tc-99m-pyrophosphate and hydroxyproline in blood and urine. *J Nucl Med* 17: 711–714, 1976

17. KAYE M, SILVERTON S, ROSENTHALL L: Technetium-99m-pyrophosphate: studies in vivo and in vitro. *J Nucl Med* 16: 40–45, 1975

18. RITZ E, CLORIUS JH: Scintigraphy in uremic bone disease. *Nephron* 17: 321–324, 1976

19. SY WM: Bone scan in primary hyperparathyroidism. *J Nucl Med* 15: 1089–1091, 1974

20. KRISHNAMURTHY GT, BRICKMAN AS, BLAHD WH: Technetium-99m-Sn-pyrophosphate pharmacokinetics and bone image changes in parathyroid disease. *J Nucl Med* 18: 236–242, 1977

21. LENTLE BC, RUSSELL AS, PERCY JS, et al: Bone scintiscanning updated. *Ann Intern Med* 84: 297–303, 1976

22. FRANCIS MD, RUSSELL RGG, FLEISCH H: Diphosphonates inhibit formation of calcium phosphate crystals in vitro and pathological calcification in vivo. *Science* 165: 1264–1266, 1969

23. GENANT HK, BAUTOVICH GJ, SINGH M, et al: Bone-seeking radionuclides: An in vivo study of factors affecting skeletal uptake. *Radiology* 113: 373–382, 1974

24. ZIMMER AM, ISITMAN AT, HOLMES RA: Enzymatic inhibition of diphosphonate: a proposed mechanism of tissue uptake. *J Nucl Med* 16: 352–356, 1975

25. JONES AG, FRANCIS MD, DAVIS MA: Bone scanning: Radionuclide reaction mechanisms. *Semin Nucl Med* 6: 3–18, 1976

26. VAN LANGEVELDE A, DRIESSEN OMJ, PAUWELS EKJ, et al: Aspects of ^{99m}Technetium binding from an Ethane-1-hydroxy-1, 1-diphosphonate-^{99m}Tc complex to bone. *Eur J Nucl Med* 2: 47–51, 1977