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Review Article

Molecular Imaging of the Skeleton using Skeletal Scintigraphy from an Anatomist's Perspective

Meena Negi[1], Leesa Thakur[2], Vandana K Dhingra[3], Kumar Satish Ravi[4]

[1]PhD Scholar, Department of Nuclear Medicine, All India Institute of Medical Science, Rishikesh, Uttarakhand, India, [2]Nuclear Medicine Technologist, All India Institute of Medical Science, Rishikesh, Uttarakhand, India, [3]Additional Professor, Department of Nuclear Medicine, All India Institute of Medical Science, Rishikesh, Uttarakhand, India, [4]Additional Professor, Department of Anatomy, All India Institute of Medical Science, Rishikesh, Uttarakhand, India

Abstract

Imaging of the skeleton includes anatomical imaging modalities using radiographs, computed tomography (CT) scan or magnetic resonance (MR) imaging as well as functional imaging modalities like radionuclide imaging also known as molecular imaging. In the past few decades the concept of hybrid imaging using fusion of the two techniques such as single-photon emission CT/CT (using Gamma Camera) or positron emission tomography/CT (PET/CT) and recently PET/ MR. Understanding the concepts of imaging is of importance to the clinician as well as the anatomist for better utilization of the existing modalities as well as for development of better modalities for better patient management. We introduce the concept of molecular imaging of the skeleton with focus on skeletal scintigraphy known as the "bone scan" for the interest of the anatomist.

Key words: Anatomist, Bone scan, Molecular imaging, Single-photon emission computed tomography/computed tomography, Skeleton

INTRODUCTION TO THE SKELETON

Around 206–210 bones are present in adult human skeleton. At the time of birth, the young one is composed of 270 bones, but later it decreases to 70–80 bones. There are about 126 bones in axial skeleton and there are almost 20 major bones in appendicular skeleton.[1]

Bone tissue: Bone consists of collagen and non-collagenous tissue.[2] The rigid part of the bones helps to make the skeleton. The types of bone tissue are cortical bone tissue, cancellous bone tissue, and other types of bone tissue include bone marrow, endosteum, periosteum, nerves, blood vessels, and cartilage.[2]

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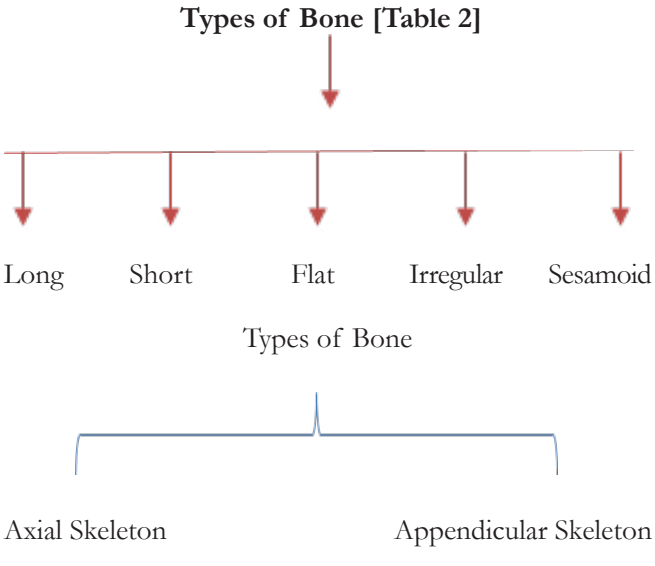
Bone cells are classified into four types:[Table 1][3]
Structure of bone: Bone consists of different parts: Diaphysis, epiphysis, metaphysis, articular cartilage, periosteum, medullary cavity, and endosteum. The central part of any long bone is diaphysis and the proximal and distal part of the bone is epiphysis and the region between diaphysis and epiphysis is metaphysis. Articular cartilage covers the epiphysis part where bone makes an articulation with other bone. Periosteum covers the outer surface of bone which is not covered by articular cartilage. It helps in growth of bone in thickness but not in length. Medullary cavity is an empty space within the diaphysis which contains yellow bone marrow. The spongy part of bone of epiphysis and metaphysis contains red marrow (having red blood cells). Endosteum lines the internal bone surface.[4-6]

Bone comprises about 80% compact bone and 20% spongy bone. Compact bone is the strongest part of bone. It is also known as cortical or dense bone. It does not have any hollow space. It contains blood vessels, lymphatic vessels and nerves. Spongy bone is also known as cancellous bone which contains red bone marrow (having red blood cells).[1]

Corresponding Author: Dr. Vandana K Dhingra, Department of Nuclear Medicine, All India Institute of Medical Science, Rishikesh, Uttarakhand, India.

BONE IS CLASSIFIED INTO DIFFERENT TYPES



Axial skeleton	
Cranial bones	• Parietal (2) • Temporal (2) • Frontal (1) • Occipital (1) • Ethmoid (1) • Sphenoid (1)
Facial bones	• Maxilla (2) • Zygomatic (2) • Mandible (1) • Nasal (2) • Platine (2) • Inferior nasal concha (2) • Lacrimal (2) • Vomer (1)
Auditory Ossicles*	• Malleus (2) • Incus (2) • Stapes (2)
Hyoid	
Vertebral column	• Cervical vertebrae (7) • Thoracic vertebrae (12) • Lumbar vertebrae (5) • Sacrum (1) • Coccyx (1)
Thoracic cage	• Sternum (1) • Ribs (24)
Appendicular	
Pectoral girdles	• Clavicle (2) • Scapula (2)
Upper extremity	• Humerus (2) • Radius (2) • Ulna (2) • Carpals (16) • Metacarpals (10) • Phalanges (28)
Pelvic girdle	• Sacrum • Hip bones (2)
Lower extremity	• Femur (2) • Tibia (2) • Fibula (2) • Patella (2) • Tarsals (14) • Metatarsals (10) • Phalanges (28)

HISTOLOGY

Tissue Preparation for Transmission Electron Microscopy

Animal is sacrificed & bone sample is taken out

↓

Place sample in formalin (primary fixative)

↓

Place sample in Osmium Tetroxide (Secondary fixative)

↓

Place sample in different concentration of ethanol (30% → 50% → 70% → 90% → 100%) for 1hr each

↓

Place 1:1 mixture of alcohol with propylene oxide

↓

Place sample in propylene oxide

↓

Place sample in 1:1 mixture of propylene oxide with resin

↓

Place sample in pure resin (for Plasticization process)

↓

Slice sample with ultramicrotome & collect the tissue sections

↓

Place tissue in Grid (meshwork of copper wires)

↓

Bombardment of electrons on the tissue to get image on the screen

Tissue Preparation for Scanning Electron Microscopy

Animal is sacrificed & bone was taken out

↓

Place sample in formalin (primary fixative)

↓

Place sample in Osmium Tetroxide (Secondary fixative)

↓

Place sample in different concentration of ethanol (30% → 50% → 70% → 90% → 100%) for 1hr each

↓

Physical drying is achieved by critical point drying (Remove solvent from the sample with no latent heat of vaporization)

↓

Acetone is replaced from the tissue with liquefied carbon dioxide in critical point drying unit (By critical point drying technique)

↓

Tissue is fractured by freeze fracture technique (For internal structure visualization)

↓

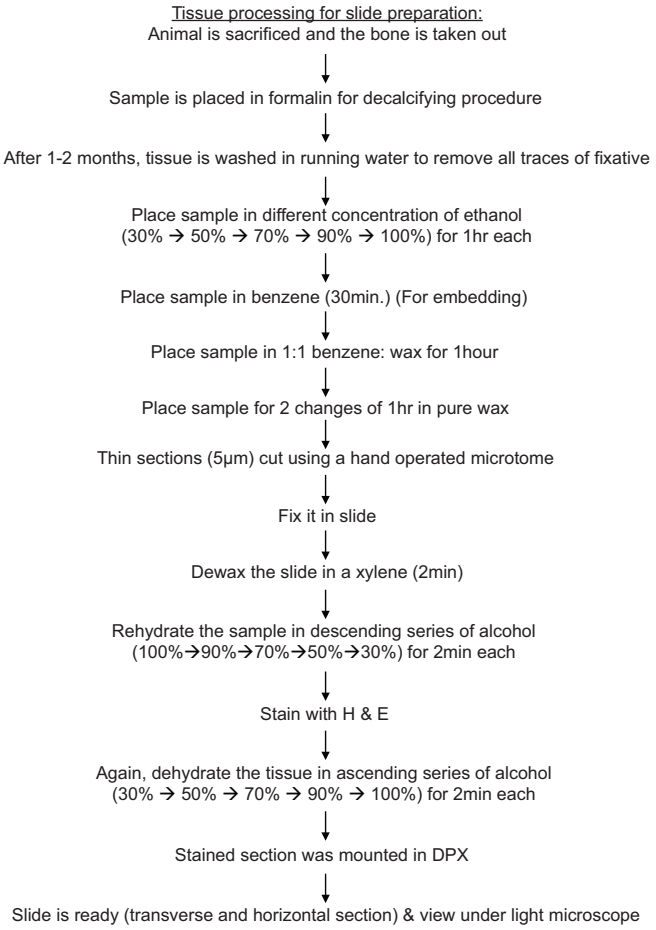
Tissue is coated with a thick layer of metal such as gold, platinum and palladium in Sputter coating machine

↓

Electrons are bombarded on the metal coated tissue which produces lines on the screen

↓

Scan the tissue for getting scanning image of the tissue



Bone is studied histologically by transverse and horizontal section of bone tissue. In transverse section, the central canal, concentric lamellae, osteon in Figure 1.

Skeletal scintigraphy is one of the most sensitive studies for imaging of the skeletal disorders. It finds application in detection of bone disease like metastasis which may be located anywhere in the body and whether the patient has symptoms or not. It is cost effective and easily available at reasonable cost; however, one of the major limitations is low specificity. This may lead to false positive studies and clinical as well as radiological correlation is required. An abnormal or positive bone scintigraphy shows an ongoing osteoblastic process which may represent bone disease. It is most useful in evaluation of skeleton for metastasis especially in tumors such as prostate, breast, and lung carcinoma which have common metastasis to the bones. It is useful in assessment of bone involvement in other conditions such as renal cell carcinoma, primary tumors such as multiple myeloma and leukemia, metabolic bone disease - hyperparathyroidism, Osteoporosis, and Paget's disease and benign bone tumors such as osteoid osteoma. In addition, three phase bone scan differentiates Soft Tissue infection/inflammation from skeletal lesions, painful joint prosthesis, skeletal trauma - fracture detection, complex regional pain syndrome, stress fracture, and bone grafting. It also shows uptake in bone scan in evaluation of cases suspected in battered baby syndrome or child abuse - detects recent fractures which is not detected in radiography (3–5 days) and detect old fractures in patients with burns and other findings suggesting child abuse.

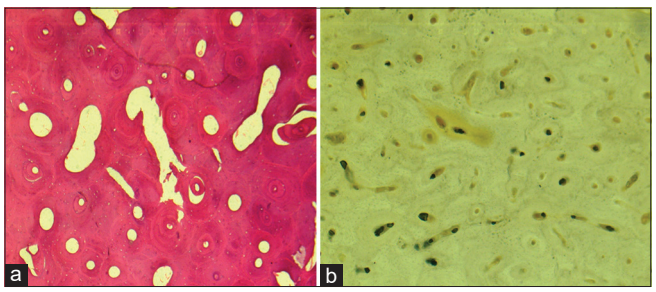


Figure 1: Transverse bone tissue section at ×5: (a) with H and E stain (b) Unstained section 99mTc MDP whole body bone scan

The uptake mechanism of bone seeking radiopharmaceuticals like 99mTc Methylene diphosphonate (MDP), 99mTc HMDP and 99mTc HEDP occur by chemo-adsorption on hydroxyapatite crystals. The radiotracers readily distribute into the extracellular fluid and after that, it resides into the bone. Its accumulation depends upon the osteogenic activity of cells and amount of blood flow.[7] The tracer used in positron emission tomography (PET) for bone imaging-Na18F in which there is an exchange mechanism of the 18F ions with hydroxyl ions (OH^-) on the surface of the hydroxyapatite to form fluoroapatite. This is cleared fast from the blood which leads to high bone to background ratio.[8]

Different technologies such as single-photon emission computed tomography (SPECT) and PET are available for bone imaging. In SPECT, 99mTc diphosphonate such as 99mTc HEDP, 99mTc HDP, and 99mTc MDP are commonly used. Radiopharmaceuticals - 47Ca, 85Sr, and 87mSr were used earlier but due to their drawbacks, these are not used nowadays. In case of lymphoma, 67Ga is used in detecting bony lesions in addition to soft-tissue masses. It is also used in assessing the response to therapy. 99mTc-Sulphur colloid is used for evaluating bone marrow metastases.[1] In PET, Na18F is used in benign bone disorders - Paget's disease which is superior for the assessment of bone formation. In combination with dynamic PET acquisition, ^{18}F-NaF allows for quantitative kinetic modeling of bone blood flow and metabolism.[9,10] ^{18}F-FDG PET is used for imaging of osteomyelitis which has excellent sensitivity and specificity for bone infection, with higher accuracy than ^{99m}Tc-hexamethylpropyleneamine oxime or ^{111}in-labeled white blood cell scintigraphy [Table 3].[11]

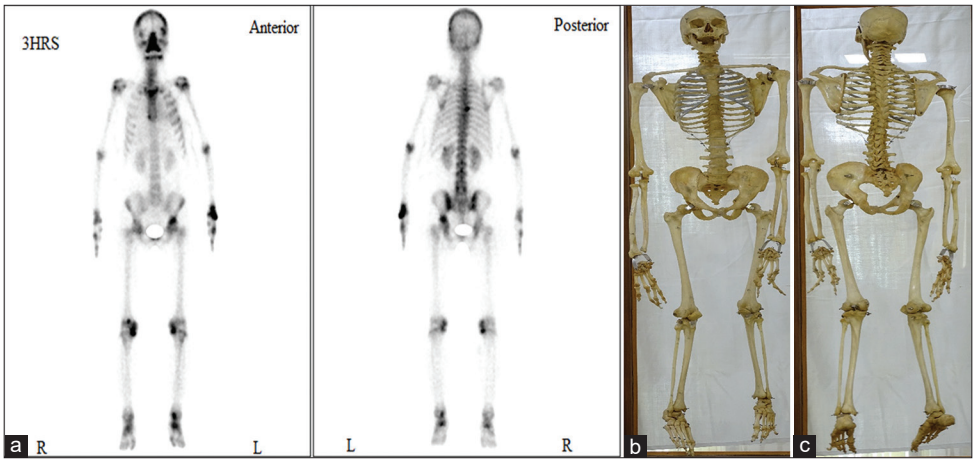


Figure 2: (a) Anterior and posterior whole body bone scan views with (b and c) corresponding anatomical skeleton images

Comparison of skeletal views with bone scan (gamma camera images)

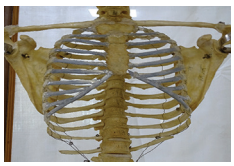
S. No	Region	Anatomical image (a)	Gamma camera images (b)
1	Skull Anterior		 R L
	Skull Posterior		 L R
	Skull Left Lateral		
	Skull Right lateral		
2	Thorax Anterior		 R L

Figure 3: Understanding various standard views of a bone scan (1a-g): Compared with corresponding images of anatomical skeleton 1

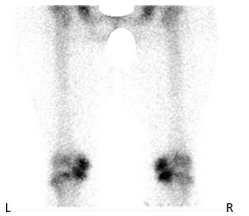
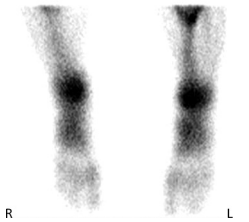
	Thorax Posterior		 L R
3	Lumber-pelvis Anterior		 R L
	Lumber-pelvis Posterior		 L R
4	Thighs Anterior		 R L
	Thigh Posterior		 L R
5	Feet Anterior		 R L
	Feet Lateral	 	 R L

Figure 3 : ***(Continued)***

6 Hands

Anterior

Posterior

Figure 3: ***(Continued)***

Table 1: Type of cells in bone

Bone cells	Function
Osteoblasts	New bone or bone-forming cell
Osteocytes	Maintain bone metabolism
Osteoclasts	Repair and remodeling of bones
Osteogenic cells	Stem cell

Table 2: Classification

Long bones	Short bones	Flat bones	Irregular bones	Sesamoid bones
Lower limbs • Femora • Tibiae • Fibula	Foot • Tarsals	Skull • Occipital • Parietal • Frontal	Vertebra	Patella
Upper limbs • Humerus • Radius • Ulna	Hands • Carpals	Nasal	Sacrum	Pisiform (smallest of the carpals)
Hands • Metacarpals		Lacrimal	Mandible	2 small bones at the base of the 1st metatarsal
Feet • Metatarsals		Vomer		
Fingers and toes • Phalanges		Scapula		
Clavicles		Ilium (hip bone) Sternum Ribs		

PROCEDURE OF BONE SCINTIGRAPHY WITH 99MTC MDP

Radiopharmaceutical: 99mTc MDP is used for whole body bone imaging.

Dosage

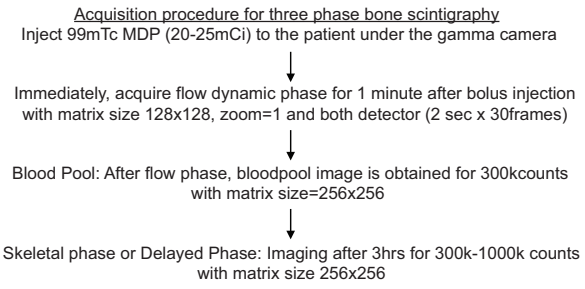
The usual administered activity for adult patients is 740–1.110 MBq (20–30 mCi) injected intravenously. For pediatric patients, the administered activity is 9–11 MBq/ kg (250–300 μCi/kg), with a minimum of 20–40 MBq (0.5–1.0 mCi).

Acquisition

Delayed images are usually obtained from 2 to 4 h after injection. Whole-body bone scintigraphy is accomplished with multiple overlapping images (i.e., spot images) [Figure 3] or with continuous images (i.e., whole-body scan) [Figure 2] obtained in anterior and posterior views with a

Table 3: Overall impact of molecular imaging for bone: Bone scan

Major advantages	Limitations
Non-invasive imaging, cost effective technique	• Radiation exposure – however radiation exposure is lesser than that received for a diagnostic contrast-enhanced computed tomography scan
Highly sensitive	• Time consuming - one bone scan may take 20–30 min compared to few seconds for computed tomography scan
Whole body Imaging vis –a- vis regional for most anatomical imaging modalities	• Does not provide soft tissue details like magnetic resonance imaging – may be partly overcome with positron emission tomography /magnetic resonance imaging
Hybrid Imaging – single-photon emission computed tomography/computed tomography, positron emission tomography/ computed tomography - One stop shop for anatomical and functional information	–
Non-claustrophobic unlike magnetic resonance imaging	–
Most useful in conditions: Metastasis, stress fractures, osteomyelitis, and avascular necrosis	• Limited use in conditions: Diagnosis of primary bone tumors (may help in assessment of extent of involvement), osteolytic lesions like those of multiple myeloma



high-resolution low energy collimator dual head gamma camera. Whole-body views are obtained in a 256 × 1024 matrix. In case of pediatric patients, spot views are taken as the primary method of acquiring bone images, the areas of bony skeleton covered by the spot views are made to over-lap to avoid missing regions of the skeleton. Spot views are acquired for approximately 500,000–1 million counts using 256 × 256 matrix. In addition, SPECT/CT is acquired for more clarification [Figure 3].[1]

CONCLUSION

Molecular imaging with radioisotopes has its use in management of various diseases. For skeletal imaging, the most commonly use modality is the bone scan. It is imperative to understand the anatomy of the skeleton to correctly understand the images of bone scan and it may also be of interest for an anatomist to be introduced to the various basics of this technique. This is important for application of the techniques to their fullest as well as for future development of newer techniques for better clinical outcomes.

REFERENCES

1. Ziessman HA, O'Malley JP. Nuclear Medicine: The Requisites. Netherlands: Elsevier Health Sciences; 2013.
2. Aerssens J, Dequeker J, Mbuyi-Muamba JM. Bone tissue composition: Biochemical anatomy of bone. Clin Rheumatol 1994;13:54-62.
3. Webster TJ, Ergun C, Doremus RH, Siegel RW, Bizios R. Enhanced functions of osteoblasts on nanophase ceramics. Biomaterials 2000;21:1803-10.
4. Gray H. Gray's Anatomy. United Kingdom: Arcturus Publishing; 2009.
5. Tortora GJ, Derrickson BH. Principles of Anatomy and Physiology. United States: John Wiley and Sons; 2018.
6. Guyton AC, Hall JE. In: Gökhan N, Çavuşoğlu H, editor. Medical Physiology. Amsterdam: Elsevier Saunders; 2006. p. 3.
7. Wong KK, Piert M. Dynamic bone imaging with 99mTc-labeled diphosphonates and 18F-NaF: Mechanisms and applications. J Nuclear Med 2013;54:590-9.
8. Hsu WK, Feeley BT, Krenek L, Stout DB, Chatziioannou AF, Lieberman JR. The use of 18 F-fluoride and 18 F-FDG PET scans to assess fracture healing in a rat femur model. Eur J Nuclear Med Mol Imaging 2007;34:1291-301.
9. Timmermans AJ, Quak JJ, Hagen PJ, Colnot DR. 18F-NaF PET/CT imaging of bone formation induced by bioactive glass S53P4 after mastoid obliteration. Eur J Hybrid Imaging 2019;3:1-7.
10. Wong KK, Piert M. Reply: Regarding dynamic bone imaging with 99mTc-Labeled diphosphonates and 18F-NaF: Mechanisms and applications. J Nuclear Med 2013;54:2190-1.
11. Li Y, Schiepers C, Lake R, Dadparvar S, Berenji GR. Clinical utility of 18F-fluoride PET/CT in benign and malignant bone diseases. Bone 2012;50:128-39.

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