Altered Biodistribution of Radiopharmaceuticals Used in Bone Scintigraphy
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Introduction
Bone scintigraphy has remained a mainstay of clinical nuclear medicine for more than 4 decades and is typically performed to assess 1 or more focal abnormalities of bone including metastases, osteomyelitis, and a host of other degenerative, inflammatory, and orthopedic disorders. Generally, 99mTc-labeled phosphonates are employed for routine planar or tomographic single-photon imaging of the skeleton. The commonly used radiopharmaceutical 99mTc-methylene diphosphonate (MDP) represents this group in our discussion. Although 18F-NaF positron emission tomographic imaging is being performed more frequently to assess bony abnormalities, routine clinical experience with this agent, especially with respect to artifacts, is much more limited than that of MDP.

Delayed phase bone scintigraphy is typically performed at 2-5 hours after intravenous injection of a radiopharmaceutical. As a general rule, at this point, skeletal uptake is relatively uniform and soft tissue activity is negligible, with the exception of a variable amount of radiopharmaceutical retained in the renal parenchyma, collecting system, and urinary bladder. Unanticipated deviations from this normal distribution may occur on occasion and are the subject of this review. In some cases, a global variation in bone uptake is encountered, whereas in others, the alteration in distribution of bone-seeking radiopharmaceuticals is regional. Abnormalities may affect bone, generalized soft tissues, and visceral organs.

By categorizing these unanticipated abnormalities and their etiology, the reader will more readily appreciate similar findings and their significance when subsequently encountered. In some instances, these anomalies may reflect serious underlying diseases, whereas in others, they are merely curiosities related to benign underlying medical conditions. In yet other cases, unanticipated biodistribution may be due to errors and blunders, colloquially termed “artifacts” in the medical imaging literature. This article focuses on identifying and understanding the clinical importance of these deviations from expected biodistribution. Abnormalities in radiopharmaceutical distribution related to focal bone pathology, the usual and intended purpose of bone scintigraphy, have not been included in this review nor are primary bone disorders such as Paget disease, fibrous dysplasia, or other similar entities that lead to regional abnormalities in MDP uptake. Abnormalities of urinary tract structure, a separate and specialized topic in its own right, is beyond the scope of this review.

Normal Distribution of MDP
In current practice, approximately 740-1110 MBq (20-30 mCi) of 99mTc-MDP is injected intravenously for the...
The purpose of bone scintigraphy is to visualize the distribution of a radiopharmaceutical in the body. Typically, imaging is performed 2-5 hours after administration to allow for clearance of the radiopharmaceutical from the intravascular compartment and from the extracellular nonosseous soft tissues. Plasma clearance half-time of MDP in patients with normal renal function is of the order of 3-4 minutes.

A fundamental aspect of understanding the biodistribution of MDP is that it is primarily cleared by 2 pathways: renal and osseous. Administered MDP is partitioned according to the relative magnitude of these clearances. Therefore, the degree of osseous uptake depends not only on factors relating to bone metabolism but also on renal clearance of MDP, the latter being closely approximated by the glomerular filtration rate. Assuming normal clearance values of 40 mL/min for bone and 100 mL/min for renal, whole-body retention of MDP at 24 hours is estimated to be 30%.

Alteration in Osseous Uptake

Diffusely Increased Osseous Uptake

Concept of the “Superscan”

Causes of diffusely increased skeletal uptake are not infrequently encountered in the routine clinic. The usual etiologies of diffusely increased uptake are metastatic and metabolic disorders. Although focal increases in uptake are readily apparent on bone scintigraphy, paradoxically, it can be quite challenging to appreciate more widespread and diffuse abnormalities. Bone scintigraphic images are typically windowed on a relative basis and individualized for each study, such that the average intensity of the skeleton is portrayed in the middle to upper range of gray scale. Therefore, a diffuse increase in uptake may be impossible to appreciate by inspection of the bones alone because the gray scale would have been adjusted upward as well. Causes of widespread increased boney uptake simulating a normal appearance have been termed “superscans” to reflect the elevated bone to soft tissue background ratio, which renders the skeleton clearly defined. Superscans have also been reported with 18F-NaF imaging.

In a superscan, elevated skeletal activity is caused by increased osseous clearance of MDP and not by reduced renal clearance, though not infrequently, these abnormalities may coexist. Half of the total injected dosage of radiotracer is normally cleared by the kidneys, while in cases of elevated bone uptake, up to 86% of the radiotracer is retained in the skeleton. Careful scrutiny of images, with particular emphasis placed on intensity of soft tissue and urinary uptake, generally suggests aberrant uptake. Renal and bladder activity should be scrupulously assessed in all patients undergoing bone scintigraphy. Additionally, in some categories of superscan, osseous uptake may be somewhat asymmetric and inhomogenous and may differentially affect the axial and appendicular skeleton.

Superscan Due to Metabolic Disease

Superscans may result from metabolic conditions that alter the global pattern of skeletal remodeling. The pattern of uptake is unrelated to the bone marrow distribution; therefore, osseous involvement tends to be relatively diffuse and homogeneous, more accurately mimicking the normal distribution of activity within the axial and appendicular skeleton. Idiosyncratic features associated with metabolic superscans include prominent sternal activity (so-called tie sternum), beading of the costochondral junctions, and prominent uptake in the calvaria and mandible.

Endocrine disorders are an important cause of metabolic superscan, with hyperparathyroidism (primary, secondary, or tertiary) being most frequently implicated. Owing to the
important role played by the kidneys in the regulation of serum levels of calcium, phosphate, and 1,25-dihydroxycholecalciferol, renal disorders can lead to abnormalities in bone metabolism. Renal osteodystrophy—a blanket term that includes secondary and tertiary hyperparathyroidism, osteomalacia, mixed uremic osteodystrophy, and adynamic bone disease26-29—occurs in patients with end-stage renal disease and is a common cause of abnormal bony remodeling. Additional renal pathology associated with superscan includes distal renal tubular acidosis30 and Fanconi syndrome.31 Other reported metabolic causes of superscan include hyperthyroidism,32,33 acromegaly,34 hypervitaminosis A35 and D,36 and fluorosis.12

Regional Increase in Skeletal Uptake

Hypertrophic Osteoarthropathy

In hypertrophic osteoarthropathy (HO), formally known as hypertrophic pulmonary osteoarthropathy, increase in MDP uptake is limited to the distal upper and lower extremities with a predominantly peripheral (“tram track”) periosteal appearance.52 Similar findings have been noted in 18F-NaF imaging.53 HO may be associated with physical manifestations such as clubbing of the fingers.54-56 Several clinical disorders, especially those involving the thorax, have been linked to this condition, which are postulated to lead to common stimulatory pathways; implicated mediators include vascular endothelial growth factor, platelet-derived growth factor, platelets, and increased prostaglandin E2 levels.54

Complex Regional Pain Syndrome

Complex regional pain syndrome, previously termed reflex sympathetic dystrophy, results in increased blood flow to a single involved extremity, which manifests as increased bone uptake of MDP on the delayed images.57-70 There is often a history of antecedent injury or neurologic insult followed by persistent pain and skin changes. On bone scintigraphy, a periarticular accentuation of activity is typically noted58 (Fig. 3). With time, the activity seen on bone scan can normalize.

Radiation Osteitis

The progression of radiotracer uptake following irradiation was studied by King et al71 in rabbits. It was found that uptake in irradiated bone increased for the first 3 months after treatment and then decreased, eventually reaching levels lower than the baseline levels at 6 months after treatment. In patients treated with high doses (50 Gy or more), the uptake can be intense and uniform,72 with abrupt changes seen at the edge of radiation ports. The uptake generally normalizes and then decreases and, in the chronic phase, bones can appear heterogeneous owing to a combination of sclerosis and ongoing remodeling interspersed with areas of necrosis and fibrous changes appearing as cold defects.

Arterial Injection of Radiotracer

On occasion, the radiopharmaceutical is inadvertently injected into an artery rather than a peripheral vein. In these cases, the downstream tissues show a concentrated bolus of MDP leading to elevated accumulation of activity based on this “first pass” of activity,73-76 which results in a “glove” or “hot-hand” appearance (Fig. 3). The remainder of the concentrated bolus reaches the right atrium and is diluted by the systemic return, thereafter distributing throughout the body in a typical fashion.
Diffusely Reduced Osseous Uptake

Identifying globally reduced uptake on a bone scan can be challenging because of the role of windowing in compensating for depressed osseous uptake. As in the case of superscans, comparing osseous activity to that present in soft tissues and the genitourinary tract is essential.

Although soft tissue activity is negligible during delayed phase imaging in normal instances, in cases of diffusely reduced osseous uptake, there is persistent soft tissue activity noted. Trivial causes of poor bone-to-soft-tissue ratio distribution include interstitial injections and radiopharmaceutical errors.

Heavy Metal Toxicity

One of the few causes of a diffuse decrease in skeletal uptake of radiotracer is aluminum toxicity, which is reputed to block bone mineralization through deposition at the calcification fronts, resulting in osteomalacia. This pathology is most commonly encountered in patients with end-stage renal disease and has declined in incidence through the use of improved dialysis systems and the avoidance of aluminum-containing antacids. A decade ago, the incidence of elevated serum aluminum levels in dialysis patients was found to be approximately 1%.

Like aluminum, iron overload has also been found to alter the biodistribution of MDP, with a resulting global decrease in bony uptake seen in patients and animal models. It is speculated that the presence of iron facilitates dissociation of technetium from the carrier ligand (MDP) with a commensurate change in biodistribution. Iron overload is most commonly encountered in patients with hereditary hemochromatosis and individuals receiving frequent blood transfusions.

Osteoporosis and Bisphosphonate Therapy

Reports of osteoporosis being associated with slightly decreased skeletal radiotracer uptake have appeared; however, this finding is usually subtle. Etidronate, a nonnitrogenous bisphosphonate used to treat low bone mass, has also been associated with osteomalacia. Patients taking this medication while undergoing bone scintigraphy have been noted to have diffusely decreased MDP skeletal uptake. At present, the use of etidronate has been superseded by other agents in the same class. The association of decreased MDP uptake with other bisphosphonates has not been demonstrated.

Regionally Decreased Radiotracer Uptake

Previously Irradiated Bone

Irradiated bone demonstrates decreased radiotracer uptake in the chronic phase, occasionally with a mottled appearance. Typically, there is a sharp transition between treated and untreated bone, determined by the radiation port.

Electrical Injury and Frostbite

Bone scintigraphy has been used in the evaluation of nonviable bone following electrical injury. In these cases, devascularized bone appears cold on scintigraphy. It has been shown that results of bone scintigraphy correlate well with the required level of amputation. Bone scintigraphy can also be used to assess for soft tissue and bone viability following frostbite injury (Fig. 4). Areas of absent uptake on bone scintigraphy correspond to nonviable tissue.

Alteration in Soft Tissue Uptake

It is hypothesized that MDP and its analogues bind to bone by adsorption to the surface of the hydroxyapatite crystal (“chemabsorption”), with areas of new bone formation exhibiting elevated uptake owing to increased blood flow and expanded surface area. Multiple etiologies of increased soft tissue uptake of MDP have also been described, which appear related to focal calcium uptake within the soft tissues; apparently, the radiopharmaceutical also binds onto the surface of the
deposited calcium salts by chemisorption. Underlying processes leading to calcium and MDP deposition within the cellular compartment include metastatic calcification, dystrophic calcification, and metabolic deposition. We have illustrated and reviewed many of these processes in an earlier contribution to this journal. Another category of apparent soft tissue MDP activity is that which is not due to actual deposition of radiopharmaceutical within the tissues but rather derives due to a diminished or delayed clearance of activity from regional collections or compartments where the radiopharmaceutical is relatively sequestered, appearing prominent in comparison with the remainder of the soft tissues.

Finally, a number of blunders or other technical problems can also lead to apparent alterations in distribution of bone radiopharmaceuticals, colloquially termed “artifactual” in the medical imaging literature.

### Metastatic Calcification

Metastatic calcification refers to calcium (Ca\(^{2+}\)) deposition in normal tissues subjected to hypercalcemia and is typically induced by marked and rapid rise in serum Ca\(^{2+}\) and phosphate (PO\(_4\)\(^{3-}\)). Calcification (and MDP uptake) is said to most frequently affect tissues that tend to an alkaline pH, including lung, stomach, and kidney. In our experience, lung uptake, without concomitant gastric activity, is not infrequently encountered (Fig. 5). Systemic arteries and pulmonary veins, which also secrete acid and have an internal alkaline compartment, are also prone to metastatic calcification. Femoral artery uptake of MDP, especially in older patients, has frequently been noted; dystrophic changes in the vessels may also participate in this process. In some instances, MDP uptake in metastatic calcification has been shown to favor large...
muscle groups of the shoulders and thighs, possibly related to chronic subclinical trauma. Calciphylaxis, often associated with tertiary hyperparathyroidism, results in systemic medial calcification of the arteries, most commonly leading to ischemia of dermis and subcutaneous fat, with typically intense uptake noted on bone scintigraphy (Fig. 6).

The clinical conditions associated with metastatic calcification include disorders with increased secretion of parathyroid hormone (including renal failure), destruction of bone, and vitamin D–related disorders (including sarcoidosis where macrophages activate a vitamin D precursor). Aluminum intoxication, seen in patients undergoing long-term dialysis, and milk-alkali syndrome, due to excessive intake of calcium, are less common causes of metastatic calcification. In pulmonary microlithiasis, a genetic defect leads to impaired activity of the phosphate transporter which is presumably implicated in microlith formation by metastatic calcification; intense MDP uptake has been described in this condition (Fig. 7).

Dystrophic Calcification
Dystrophic calcification occurs in patients with normal Ca$^{2+}$ and PO$_4^{-}$ levels and refers to Ca$^{2+}$ deposition in tissues secondary to histologic disruption caused by trauma, ischemia, or cellular necrosis or in the enzymatic necrosis of fat. Ca$^{2+}$ is thought to bind to phospholipids present in membrane-bound vesicles, phosphatases generate phosphate groups, which in turn bind to the calcium, and the cycle is repeated until local concentrations are elevated and crystals begin to form. Hyaline collagen degeneration, a consequence of tissue damage, is particularly associated with Ca$^{2+}$ deposition.

Examples of dystrophic calcification which are often associated with MDP uptake include infarctions of the brain, heart, and muscle, including uterine myomata. Overexertion of skeletal muscle has also been associated.
with MDP uptake, presumably owing to mild degrees of damage and necrosis\textsuperscript{131} (Figs. 8 and 9). Splenic uptake may be observed in autoinfarction associated with sickle cell anemia ("autoinfarction")\textsuperscript{132-134} (Fig. 10), but it can be due to other causes, such as lymphoma, as well.\textsuperscript{135} Dystrophic calcification is likely the mechanism of uptake in deep vein thrombosis\textsuperscript{136,137} and phlebitis.\textsuperscript{138} Uptake in injection sites,\textsuperscript{139,140} scars\textsuperscript{141,142} (Fig. 11), and in soft tissue diseases such as dermatomyositis\textsuperscript{143} is likewise due to dystrophic calcification. Although historically iron dextran is implicated in MDP uptake in injection granulomata,\textsuperscript{139,140} more common causes of injection-related uptake today include subcutaneous injections of heparin\textsuperscript{144-146} and other medications that induce inflammation\textsuperscript{147} (Fig. 12).

**Figure 9** Anterior and posterior MDP images of a 48-year-old man with a brain tumor. Recent seizure resulted in multiple fractures of the thoracolumbar spine. In addition, uptake of MDP in the right deltoid and muscles of the legs bilaterally (arrows) is consistent with soft tissue injury after seizure.

**Figure 10** An 18-year-old with sickle cell anemia. Characteristic findings include prominent activity in the calvarium and at the end of long bones due to marrow expansion, as well as intense activity within the spleen, consistent with autoinfarction, related to dystrophic calcification.

**Figure 11** A 76-year-old man with renal carcinoma who underwent right nephrectomy. Anterior MIP image, CT scan, and SPECT scan demonstrate intense MDP uptake and dense calcification corresponding to scar in the anterior abdominal wall (arrow). MIP, maximum intensity projection.

**Figure 12** Anterior and posterior whole-body images demonstrate a symmetric pattern of MDP uptake (arrowheads) in the shoulders, anterior abdomen, and thighs in a 16-year-old girl receiving rotating subcutaneous injections of enfuvirtide (FUZEON), a peptide that interferes with fusion of HIV to host CD4 cells. HIV, human immunodeficiency virus. (Reprinted with permission from Pack and Zuckier.\textsuperscript{147})
Metabolic Calcification

Several metabolic mechanisms lead to formation of bone, and in turn, uptake of MDP. Osteogenic sarcoma metastases produce an osteoid matrix that binds MDP (Fig. 13).

In a similar manner, myositis ossificans represents a dedifferentiation of muscle into osteoid-producing tissue (Fig. 14).

Mucin-producing tumors possess a glycoprotein that is biochemically similar to ossifying cartilage and binds $\text{Ca}^{2+}$ salts. Classically, mucinous adenocarcinoma tumors of the lung, breast, GI tract, and ovary are associated with MDP uptake, although it may also be seen in tumors with other histology. In addition to uptake in the primary tumor, activity may also be noted in metastases within lymph nodes, lung, and liver. Rarely, MDP-concentrating metastases are disseminated in the soft tissues (Fig. 15). Pathologic uptake in breast, secondary to malignancy such as adenocarcinoma, should be differentiated from normal physiological uptake, which is generally symmetric, mild, and often prominent in the young postpubescent population. So too, fibrils of amyloidosis are said to have a physiological affinity for calcium, although the exact mechanism of uptake of MDP in amyloidosis is not known. Tumor uptake is also frequently observed in neuroblastoma, related to an intrinsic metabolic characteristic of the tumor.

Certain tissues that calcify over time, such as thyroid cartilage, can exhibit MDP uptake as a normal variant. In the past, bone scintigraphy has been used to follow up vascularization of eye prostheses, also reflecting physiological deposition onto hydroxyapatite. Meningiomas are known to calcify and frequently take up MDP (Fig. 16).
Sequestration

In some situations, MDP in soft tissues is present to an extent greater than in the background, not due to active accumulation in soft tissues, but rather, to a slower transit or washout from that region or compartment as compared to neighboring tissues. For example, venous or lymphatic obstruction may lead to an expanded extracellular space within an edematous extremity, with a reduced rate of clearance compared with the remainder of the body (Fig. 17). In this situation, a relative localized increase in activity is apparent on delayed bone-phase imaging, as clearance of the radiopharmaceutical in the affected extracellular space lags behind that of the remainder of the body. So too, pleural effusions and peritoneal ascites (Fig. 18) may be associated with uptake of MDP, a finding that correlates with exudative etiology and likelihood of malignancy. Excessive capillary permeability (typically seen in malignant effusions) permits rapid permeation of the radiopharmaceutical into the effusion when blood
concentration of the radiopharmaceutical is high. The relatively large pleural-fluid distribution volume results in slow back diffusion, resulting in a relatively higher concentration in the effusion than in other soft tissues at the typical time of imaging.164-166

Metastases to the brain frequently cause breakdown of the blood-brain barrier, and this phenomenon was exploited in early scintigraphic brain scanning,168-170 which images radiopharmaceutical after passive leakage into the brain. Uptake of MDP within brain metastases represents a combination of this leaky blood-brain barrier phenomenon and potentially, actual accretion of MDP into the tumor via dystrophic calcification or metabolic uptake mechanisms171 (Fig. 19).

Visualization of bowel activity following bone scans in patients with primary intestinal lymphangiectasia172 or protein-losing enteropathy173 can be understood as visualization of MDP-bound plasma proteins that have extravasated into the bowel and become sequestered from the circulation. Likewise, the rare occurrence of frank GI bleeding following the injection of MDP results in the trapping of radiopharmaceutical within the bowel lumen.174 A recent report has shown the administration of intravenous iodinated contrast between the injection and imaging of MDP to be related to bowel visualization in a high proportion of patients.175 Although the mechanism involved in this process is not clear, this observation may be useful in explaining previously cryptic cases of bowel MDP uptake (Fig. 20).

On occasion, radiolabeled urine may communicate with neighboring structures owing to fistulous connections,176 as noted in renal, bladder, and bowel tumors (Fig. 21), or concentration of the radiopharmaceutical is high. The relatively large pleural-fluid distribution volume results in slow back diffusion, resulting in a relatively higher concentration in the effusion than in other soft tissues at the typical time of imaging.164-166

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liver and spleen following prior marrow-imaging study or visualization of the colon following an earlier cardiac 99mTc-sestamibi perfusion study. These 99mTc-labeled compounds typically remain visible for usually no more than 1 day after administration because of the 6-hour half-life of 99mTc. On the contrary, radiopharmaceuticals incorporating longer-lived radionuclides are apparent for more extended periods of time, depending on their physical and biological clearance. For example, 131I-NaI may remain visible following thyroid ablation for months because of the large dosage, long physical half-life, and prolonged biological half-life. Inefficient collimation of the energetic 364-keV photons results in septal penetration and poorly defined appearance of the activity within the neck.

Radiopharmaceutical impurities can also cause apparent soft tissue uptake. Free pertechnetate, if present in the bone radiopharmaceutical preparation, is concentrated in the stomach and thyroid. Reduced hydrolyzed technetium, which can arise from errors in constituting radiopharmaceutical kits or due to excess aluminum ion, results in colloid formation and activity accumulating within the liver and spleen. Technetium may also exist in other chemical forms that are excreted by the liver into the biliary tree and bowel, though the exact mechanism of origin of the contaminant in these cases may not be clear. In a hospital’s experience, moderate to intense bowel uptake, usually in the ascending colon, was noted in approximately 1% of 2144 cases studied over a period of 18 months. The incidence of gall bladder or bowel visualization may reach 5%-10%. These statistics cannot be generalized as the frequency of radiopharmaceutical-based uptake depends on the specific source of reagents and particular technique used at each radiopharmacy.

**Figure 19** MDP uptake in 3 orthogonal planes through the skull in a brain metastasis located in the left hemisphere in a 67-year-old male with small cell lung cancer. Enhanced CT scan was performed 5 days before the bone scan and demonstrates additional lesions in the right hemisphere (*) that are not identifiable on bone scintigraphy.

**Figure 20** Initial planar baseline (BL) and repeat MIP study performed after 5 days (5d) demonstrate relatively intense bowel uptake seen on the initial but not repeat study (arrow). The patient had not undergone a prior nuclear medicine study nor was any other etiology of bowel uptake elicited. In retrospect, this finding is consistent with reported effect of IV contrast administration following radiopharmaceutical administration; MDP was administered at 8:45 AM and CT contrast was injected 30 minutes thereafter. Incidental note made of horseshoe kidney. IV, intravenous; MIP, maximum intensity projection.
Conclusion

With extensive experience in bone scintigraphy using single-photon radiopharmaceuticals, an extensive literature of altered biodistribution has developed. Conditions that lead to altered radiotracer uptake run the gamut from benign to malignant, biodistribution has developed. Conditions that lead to altered biodistribution have been encountered in clinical practice. Being cognizant of these unexpected abnormalities and understanding their etiology will prepare the reader to more readily appreciate the significance of these findings when encountered in clinical practice.

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Figure 21 Anterior and posterior bone scintigraphic images of a 60-year-old man with prior history of colorectal carcinoma treated with external beam radiation. Intense bowel activity is secondary to known colovesicular fistula.


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