The Use of Whole-Body Retention of Tc-99m Diphosphonate in the Diagnosis of Metabolic Bone Disease

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The limited role of bone scanning in the diagnosis of metabolic bone disease might be considerably improved by accurate quantification of skeletal uptake of the radiopharmaceutical. Using a standard shadow-shield whole-body monitor, we have measured whole-body retention (WBR) of Tc-99m HEDP up to 24 hr in 11 patients with renal osteodystrophy (mean WBR 88.6% at 24 hr); in ten patients with Paget's disease (mean 56.9%); in seven patients with osteomalacia (mean 40.7%); in five patients with primary hyperparathyroidism (mean 50.7%); in four patients with osteoporosis (mean 21.2%); and in 12 normals (mean 19.2%). The osteoporotic group could not be differentiated from the normal group, but the other groups were significantly different from the normal group at 24 hr ($p < 0.002$), and each individual result for the 24-hr WBR of Tc-99m HEDP in these groups lay outside our normal range. This test may, therefore, provide a sensitive means of detecting conditions with increased bone turnover. We obtained measurements of plasma activity of Tc-99m HEDP in these patients up to 24 hr, and 4-hr bone to soft-tissue ratios from bone-scan images, but little additional information resulted.

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There has been recent interest in the use of bone scanning in metabolic bone disease, and there emerge certain patterns of abnormality that may aid in the diagnosis of these disorders (*1–5*). Nevertheless, the scan appearances are often nonspecific and are of limited use in those cases that present the most difficulties in clinical practice. Because of the great affinity of bone for the phosphate and phosphonate tracers, quantification of their skeletal uptake may have a useful role in the detection of metabolic disorders. Simple quantification of the bone scan has been performed by measuring the bone to soft-tissue ratio (*3*), but this is a relatively crude method as the small area of bone selected may not reflect a small yet significant change in the total skeletal uptake of radiopharmaceutical. There is also the problem of standardizing the "soft tissue," since counts per unit area vary with vascularity and muscle bulk.

In an attempt to quantify total skeletal uptake of radiopharmaceuticals, we have measured the whole-body retention (WBR) of Tc-99m hydroxyethylidene diphosphonate (HEDP) sequentially over 24 hr in patients with Paget's disease and other metabolic bone disorders. We also measured bone to soft-tissue ratios from the bone scans in these patients,

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and this communication describes our findings (Table 2).

Each patient was given 50 μCi of Tc99m HEDP by i.v. injection and the whole-body count was measured at 5 min, and at 2, 4, 6, 8, and 24 hr, using a standard shadow-shield whole-body monitor (*6*). Whole-body retention of radiopharmaceutical was calculated, after appropriate background subtraction, by taking the 5-min count as 100% and correcting thereafter for radioactive decay. In addition, 10-ml blood samples (20-ml at 24 hr) were collected by venepuncture at the time of each whole-body count and plasma radioactivity was measured in an automatic gamma counter. Results were expressed as a percentage of injected activity per litre plasma, using a fraction of the injected material as a standard.

The above measurements were made in: (a) ten patients with Paget's disease (age range 47–78 yr, symptomatic, and with extensive radiologic and bone-scan evidence of disease); (b) four with osteoporosis (age range 51–72 yr, symptomatic, and with vertebral crush fractures); (c) five with primary hyperparathyroidism (age range 51–80 yr, three having parathyroid adenomas, subsequently removed, and two having hypercalcaemia with elevated parathormone levels); (d) seven with osteomalacia (age range 15–68 yr, all having bone and muscle pain and having had bone-biopsy evidence of osteomalacia); (e) 11 with renal osteodystrophy (age range 15–55 yr, creatinine clearance range 5–35 ml/min, all with biochemical and bone-biopsy evidence of renal osteodystrophy); and (f) 12 healthy volunteers with no evidence of bone disease (age range 19–31 yr).

Bone scintigrams were performed with Tc-99m HEDP in all patients, using a gamma camera with high-resolution, medium-sensitivity collimator. In addition, all images were recorded and stored in a minicomputer. The pictures were stored for later retrievel and processing on computer magnetic tape. Bone to soft-tissue ratios were measured by using the computer to define regions of interest around the L2 vertebra or, in the case of Paget's disease, an involved vertebra. An adjacent soft-tissue area clear of bone and renal activity was similarly defined (Fig. 1). The computer was used to derive mean counts per unit area for each region, and the simple ratio of these two results is defined as the bone to soft-tissue ratio.

In 35 patients bone to soft-tissue ratios were measured but in two patients (one with Paget's disease and one with primary hyperparathyroidism) the stored images were "lost." Bone to soft-tissue ratios were also measured in a control group of 80 women with breast carcinoma without clinical suspicion of bone metastases, and with bone scans considered completely normal.

Differences between groups for any parameter were tested using the Wilcoxon rank-sum test which —unlike the Student t-test—makes no assumptions about the distribution of values for the populations being compared.

RESULTS AND DISCUSSION

Table 1 shows the mean values for plasma Tc-99m activity at each sampling time for the various groups of patients. The renal osteodystrophy group was significantly higher than the normal and Paget's groups at all times, but with greatest significance at 24 hr ($p < 0.01$ and $p < 0.002$, respectively). The primary hyperparathyroidism group also differed significantly from the normal and Paget's groups up to 8 hr ($p < 0.01$), but there was no significant difference at 24 hr. The osteomalacia group was significantly different from the normal group at 24 hr only ($p < 0.02$). At 4 and 6 hr there was marginal significance ($p < 0.05$) in the difference between the osteomalacia and primary hyperparathyroidism groups. There was also marginal significance in the difference between the osteoporotic and normal groups at 24 hr ($p < 0.05$). Although these differences exist between the various group averages, there is marked overlap of individual plasma results

TABLE 1. MEAN VALUES FOR PLASMA ACTIVITY OF Tc-99m HEDP (% INJECTED ACTIVITY/LITRE PLASMA ± 1 s.d.)

	5 min	2 hr	4 hr	6 hr	8 hr	24 hr
Osteoporosis (N = 4)	20.0 ± 4.48	3.78 ± 0.84	1.99 ± 0.48	1.33 ± 0.32	0.96 ± 0.25	0.43 ± 0.12
Renal osteodystrophy (N = 11)	16.38 ± 3.98	4.01 ± 1.57	2.6 ± 1.11	1.83 ± 0.91	1.78 ± 0.78	0.64 ± 0.42
Paget's disease (N = 10)	16.35 ± 4.09	2.23 ± 0.93	1.2 ± 0.51	0.79 ± 0.27	0.58 ± 0.13	0.25 ± 0.05
Osteomalacia (N = 7)	20.44 ± 3.48	2.89 ± 0.84	1.54 ± 0.54	1.03 ± 0.42	0.94 ± 0.35	0.49 ± 0.16
Primary hyperparathyroidism (N = 7)	21.6 ± 5.56	5.21 ± 1.62	2.89 ± 1.13	1.86 ± 0.82	1.44 ± 0.67	0.52 ± 0.24
Normals (N = 10)	15.24 ± 2.68	2.78 ± 0.65	1.46 ± 0.4	0.98 ± 0.29	0.73 ± 0.23	0.29 ± 0.07

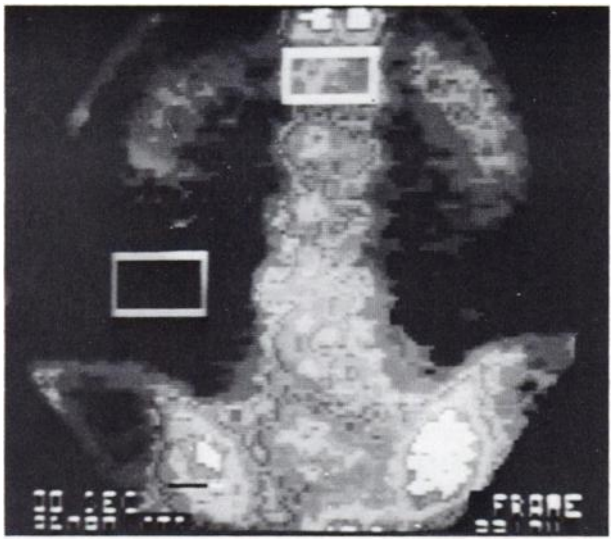

FIG. 1. Monochrome representation of color TV image of lumbo-sacral spine, showing regions defined for "bone" and "soft-tissue" activity measurements.

between all groups; accordingly—with the possible exception of the osteoporotic group—measurement of plasma activity does not provide diagnostic information beyond that derived from the measurement of 24-hr WBR of Tc-99m HEDP (discussed later).

The distribution of the bone to soft-tissue ratios is shown in Fig. 2. The primary hyperparathyroidism patients are indistinguishable from the normal group, as previous workers have found (*3*). The osteomalacic and renal osteodystrophy groups are both significantly different from the normal group ($p < 0.001$). However, there is an appreciable overlap between each of these groups and the normal range, rendering a normal result in an individual patient of no value. The bone to soft-tissue ratios for the Paget's group all lie above the normal range. In all these patients, however, the diagnosis was obvious from the bone-scan appearance [patients with Paget's disease usually have characteristic bone-scans (*7*)] and the area of bone for the bone to soft-tissue ratio was deliberately chosen as an affected area. Note further that our bone to soft-tissue ratios are of no value in those situations that often provide the greatest difficulty clinically—namely, primary hyperparathyroidism and osteoporosis.

The measurement of the bone to soft-tissue ratio is a crude means of quantifying skeletal uptake of a tracer, and although elevated values confirm increased skeletal uptake, normal values do not exclude this.

Figure 3 plots the mean whole-body retention against time for the different groups, up to the end of our study at 24 hr. The continuous curves were derived from a least-squares fit of the data to a double exponential function, using an iterative procedure. Intergroup differences are most striking at 24 hr (Fig. 3), but the osteoporosis curve lies close to the normal. The 24-hr value for whole-body retention of Tc-99m HEDP is a more convenient measurement than the 8-hr value. Also, the 24-hr value is not subject to error from failure to empty the bladder, which may cause artificially high values in the earlier hours of study. The technetium either is taken up by the skeleton or is almost totally excreted by the kidneys (*8*); in fact, almost 70% of an i.v. dose of Tc-99m HEDP is normally excreted through the urinary tract within 6 hr of injection (*9*). Therefore, by 24 hr the body burden of Tc-99m HEDP represents almost entirely skeletal uptake.

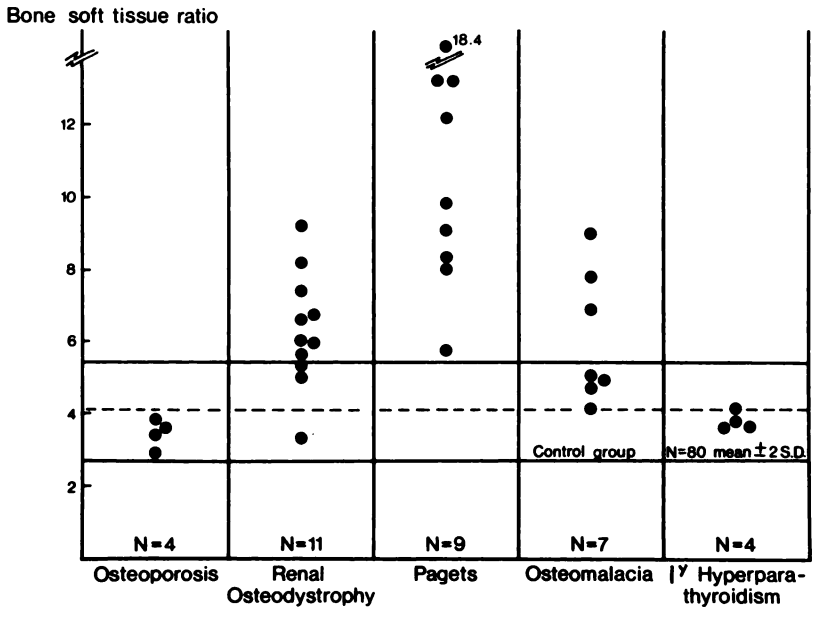

FIG. 2. Distribution of 4-hr bone/soft-tissue ratios.

TABLE 2. MEAN VALUES FOR 24-HR WBR OF Tc-99m HEDP (% INJECTED ACTIVITY ± 1 s.d.), AND 4-HR BONE TO SOFT-TISSUE RATIOS ± 1 s.d.

	No.	Mean 24-hr WBR ± 1 s.d.	Difference from normal group	Mean 4-hr bone to soft-tissue ratio ± 1 s.d.
Osteoporosis	4	21.2 ± 1.7	Not significant	3.43 ± 0.39
Renal osteodystrophy	11	88.6 ± 10.5	$p < 0.002$	6.29 ± 1.6
Paget's	10	56.9 ± 13.1	$p < 0.002$	10.87 ± 3.79
Osteomalacia	7	40.7 ± 8.0	$p < 0.002$	6.06 ± 1.85
Primary hyperparathyroidism	5	50.7 ± 14.6	$p < 0.002$	3.76 ± 0.26
Normals	12	19.2 ± 1.7	—	4.05 ± 0.69

The control group had a mean 24-hr whole-body Tc-99m HEDP of 19.18% ± 1.73 (1 s.d.), this being significantly different from the groups with Paget's disease, osteomalacia, primary hyperparathyroidism, and renal osteodystrophy (Table 2).

Figure 4 shows that in these groups all results for 24-hr WBR of Tc-99m HEDP in individual patients lay outside our normal range. The osteoporotic group could not be differentiated from the controls, but since there were only four patients in this group, it requires further study.

The 24-hr whole-body retention of Tc-99m HEDP in the renal osteodystrophy group (mean 88.6% ± 10.5) was much higher than in all other groups ($p < 0.002$). Although very high values for WBR of Tc-99m HEDP can be expected in any patient unable to excrete the tracer due to severe renal impairment (e.g., in acute renal failure, obstructive uropathy, or end-stage chronic renal failure), we find that in our patients with renal osteodystrophy the high retentions were largely due to increased skeletal uptake of the tracer. This was shown by elevated bone to soft-tissue ratios (Fig. 2) and the high-contrast scintigrams (Fig. 5). On the other hand, two patients with acute renal failure, who previously had normal renal function, had low bone to soft-tissue ratios (2.0 and 2.6 against the normal of 4.05 ± 0.69) and their bone images were of poor quality due to high soft-tissue background (Fig. 5). These patients with previously normal bones were anuric, and their WBR of Tc-99m HEDP (although not measured) must have been 100%. Although increased soft-tissue retention no doubt made some contribution to the high WBR in our patients with renal osteodystrophy, the increased skeletal uptake appears to be the dominant factor.

A high WBR of Tc-99m HEDP cannot differentiate between uraemic patients with significant renal osteodystrophy and those with other forms of severe renal impairment, but the bone scintigram clearly shows the high bone uptake and low soft-tissue background typical of renal osteodystrophy.

Whereas the 24-hr whole-body retention of Tc-99m HEDP in the Paget's group showed marginal significance in its difference from the primary hyperparathyroidism group ($p < 0.05$), neither group differed significantly from the group with osteomalacia. Moreover, the scatter of individual results in

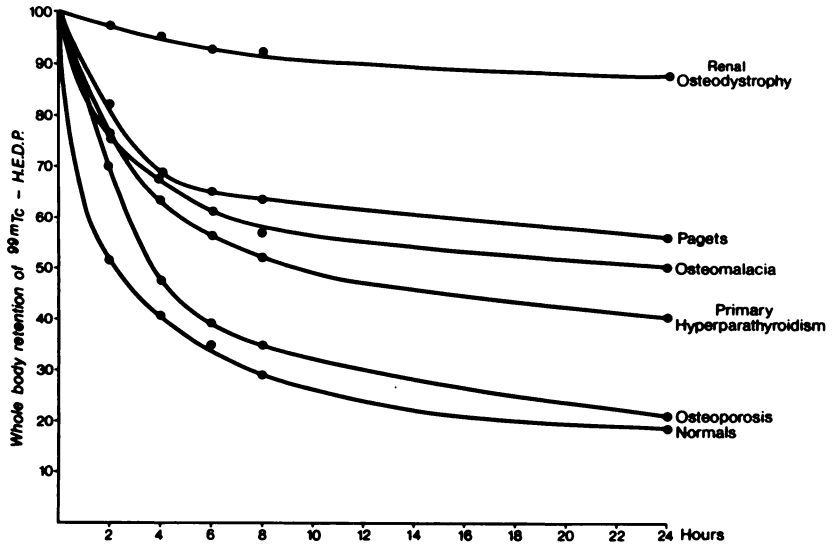

FIG. 3. Mean whole-body retentions of Tc-99m HEDP up to 24 hr.

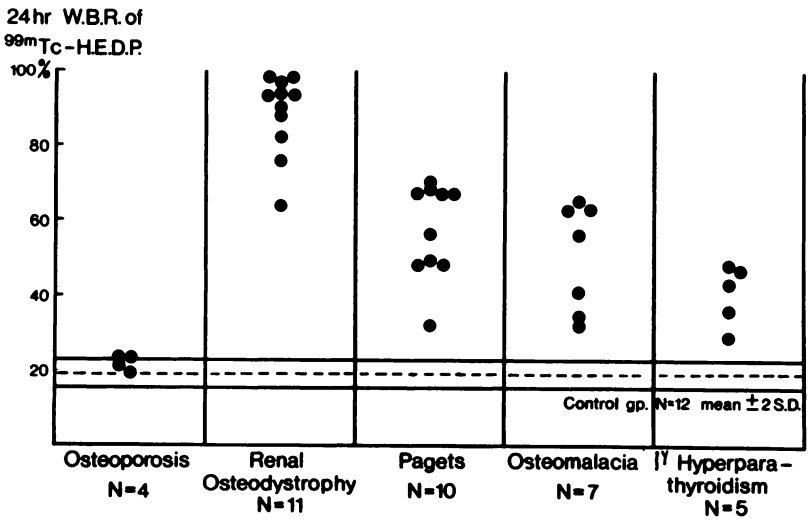

FIG. 4. Distribution of individual 24-hr whole-body retentions of Tc-99m HEDP.

these groups was such that no diagnostic value could be attached to them. However, they show clear demarcation between normal and abnormal, and when the diagnosis is already established or strongly suspected (as is often the case), the knowledge that the result is either higher or lower than the group mean may provide additional information as to the severity of the disease.

Elevated values for 24-hr whole-body retention of Tc-99m HEDP have also been found in two patients in whom primary hyperparathyroidism was suspected, but definite confirmation of diagnosis has not yet been obtained. In each case transileal bone biopsies were abnormal, showing increased bone resorption in keeping with hyperparathyroidism. Therefore, in every case where we have found an elevated value for 24-hr whole-body retention of Tc-99m HEDP this could be correlated with conditions known to cause increased bone turnover (Table 2) or else there was histological evidence of increased bone turnover. The measurement of whole-body Tc-99m HEDP may therefore provide a sensitive means of detecting conditions with rapid bone turnover. It can be used as a screening test for various metabolic bone disorders, and in particular for primary hyperparathyroidism, which at times can present a considerable diagnostic problem (*10*). Although patients with osteoporosis seem to have results in the normal range, this test may help to differentiate those cases where rapid bone loss is due to an underlying condition such as thyrotoxicosis. Also, it may be that plasma activity of Tc-99m HEDP at 24 hr may be of some help in diagnosing osteoporosis, since a marginally significant difference ($p < 0.05$) has been found between this group and the normals, and an elevated plasma result would tend to support the diagnosis of osteoporosis.

As indicated in the discussion on renal osteodystrophy, a knowledge of renal status is essential when one is interpreting the WBR of Tc-99m HEDP. All patients in the present study, except those with renal osteodystrophy, had normal renal function.

The use of a whole-body monitor to calculate the 24-hr whole-body retention of Tc-99m HEDP provides an overall measurement of skeletal retention of radiopharmaceutical as contrasted with measurement of the bone to soft-tissue ratio, which uses only a small and perhaps nonrepresentative area of bone. Measurement of whole-body retention is a simple noninvasive test that provides accurate and reproducible results (*11*). It can be performed as an outpatient investigation. Very small amounts of radioactivity are used and this test can therefore be repeated safely. This may be of use when one is following the progression of disease or monitoring the effect of treatment.

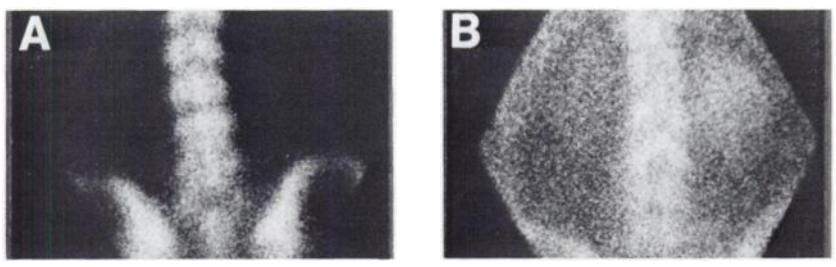

FIG. 5. Bone scintiphotos of lumbosacral spine, posterior view. (A) Chronic renal failure. Note high skeletal uptake of tracer. Kidney images are not seen. (B) Acute renal failure. Poor-quality image due to high tissue background.

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REFERENCES

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

2. 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

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

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

5. 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

6. WARNER GT, OLIVER R: A whole-body counter for clinical measurements utilizing the "shadow-shield" technique. *Phys Med Biol* 11: 83, 1966

7. SERAFINI AN: Paget's disease of bone. *Sem Nucl Med* 6: 47–58, 1976

8. MCDOUGALL IR, CITRIN DL: Bone scanning: The current position. *Scot Med J* 20: 149–151, 1975

9. CITRIN DL, BESSENT RG, MCGINLAY E, et al: Dynamic studies with ^{99m}Tc H.E.D.P. in normal subjects and in patients with bone tumours. *J Nucl Med* 16: 886–890, 1975

10. DRAGO JR, ROHNER TJ JR, SANFORD EJ, et al: Diagnosis of hyperparathyroidism. *Urology* 7: 4–6, 1976

11. ANDREWS GA, GIBBS WD, MORRIS AC JR, et al: Whole-body counting. *Sem Nucl Med* 3: 367–388, 1973