24-Hour/4-Hour Ratio of Technetium-99m Methylene Diphosphonate Uptake in Patients with Bone Metastases and Degenerative Bone Changes

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The uptake of [^{99m}Tc]MDP in metastatic lesions of the vertebrae was compared with the uptake in normal vertebrae. The ratio of these lesion-to-nonlesion uptakes at 4 and 24 hr was called the 24-hr/4-hr ratio (TF ratio). A similar ratio was measured for lesions in the spine due to degenerative bone disease. Lesions in vertebrae with degenerative bone disease and treated metastases had a significantly lower TF ratio than lesions in vertebrae with untreated bone metastases. These findings suggest that the TF ratio might be a reliable method for separating metastatic lesions from degenerative changes in the vertebral column, and could be especially useful in cancer patients whose bone scans demonstrate a single lesion in the spine.

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Skeletal scintigraphy is usually performed 2 to 4 hr following i.v. injection of technetium-99m- (^{99m}Tc) labeled organic phosphates. It has been shown that the uptake of organic phosphates in metastatic bone lesions, in contrast to normal bone, continues after the 2- to 4-hr interval (*1*). This finding is supported by the clinical observation that some metastatic bone lesions not clearly distinguished on a 2- to 4-hr study become evident at 24 hr (*2*). This finding, however, is not unique to metastatic bone disease.

In a group of patients having bone scintigraphy we have developed a lesion-to-nonlesion ratio for technetium-99m methylene diphosphonate ([^{99m}Tc]MDP) uptake as measured at 24 and 4 hr (TF ratio). We report our findings in patients with both treated and untreated bone metastases and in patients with and without primary cancer having bone changes due to degenerative bone disease.

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MATERIALS AND METHODS

Our study group included 89 consecutive patients, 26 males and 63 females aged 33–78 (mean 71.6), investigated at our institution during a 30-mo period. Patients had an extensive workup to clearly establish a definite diagnosis of metastatic or degenerative bone disease identified on scintigraphy. This included a general radiographic bone survey and spot radiographs within 2 days of abnormalities that were identified by scintigraphy. Patients were followed for at least 12 mo and when other diagnostic tests were inadequate, bone biopsy was performed. Diagnosis was established for each vertebra included in the study.

Patients were injected i.v. with 15–20 mCi (240–555 MBq) of [^{99m}Tc]MDP and were investigated 4 and 24 hr after the injection. A large-field-of-view digital camera* was used, collecting 600,000 counts for the 4-hr study and 150,000 counts for the 24-hr study. Only lesions of the spinal column were analyzed. Data were displayed using a 256 × 256 matrix and a region of interest (ROI) was taken over the bone lesion in the spine with the number of counts recorded. The same ROI was placed over a normal vertebra in the same region (lum-

TABLE 1
Clinical Findings and L/N Ratios in 89 Patients with Bone Lesions

Group	Diagnosis		No. patients	No. sites	L/N* 4 hr	L/N* 24 hr
Group A	Untreated metastases		15	31 (3 solitary lesions)	2.3 ± 1.18	3.4 ± 2.04
	Breast	8				
	Prostate	2				
	Endometrium	1				
	Lung	1				
	Rhabdomyosarcoma	1				
	Unknown Origin	1				
	Hypernephroma	1				
Group B	Treated metastases		27	80 (2 solitary lesions)	1.9 ± 0.99	2.2 ± 1.35
	Breast	18				
	Prostate	6				
	Lung	2				
	Esophagus	1				
Group C	Degenerative joint disease in oncologic patients		33	52 (15 solitary lesions)	1.3 ± 0.21	1.4 ± 0.24
Group D	Degenerative joint disease in nononcologic patients		14	19 (7 solitary lesions)	1.3 ± 0.26	1.4 ± 0.27

* L/N = Lesion-to-nonlesion ratio.

bar, thoracic, or cervical) and the lesion-to-nonlesion ratio (L/N) was calculated for the 4-hr study. A similar technique was used to determine the L/N ratio for the same lesion at 24 hr. The same vertebral bodies and ROIs were used on the 4- and 24-hr measurements. Scintigraphic evaluation of all patients was done without knowledge of clinical, radiographic, or histologic findings.

The 24-hr/4-hr ratio (TF ratio) was calculated by dividing the L/N ratio at 24 hr by the L/N ratio at 4 hr.

$$\text{TF ratio} = \frac{\text{L/N 24 hr}}{\text{L/N 4 hr}}$$

RESULTS

Table 1 lists four groups of patients included in the study. In Group A were 15 patients with untreated cancer, in whom bone metastases were first identified at the time of the study. Group B included 27 patients with known bone metastases, who had hormonal or chemical treatment that was started at least 6 mo before scintigraphy. Group C included 33 patients with known primary cancer, with no evidence of metastases in the bones or elsewhere in the body but with vertebral lesions due to degenerative bone disease, which included osteoarthritis and spondylosis. Group D included 14 patients investigated for suspicion of a loosening hip or knee prosthesis, with no evidence to suggest cancer. The L/N ratios at 4 and 24 hr of the four groups are shown in Table 1 and Fig. 1.

The average TF ratio was calculated for the vertebrae with metastatic lesions (Group A), treated metastatic lesions (Group B), and degenerative bone disease in patients with (Group C) and without (Group D) primary cancer. The differences between the mean TF ratio of vertebrae with degenerative bone disease and treated bone metastases were compared with that of vertebrae with untreated bone metastases, using the Student's t-test. The results are expressed as mean ± s.d. in Table 2. Vertebrae with degenerative changes in patients with (Group C, TF = 1.0 ± 0.06) and without (Group D, TF = 1.0 ± 0.04) primary cancer, and vertebrae with metastases in patients who had chemical or hormonal treatment (Group B, TF = 1.1 ± 0.13), all had significantly lower TF ratios than vertebrae with untreated metastatic lesions (Group A, TF = 1.5 ± 0.4). Based on ROC analysis, a TF ratio of 1.12 was selected for the calculation of sensitivity, specificity, accuracy, and predictive value. The sensitivity of the test is 0.77, the

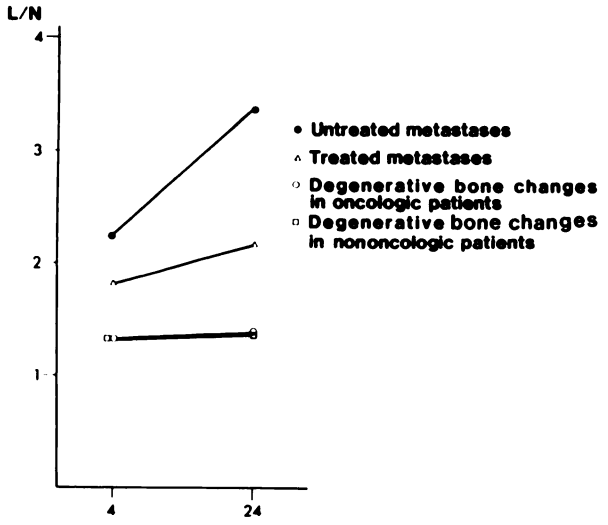

FIGURE 1
Lesion-to-nonlesion ratios at 4 and 24 hr in patients with metastases and degenerative changes

TABLE 3
Utility of 1.12 TF Ratio

Item	Total no. of sites* (102)	
	With metastases 31	With degenerative disease 71
TP†	24	
Sensitivity	0.77	
TN‡	—	59
Specificity	0.83	
Accuracy	0.81	
Predictive value	0.66	

* Patients with treated metastases not included.
† True-positive; number of sites with metastases with TF > 1.12.
‡ True-negative; number of sites with degenerative disease with TF < 1.12.

specificity 0.83, the accuracy 0.81, and the predictive value 0.66 (Table 3).

DISCUSSION

Normal and metastatic bone differ in histological structure. Normal bone is mainly lamellar while metastatic bone is formed in large part from new woven bone (*3–5*). The woven bone has a much larger surface area than the more stable lamellar bone, and is lined with metabolically active osteoblasts. In addition, the crystalline structures in woven bone are smaller and have a larger surface area available for absorption of bone-seeking radiopharmaceuticals.

Uptake of bone-seeking radiopharmaceuticals continues in the new woven bone longer than in the lamellar bone (*1,2*). When uptake was measured in bone metastases using both [^{99m}Tc]MDP and technetium-99m hydroxyethylidene diphosphonate, it continued to rise between 4 and 24 hr, while uptake in normal bone fell progressively during this period (*6*). This constitutes a major difference in the metabolic handling of the radiopharmaceuticals between the normal lamellar bone and the metastatic woven bone, which we sought to exploit in this study.

TABLE 2
Comparison of TF Ratio From Vertebrae with Degenerative Changes and Treated Metastases, with TF Ratio From Patients with Untreated Metastases

Group	TF ratio (mean ± s.d.)	Significance, as compared with Group A
A	1.5 ± 0.4	—
B	1.1 ± 0.13	$p < 0.001$
C	1.0 ± 0.06	$p < 0.001$
D	1.0 ± 0.04	$p < 0.001$

The present results show a rise in the lesion-to-nonlesion ratio of metastatic bone lesions significantly different from benign degenerative bone lesions. Degenerative bone changes have increased amounts of lamellar bone that do not show significantly increased ratios of radioactivity uptake between 4 and 24 hr.

The TF ratio has the potential of being a straightforward scintigraphic method for separating metastatic lesions from degenerative lesions in the vertebrae, where subjective criteria based on visual evaluation of images without x-ray follow-up or histologic examination are not useful. This may be especially useful when a single lesion appears in the bone study. In our material, 27 sites of abnormal uptake appeared as solitary lesions. Five were metastatic and 22 degenerative (Table 1).

It is somewhat puzzling that all patients with bone metastases receiving chemotherapy or hormone therapy showed a decrease in the ratio as compared with patients with metastases who received no treatment. This was noted irrespective of the type of treatment and treatment response, i.e., full response, partial response, or no response. Since all the patients in our study received treatment for at least 6 mo, we are currently studying patients at shorter time intervals to evaluate the early TF ratio response to therapy.

FOOTNOTE

* Apex 415, Elscint, Israel.

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