Technetium-99m-Pyrophosphate Bone Scans in Hyperparathyroidism

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Most patients with primary hyperparathyroidism have normal 5-hr bone-to-soft-tissue ratios for ^{99m}Tc-pyrophosphate. In contrast, all five patients with advanced secondary hyperparathyroidism in this study showed significant ($p < 0.001$) increases of bone uptake. In the early period after parathyroidectomy, there was no quantitative or qualitative change in uptake. A limited decrease of bone uptake was observed only after prolonged periods of observation. In itself, parathyroid activity seems to have little direct influence on bone uptake of ^{99m}Tc-pyrophosphate.

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External bone imaging with ^{99m}Tc-phosphate complexes has been successfully used to recognize metabolic bone disease (*1–4*). High uptake has been described in patients with osteomalacia, Paget's disease, renal osteodystrophy, and hyperparathyroidism (*1,2*). Some controversy exists as to the basis of this bone-imaging abnormality, and it has been ascribed directly to the effects of hyperparathyroidism (*3*). On the other hand, the bone uptake of ^{99m}Tc-phosphates may be related to collagen metabolism (*4–6*); such accumulation is more prominent in bone-forming than in resorbing surfaces (*7*).

This report describes our findings in the use of ^{99m}Tc-pyrophosphate (^{99m}Tc-PP_i) bone scans in 27 patients with parathyroid disorders, 12 of whom were studied before and after parathyroidectomy.

MATERIALS AND METHODS

The study group consisted of 20 patients with primary hyperparathyroidism (14 women, 6 men); five with advanced secondary hyperparathyroidism (three women, two men); one woman with a functioning parathyroid adenocarcinoma; and one woman with a renal transplant of 2 years' duration who underwent parathyroidectomy for treatment of progressive soft-tissue ulcerations and vascular calcification. In 24 cases the clinical diagnosis was confirmed, either by neck exploration (S), autopsy (A), or both. In three patients, diagnosis was made from clinical laboratory data (C) alone. Typical subperiosteal erosions (ER) were seen on x-rays in 14 patients. Five patients also had previous renal-stone disease (Table 1).

Bone scans were obtained using a scintillation camera interfaced with a data processor as previously described (*2*). Five hours after the injection of 15 mCi of ^{99m}Tc-PP_i, the distal epiphyseal region of the femur was counted. The counting was repeated over the thigh to measure soft-tissue activity. A bone-to-soft-tissue ratio (5-hr B/ST) was calculated for both extremities and the average taken for analysis. Scan findings obtained before the introduction of the quantitative 5-hr B/ST ratio are expressed qualitatively on a scale ranging from normal (N) to slightly increased (N+) (Table 1).

RESULTS

The clinical data and results of bone scanning are detailed in Table 1. The 5-hr B/ST of 4.48 ± 0.59 (mean ± s.e.m.) in primary hyperparathyroidism showed no significant difference from the mean in normal controls (3.56 ± 0.2) reported previously (*6*). Eleven ratios were entirely normal, five were borderline-high (Cases 10, 13, 17–19), and four were clearly elevated (Cases 11, 14–16). High up-

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TABLE 1. CLINICAL DATA AND 5-HR B/ST RATIOS IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM (PRIM. HYP.) AND SECONDARY HYPERPARATHYROIDISM (SEC. HYP.), PARATHYROID ADENOCARCINOMA, AND CUTANEOUS ULCERATIONS

Patient No.	Age	Sex	Diagnosis*	Diagnostic basis	5-hr B/ST ratios: last preop.	5-hr B/ST ratios: first postop.	PTH	Alk p'ase	Ca	X-ray†	Comment
1	73	F	—	C	3.5	—	317	15.0	13.2	—	Prim. hyp.
2	65	F	—	C	2.5	—	245	16.8	12.3	OP	Prim. hyp.
3	75	M	—	C	3.4	—	273	9.0	11.5	—	Prim. hyp.
4	87	F	HP	A	3.6	—	—	8.7	13.7	—	Prim. hyp.
5	64	M	AD	S, A	2.1	—	1,935	9.4	11.8	ER	Prim. hyp.
6	88	F	MA, HP	S	2.6	—	737	12.0	16.0	ER	Prim. hyp., colloid goiter
7	81	F	AD	S	2.1	—	355	14.3	16.8	OP	Prim. hyp., nod. goiter, papill. thyroid Ca
8	60	F	AD	S	3.6	—	357	7.7	12.5	ER	Prim. hyp., stone former
9	42	F	AD	S	3.5	—	209	10.9	11.9	—	Prim. hyp.
10	52	M	AD	S	4.7	—	—	16.9	12.7	—	Prim. hyp., renal tuberculosis, stone former
11	34	M	AD	S	—	6.6	302	9.4	11.6	ER	Prim. hyp., status post gastrectomy, ? MEA
12	73	M	AD	S	3.8	2.6	274	10.6	11.6	ER OP	Prim. hyp., stone former
13	43	F	AD	S	4.7	3.1	—	19.0	16.0	—	Prim. hyp., stone former, colloid goiter
14	52	F	HP	S	6.5	6.5	—	8.5	12.8	—	Prim. hyp., stone former
15	52	F	AD	S	7.7	8.0	—	12.6	11.9	—	Prim. hyp.
16	52	F	AD	S	8.5	6.9	—	8.5	13.7	ER	Prim. hyp.
17	55	F	AD	S	N	N	—	15.6	12.9	OP	Prim. hyp.
18	36	F	HP	S	N+	—	—	13.6	13.4	—	Prim. hyp., colloid goiter
19	58	F	HP	A	N+	—	—	160.0	11.5	OP	Prim. hyp., colloid goiter
20	64	F	AD	A	N-+	—	—	47.0	15.6	ER OP	Prim. hyp., colloid goiter
21	22	F	CA	S	12.0	10.3	196	20.1	18.0	OP ER	Parathyroid carcinoma
22	20	F	HP	S	N	4.45	—	11.0	10.7	OP ER	Post-transplant ulcerations, subcutaneous calcifications
23	53	F	HP	S	8.0	7.2	—	12.0	10.0	ER	D.M. Ren. failure since 1969, dialysis for 2 months, subcutan. calcification, ulcerations
24	52	F	HP	S	6.0	4.6	—	9.5	10.6	ER	Sec. hyp. Dialysis since 1964, colloid goiter
25	18	M	HP	S	9.6	—	—	30.0	11.0	ER	Sec. hyp. Dialysis since 1969
26	37	M	HP	S	10.0	10.1	—	—	—	ER	Sec. hyp. Dialysis since 1966
27	48	F	HP	S	10.4	10.6	—	—	—	ER	Sec. hyp. Dialysis since 1969

* Diagnosis: (AD) adenoma; (MA) microadenoma; (HP) hyperplasia.
† (ER) subperiosteal erosion; (OP) osteoporosis.

take was seen in the functioning parathyroid carcinoma (Case 21) and a borderline result was obtained in the post-transplant patient (Case 22). Typical scans are illustrated in Figs. 1 and 2.

All five patients with advanced secondary hyperparathyroidism had an elevated 5-hr B/ST. The mean ratio of 8.8 ± 1.0 was higher ($p < 0.001$) than those obtained in patients with primary parathyroid disease or in normal controls. In comparison, a mean ratio of 6.9 ± 1.0 was found in a previous study of 26 patients with renal failure (*6*). In six patients, the 5-hr B/ST showed little or no change within 1 month after parathyroidectomy. In another two patients, there was no qualitative change 1 and 3 months after surgery. Two or more months after parathyroidectomy, a limited decrease of the 5-hr B/ST was found in five cases (Fig. 3).

Parathyroid hormone (PTH) levels were abnormal with respect to concomitant serum calcium measurements in primary hyperparathyroidism ($n = 11$).

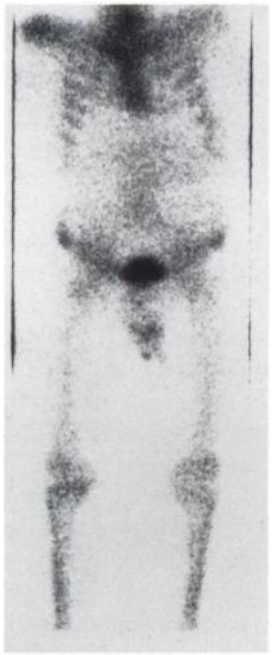

FIG. 1. Primary hyperparathyroidism (Case 12): 73-year-old man with B/ST ratio of 3.8 (within normal limits).

The relationship with the 5-hr B/ST was not significant. Furthermore, no significant correlation between the bone uptake and serum levels of alkaline phosphatase was found in either primary or secondary disease. Biochemical differences between primary and secondary hyperparathyroidism are summarized in Table 2. Table 3 shows the relationship between the 5-hr B/ST, the alkaline phosphatase, and other biochemical parameters in primary disease.

DISCUSSION

Abnormal bone scans with ^{99m}Tc-phosphate complexes have been reported in some cases of primary hyperparathyroidism. Sy (*1*) showed increased uptake in four such patients, but the results were not quantitated. Rosenthall and Kaye reported abnormal scans and 5-hr B/ST in a variety of metabolic bone diseases, including primary hyperparathyroidism and renal osteodystrophy (*2*). Increased uptake in patients on chronic hemodialysis were also reported by Sy and Mittal (*3*), who concluded that the abnormality was primarily due to the effects of hyperparathyroidism.

On the other hand, increased bone uptake of ^{99m}Tc-phosphates is seen in conditions not related to hyperparathyroidism: in the osteomalacia of vitamin-D deficiency and renal disease (*3*) and in cases of malnutrition, polychondritis, scleroderma, systemic lupus erythematosus, and thyroid disorders (*6*). Many of these conditions are associated with disorders of collagen metabolism (*8*). We have recently presented experimental (*5*) and clinical (*6*) observations supporting the view that ^{99m}Tc-phosphate uptake by bone is related to changes in collagen metabolism.

Delayed collagen maturation is found in both vitamin-D deficiency and renal failure. Thus the high bone uptake of ^{99m}Tc-phosphates in these conditions could be explained if the complex is bound by the

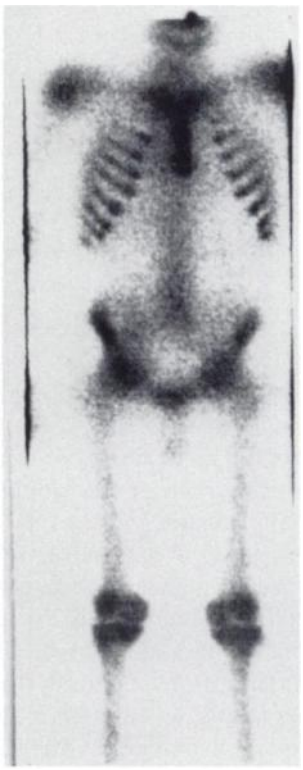

FIG. 2. Secondary hyperparathyroidism: 24-year-old man on hemodialysis for 2 years. B/ST ratio of 9. Note increased uptake of ^{99m}Tc-PP$_i$ about knees and costochondral junctions of ribs.

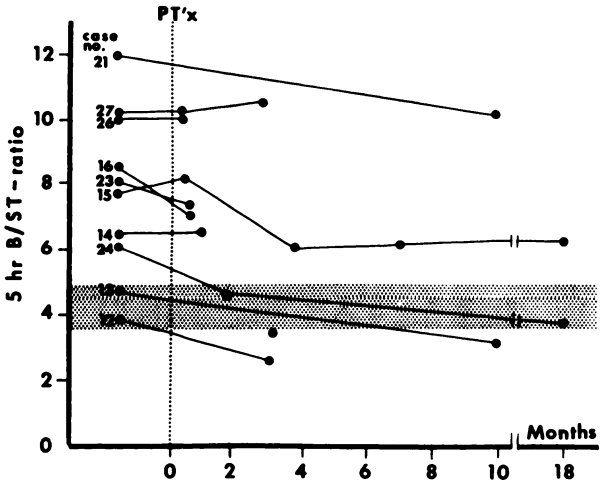

FIG. 3. Comparison of 5-hr B/ST ratios before and after parathyroidectomy. Shaded band represents mean normal values plus 2 s.d. Cases 17 and 22 are not included.

TABLE 2. COMPARISON OF BIOCHEMICAL PARAMETERS BETWEEN PRIMARY AND SECONDARY HYPERPARATHYROIDISM (mean ± s.e.m.)

Variable	Primary (n = 20)	Secondary (n = 5)	Difference p (t-test)
Ca^{2+} (mg%)	12.4 ± 0.5	9.7 ± 0.45	<0.025
PO_4^{3-} (mg%)	3.2 ± 0.5	6.2 ± 0.5	<0.005
Cl (meq/liter)	109.3 ± 3.9	99.2 ± 6.5	<0.001
Ca × PO_4 (product)	37.8 ± 3.0	20.5 ± 5.4	<0.01
5-hr B/ST	4.48 ± 0.6	8.8 ± 0.8	<0.005
Alk. p'ase	12.3 ± 1.5	14.4 ± 5.4	NS (>0.6)
Urine Ca (mg/24 hr)	403.3 ± 44.3	—	
Urine PO_4 (gm/24 hr)	0.63 ± 0.1	—	
PTH (pg/ml)	472.7 ± 152.74	—	

immature collagen fibrils (*4*). Apart from osteitis fibrosa, osteomalacia is a major component of renal osteodystrophy. Its presence would explain the uniformly high uptake in secondary hyperparathyroidism. Osteomalacia is also present in some cases of primary hyperparathyroidism and would explain the occasional abnormal bone scan in this disease (*9*).

Increased resorption and turnover of bone could explain the high ^{99m}Tc-phosphate uptake in hyperparathyroidism. If so, one would expect decreased uptake following parathyroidectomy, when patients are, in fact, temporarily hypoparathyroid. However, we did not observe this. In addition, most of the patients with primary hyperparathyroidism have normal bone scans. Bone involvement in osteitis fibrosa may be variable; the level of alkaline phosphatase is used as the indicator for this process. However, there was no significant difference in enzyme activity between primary and secondary hyperparathyroidism (Table 2). Furthermore, no significant correlation was found between enzyme activity and bone uptake or any other parameters of parathyroid disease (Table 3). In particular, we could not find a significant relationship between uptake and PTH levels. High rates of resorption or turnover thus do not appear to show any significant relation to ^{99m}Tc-phosphate uptake. Recent observations in animals by Garcia et al. (*7*) showed similar uptakes in normal and resorbing bone, and high uptake in forming bone only.

In the evaluation of metabolic bone disease, the B/ST ratio is currently the only quantitative method applicable to patients, short of bone biopsy or in vitro bone assays. Some caution must be exercised, however, in interpreting the B/ST ratios since standards are still incompletely defined. In particular, undue variation might arise from differences in the patient's size or habitus. Technetium-99m has a photon emission of 140 keV, with a half-value thickness of 4.5 cm in soft tissues. Less than 15% of counts will therefore be derived from a tissue depth beyond 12 cm. In our experience this degree of soft-tissue thickness is easily reached at the thigh in all patients. In thick individuals more counts could be contributed from greater tissue depth, thus lowering the B/ST ratio. Given equal doses of ^{99m}Tc, as was the case in our patients, however, one would expect a lower overall soft-tissue concentration in a thicker patient, and this would lead to a higher B/ST ratio. These effects seem to be compensatory. Other as yet undefined variables remain to be determined.

In summary, bone resorption, alkaline phosphatase, and parathyroid hormone activity show no significant relationship to ^{99m}Tc-PP_i uptake by bone. This is consistent with previous conclusions from this laboratory, and it appears that elevated uptake of ^{99m}Tc-phosphate complex in metabolic bone disease primarily reflects abnormal collagen metabolism. Such abnormality with an excess of immature collagen is characteristic of osteomalacia and is found in vitamin-D deficiency states, in renal failure, and in some patients with primary hyperparathyroidism.

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TABLE 3. RELATIONSHIP (CORRELATION COEFFICIENT r) AMONG THE 5-HR B/ST, ALKALINE PHOSPHATASE, AND BIOCHEMICAL PARAMETERS IN PRIMARY HYPERPARATHYROIDISM

	Urine (n = 14)		Serum (n = 20)			Serum (n = 11)
Variable	Ca	PO_4	PO_4	Cl	Alk. p'ase	PTH
5-hr B/ST	0.479	0.723†	0.508*	0.331	0.293	0.202
Alk. p'ase	−0.271	0.049	−0.015	0.788†	1.000	−0.335
CO_2	−0.506*	−0.609*				

* Significance of correlation coefficient $r < 0.05$.
† Significance of $r < 0.005$.

REFERENCES

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

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

3. 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

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

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

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

7. GARCIA DA, TOW DE, KAPUR KK, et al.: Relative accretion of ^{99m}Tc-polyphosphate by forming and resorbing bone systems in rats: Its significance in the pathologic basis of bone scanning. *J Nucl Med* 17: 93–97, 1976

8. LAITINEN O: Clinical applications of urinary hydroxyproline determination. *Acta Med Scand* 197: Suppl 577, 21–25, 1974

9. STANBURY SW: Osteomalacia. Clin Endocrinol Metabol. *Calcium metabolism and bone disease*, MacIntyre I, ed. London, W. B. Saunders, 1972, pp 239–266

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