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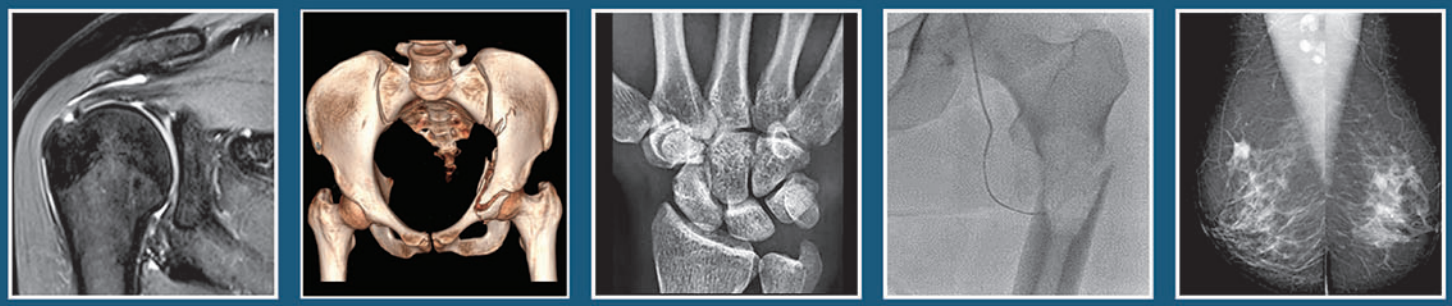

DIAGNOSTIC RADIOLOGY

Musculoskeletal and Breast Imaging

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CHAPTER 2

Nuclear Medicine Imaging for Musculoskeletal Disorders

Rakesh Kumar, Madhavi Tripathi, Shamim Ahmed Shamim

INTRODUCTION

Musculoskeletal system is a dynamic organ system, which responds to systemic as well as to localized stress and, hence, apart from anatomical visualization, it requires physiological evaluation. Nuclear medicine techniques provide the physician with physiologically detailed images that can give insight, which cannot always be accomplished, from plain radiograph or even with computed tomography (CT) and magnetic resonance imaging (MRI). The major advantage of nuclear medicine imaging stems from the fact that functional changes appear much before anatomical changes. Hence, nuclear medicine imaging allows early detection of diseases affecting musculoskeletal system. The present chapter summarizes the nuclear medicine techniques used for musculoskeletal imaging and their utility in various benign and malignant pathologies involving the musculoskeletal system.

Table 1: Radiotracers used for skeletal scintigraphy.

Tracers for skeletal imaging	*Nonspecific*	*Tumor-specific*
Planar and SPECT	^{99m}Tc MDP	
	^{99m}Tc HEDP	
PET	18F-Fluoride	*Ga-68 DOTANOC-NET
	*18F FDG	*!Ga-68 PSMA-prostate cancer

*Localizes in bone marrow and bone metastases.
!This tracer localizes to prostate-specific membrane antigen (PSMA) expression on prostate cancer cells and also in neovascularization, thus has been found to localize to bone metastases in breast, anaplastic thyroid cancer, adrenocortical cancer (ACC), etc.
(FDG: fluorodeoxyglucose; HEDP: hydroxyethylidene diphosphonic acid; MDP: methylene diphosphonate; NET: neuroendocrine tumor; PET: positron emission tomography; SPECT: single photon emission computed tomography)

BONE SCINTIGRAPHY

In spite of newer developments in the field of nuclear medicine, bone scintigraphy (BS) remains the most commonly employed method for musculoskeletal imaging. It is performed following the intravenous administration of bone-seeking radiopharmaceuticals. These compounds are usually phosphonates labeled with ^{99m}Technetium (^{99m}Tc). The most widely used is ^{99m}Tc-methylene diphosphonate (MDP) **(Table 1)**. Others are ^{99m}Tc-ethylene hydroxy-diphosphonate (EHDP) and ^{99m}Tc-hydroxymethylene diphosphonate (HDP). The presence of P-C-P bonds makes these compounds resistant to hydrolysis by bone phosphatases, thereby increasing the biological half-life. 3–4 hours after intravenous injection about 25–35% of radiotracer is retained in the normal adult skeleton, the rest is excreted in the urine via the kidney. These phosphorus-containing complexes attach themselves to the hydroxyapatite crystal on the bone surface by chemisorption.[1] Thus, they localize at the site of direct and indirect osteoblastic activation. Autoradiographic studies revealed that the ^{99m}Tc-labeled phosphonates are mainly taken up in the mineral phase of skeletal bone at the site of reactive bone formation. This osteoblastic activation can be seen because of wide array of pathologies, thereby decreasing the specificity. The routine BS employs whole body anterior and posterior sweep images. In addition, dynamic flow and pool images are acquired in selected cases.

SPECT AND SPECT/CT

Given the lack of anatomical information provided by planar BS, especially in the regions of complex anatomy, additional methods are employed. Single photon emission tomography (SPECT) is being routinely used in such a scenario. It gives three-dimensional pictures and is beneficial in patients with normal planar images despite symptoms and in those with equivocal findings.[2] SPECT imaging is most useful for the evaluation of the thoracolumbar spine, skull, and pelvis. These areas have extensive surrounding soft tissue and/or complicated body contours, and thus superior image contrast provided by SPECT improves lesion detection. The decision to perform single field-of-view SPECT studies has been guided by suspicious findings on planar imaging or localized clinical symptoms. However, even with plain

SPECT, correlation with anatomical imaging is usually needed. SPECT/CT imaging with hybrid cameras has been introduced to overcome this shortcoming and to provide both anatomical and functional information in a single setting.

PET AND PET/CT

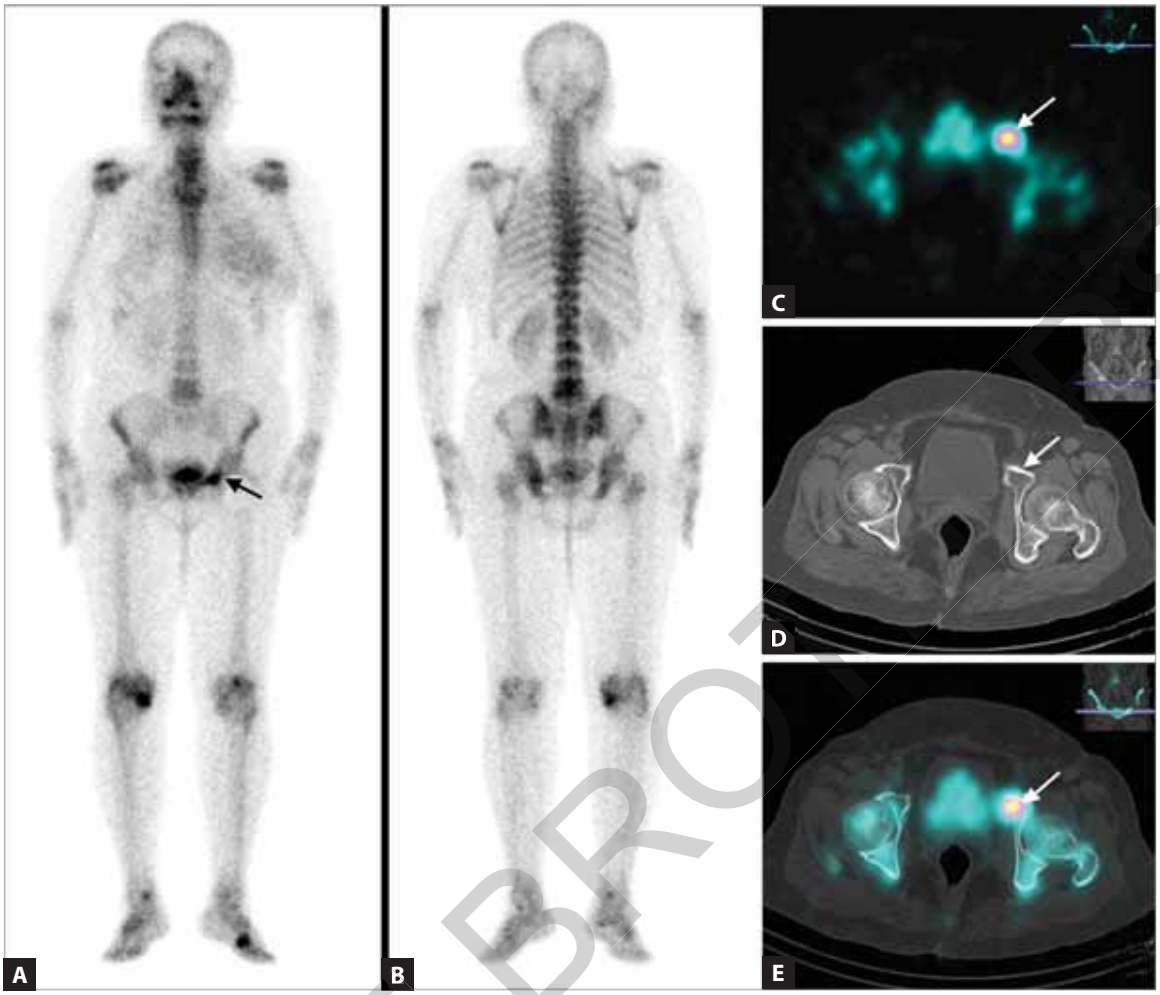
In contrast to routine gamma camera imaging, positron emission tomography (PET) imaging is based on the detection of high energy (511 KeV) annihilation photons emitted by positron-emitting radionuclides. The inherent physics of positron decay allows tomographic imaging without the need for collimators, thereby improving the sensitivity and resolution. The lack of anatomical information on PET alone has been overcome with introduction of hybrid PET/CT. In fact, the availability of hybrid PET/CT systems has made PET alone redundant. Although, PET and PET/CT had greatest impact in the field of cancer imaging, its application for other areas including musculoskeletal disorders is being actively investigated. In clinical practice, most PET studies are performed with 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG), a glucose analog. It is actively taken up by cells with increased glucose metabolic rate via specific glucose transporters (GLUT-1 and GLUT-4) and is phosphorylated by hexokinases to FDG-6-phosphate, which is retained.[3] Nowadays, FDG-PET is being increasingly used for imaging primary and secondary musculoskeletal tumors as well as infections. Another important tracer in the context of skeletal imaging is ^{18}F-fluoride **(Table 1)**. It can also be used for quantitative studies of skeletal kinetics.[4] Although there are differences between ^{18}F-fluoride and ^{99m}Tc-diphosphonate, it is probable that the mechanism of uptake in bone is the same, i.e., adsorption onto bony surfaces with predilection for sites of active bone formation.[5] The uptake of ^{18}F-fluoride is approximately twofold higher and its blood clearance is significantly faster compared with the ^{99m}Tc-diphosphonates, resulting in an increased bone-to-background ratio. Ga-68 prostate-specific membrane antigen (PSMA) PET-CT is a new addition, is used for prostate cancer staging, particularly for bone metastasis, and shows high sensitivity and specificity for bone metastasis. In addition, PET offers high sensitivity and high resolution, and therefore enables to perform highly accurate whole-body screening for metastases.[6]

MUSCULOSKELETAL TUMOR IMAGING

Metastasis

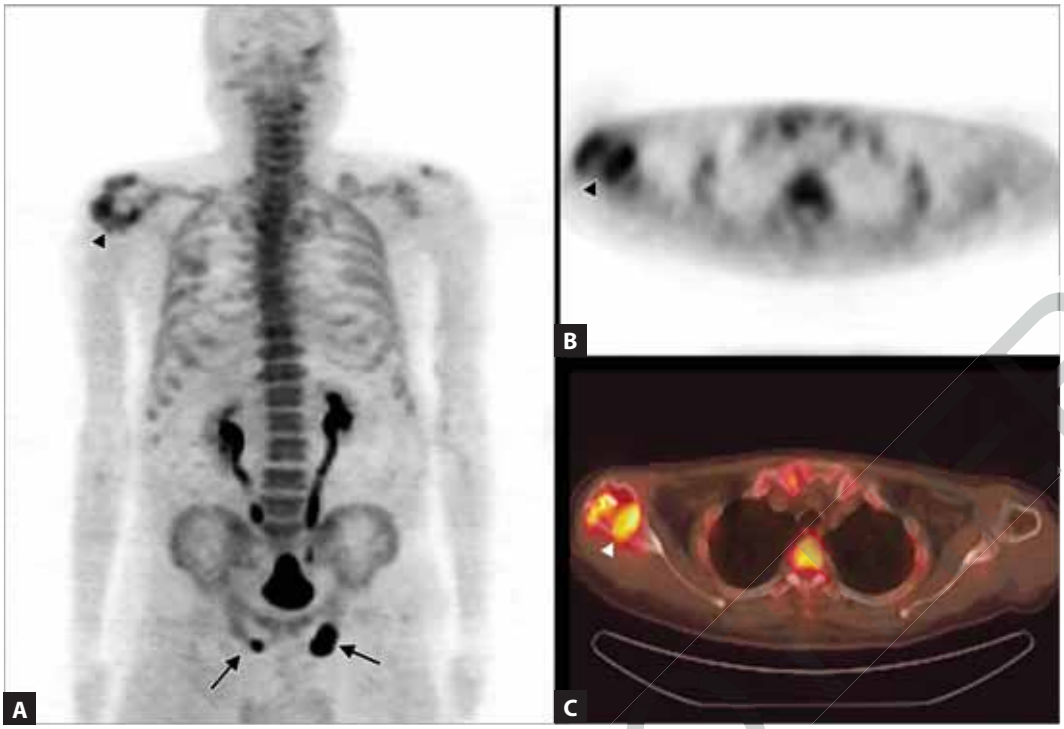
Skeletal metastasis is the most common bone malignancy. It affects approximately two-thirds of cancer patients, with breast cancer being the leading cause in women, prostate cancer in men, followed by lung cancer in both genders. Accurate assessment of skeletal involvement is essential for optimal management of these patients.[7] Many patients with bone metastases are identified during initial staging, routine follow-up, or on investigation for rising tumor markers. For the past few decades, planar BS has been the most frequently performed imaging study in the evaluation of metastatic bone disease. Although scintigraphic findings alone are often nonspecific for skeletal pathologies, this technique reportedly has an exquisite sensitivity. Radiographs are found to be negative in 30–50% of patients with positive bone scan. The most common pattern of bone metastasis is multiple "hot" spots distributed randomly throughout the skeleton.[8] A lytic metastasis usually presents as a photopenic area with increased activity at the margin of the lesion. False negative results in BS are seen in avascular lesions, in the presence of rapidly growing pure osteolytic metastases with no reactive increased osteoblastic activity, or in lesions with low bone turnover (multiple myeloma and hepatocellular cancer). Specificity of BS is generally lower, due to a known increased blood flow and bone remodeling in response to a variety of disease processes, including trauma, infection, inflammation, and osteoarthritis. Therefore, further assessment with other imaging modalities, mainly CT and MRI, and in some cases, histologic confirmation may be required for precise diagnosis.[9]

Addition of SPECT has been reported to detect 20–50% more lesions in the spine compared with planar scintigraphy.[10] It increases both the sensitivity and specificity of bone scans.[11] The use of SPECT for the assessment of suspicious vertebral lesions on planar BS had a negative predictive value of 98%. The sensitivity and specificity of bone SPECT for diagnosis of bone metastases are 87–92 and 91–93%, respectively.[12] The decision to perform single field-of-view SPECT studies has been guided by suspicious findings on planar imaging or localized clinical symptoms. Newly developed half-time whole body SPECT protocols provide tomographic assessment of the entire skeleton within an acceptable image acquisition time, with subsequent improvement in sensitivity and an increased detection rate of asymptomatic small skeletal metastases.[13] However, even with SPECT correlation with high-quality anatomic images, CT or MRI may still be needed for diagnosis. Hybrid SPECT/CT devices equipped with multislice CT scanners further improve the sensitivity and specificity of BS. It has been shown to be superior to planar BS and SPECT for skeletal metastasis of breast and lung cancers.[14,15] Foci of increased tracer activity on BS, suspicious of representing malignant bone lesions, may not show any morphologic abnormality on CT as functional changes precede anatomical changes, and therefore cannot be confirmed as such. The present consensus is to do SPECT/CT of suspicious planar BS lesions only if the lesion remains equivocal even after SPECT **(Figs. 1A to E)**.

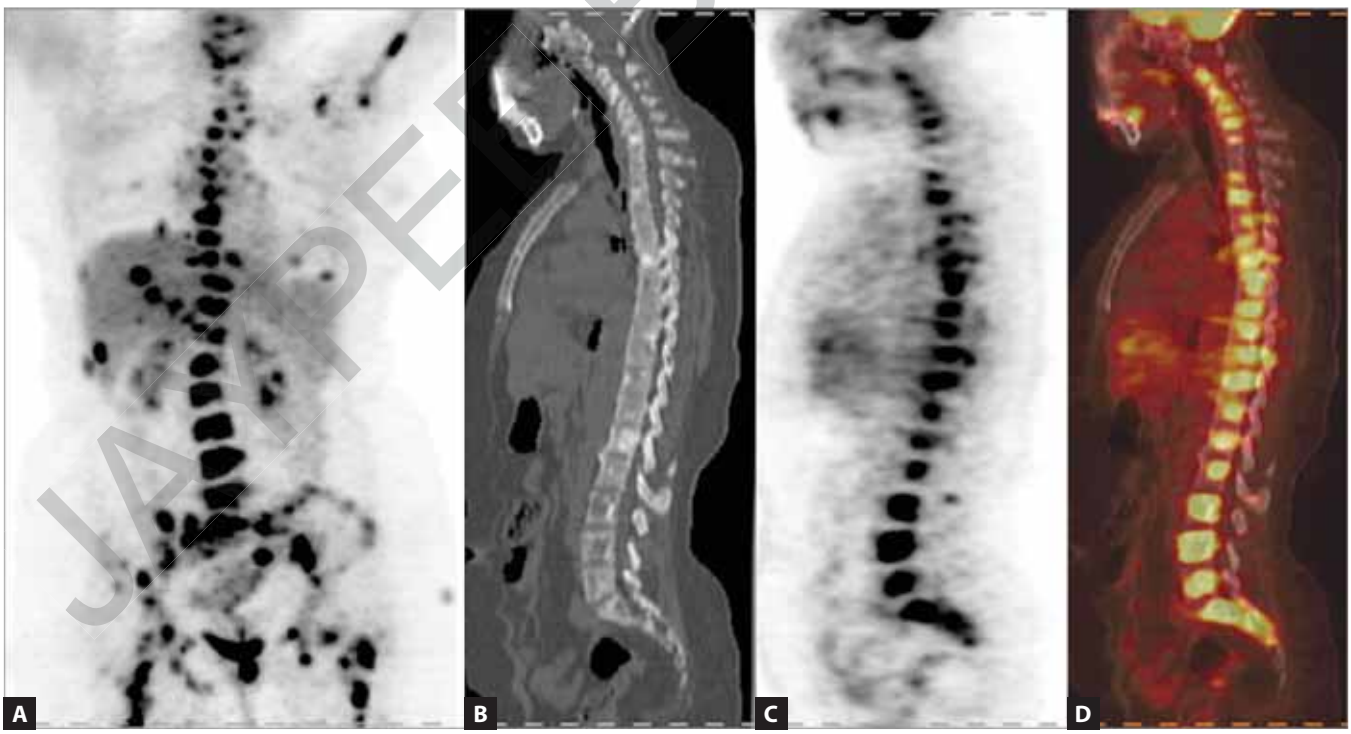


Figs. 1A to E: A 37-year-old carcinoma of breast patient for staging. (A and B) Planar bone scintigraphy showed a suspicious focal uptake in left superior pubic rami (arrow). SPECT (C), CT (D), and SPECT (E) images showed lytic lesion with increased tracer uptake (arrows) suggesting metastasis.

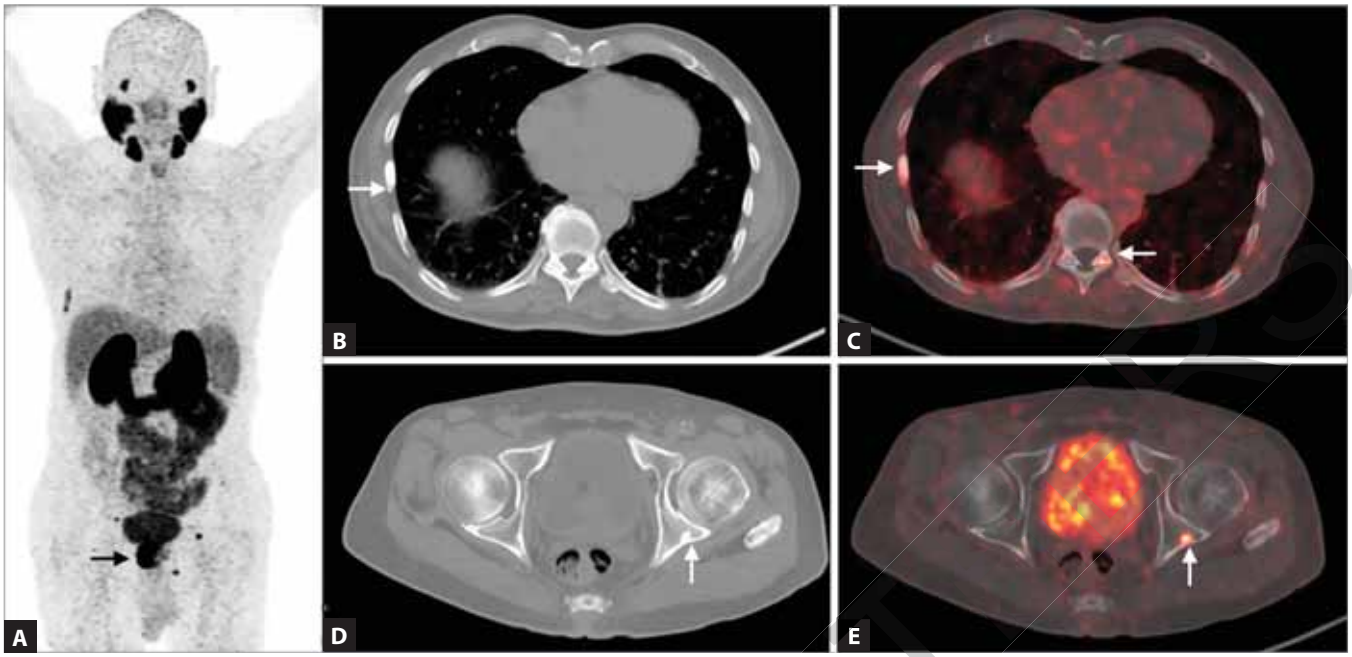
Several studies have shown the superiority of the ^{18}F-fluoride PET over BS for the diagnosis of skeletal metastases; the former demonstrated a higher number of the lesions and a higher contrast between normal and abnormal bone.[16] Although the superb resolution and high abnormal-to-normal bone ratio of ^{18}F-fluoride PET can potentially lower the specificity, hybrid PET-CT imaging should help differentiate benign versus malignant lesions **(Figs. 2A to C)**.[17] ^{18}F-fluoride has shown to be highly sensitive for detecting lytic and sclerotic bone metastasis in breast cancer,[18] prostate cancer,[19] and lung cancer.[20] There has been the suggestion that ^{18}F-fluoride could be more cost effective than the bone scan and that a case can be made for it replacing the bone scan.[21] Increased FDG activity at the sites of skeletal lesions represents active tumor itself, whereas increased ^{99m}Tc-MDP or ^{18}F-fluoride activity represents a blastic activity/reparative process in response to tumor and destroyed bone. Compared with BS or ^{18}F-fluoride, FDG-PET is reported to be more sensitive for lytic lesions and bone marrow disease but less sensitive for blastic lesions.[22] It has an additional advantage: the ability to assess extraskeletal metastatic disease, including muscle metastasis.[23] Recent data almost invariably have shown that BS is more sensitive than FDG-PET for detection of blastic/sclerotic lesion, whereas FDG-PET is more sensitive for lytic lesions and bone marrow involvement **(Figs. 3A to D)**.[24] The lower sensitivity of FDG-PET for detecting sclerotic lesions can be complemented by CT, which may obviate the need for BS.[2] For prostatic bone metastasis, Ga-68 PSMA can be used in addition to BS **(Figs. 4A to E)**. It is generally agreed that the overall sensitivity of FDG-PET and BS for all lesions is comparable, but PET has a higher specificity, resulting in an overall higher accuracy. The utility of FDG-PET-CT for bone metastasis has already been shown in breast cancer, lung cancer, lymphoma, multiple myeloma, and neuroblastoma.[25-27] Another very important advantage of FDG-PET-CT is its ability to assess response to therapy in bone metastasis. Although BS has been used to assess the efficacy of treatment and to follow breast cancer patients,



Figs. 2A to C: A 60-year-old male with carcinoma of prostate and rising prostate-specific antigen (PSA). (A and B) ^{18}F-fluoride PET maximum intensity projection (MIP) images show focal tracer uptake in bilateral pubic rami (arrows) suggestive of metastasis. Also, noted was tracer uptake in right shoulder (arrowhead); (C) On PET-CT images, this uptake was diagnosed to be degenerative change (arrowhead).



Figs. 3A to D: A 35-year-old female with known breast cancer underwent PET-CT scan for staging. ^{18}F-FDG whole body projection image (A) shows focal areas of increased radiotracer uptake suggestive of metastases. Lytic sclerotic bone lesions and FDG uptake in multiple vertebrae in CT, PET, and PET-CT sagittal sections (B to D). There are many lesions showing focal FDG uptake no sclerosis on CT suggestive of marrow metastases.



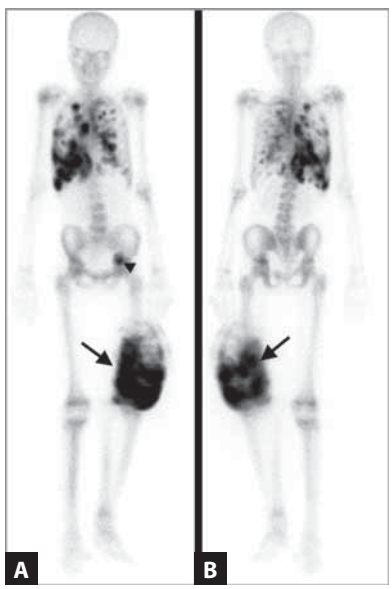
Figs. 4A to E: (A) ^{68}Ga-PSMA PET/CT maximum intensity projection image showing heterogeneous increased uptake in prostatic bed with focal uptake in left hip region and physiological uptake in salivary gland, kidney, and bowel loops; (B) Axial CT image showing sclerotic lesion in the rib and left pedicle of vertebra, (C) corresponding fused PET/CT image showing focal uptake (arrows)—consistent with metastases; (D) Axial CT image showing sclerotic lesion in the left acetabulum, corresponding fused PET/CT image (E) showing focal uptake—consistent with metastasis.

the early response to any treatment cannot be assessed by BS. Moreover, BS may show persistent increased activity even in treated lesions for several weeks to months. In most malignancies, FDG-PET has proved an effective modality for early assessment of therapeutic response by showing rapid reduction in FDG uptake by the tumors in responders following chemotherapy.[28] The changes in FDG standard uptake value (SUV) with therapy showed correlation with the overall clinical assessment of response as well as with the change in tumor marker value. Flare phenomenon which is considered to be a marker of response on BS has also been described on FDG-PET but only associated with antiestrogen therapy.[29]

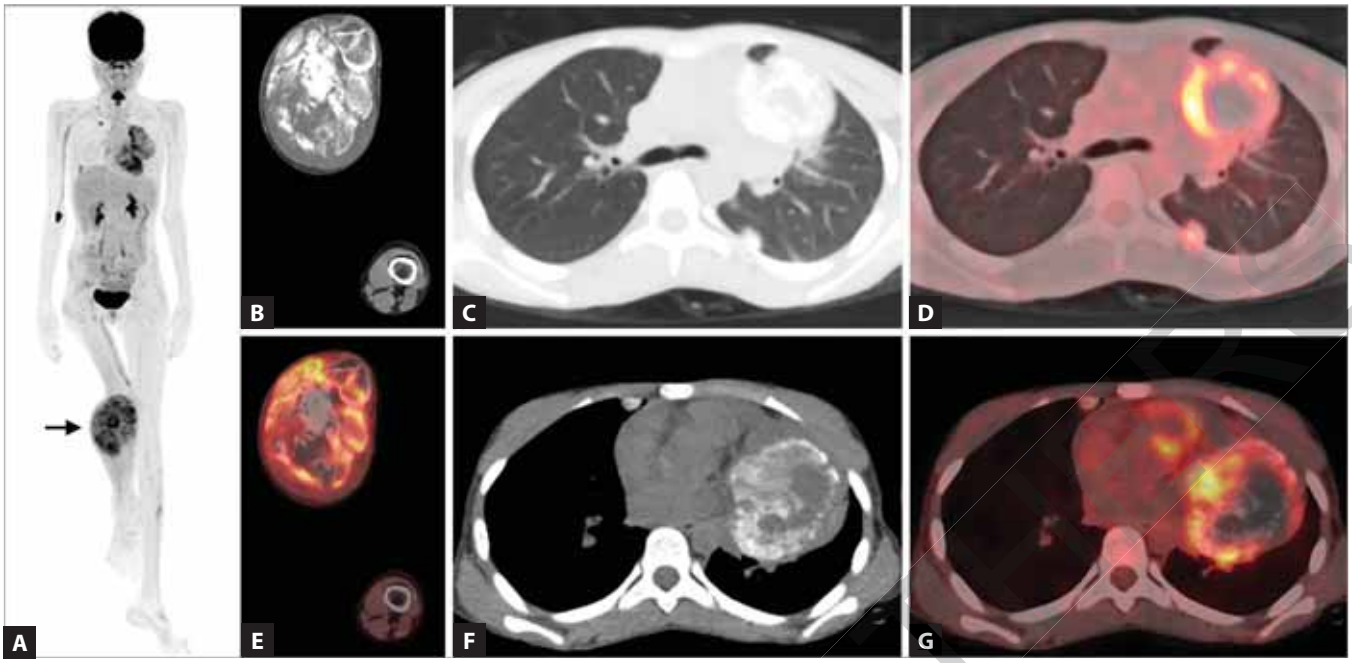
Primary Malignant Tumors

Bone scan has no role in the initial diagnosis or assessment of the extent of primary malignant bone tumors for which MRI is considered the imaging modality of choice. Rather, whole-body BS is generally reserved for evaluation of metastatic bone disease **(Figs. 5A and B)** in these patients. Calcified pulmonary metastases, especially in patients with osteosarcoma, are occasionally identified on BS as focally increased tracer uptake **(Fig. 5A)** that can be accurately localized using SPECT/CT. High-resolution CT is the mainstay for the evaluation of pulmonary metastases.

Functional imaging with FDG-PET provides unique information with regard to the metabolic activity of bone and soft tissue tumors **(Figs. 6A to G)**. This may help characterize indeterminate lesions and guide targeted biopsy of the most metabolically active area within larger tumors. This aspect is particularly important in many soft



Figs. 5A and B: A 16-year-old male with osteosarcoma of left femur. Planar bone scintigraphy (A and B) shows mass in left femoral shaft with heterogeneous tracer uptake (arrows), consistent with primary tumor. In addition, it showed bone metastasis (arrowhead) and osteogenic pulmonary metastasis.



Figs. 6A to G: (A) ^{18}F-FDG PET/CT maximum intensity projection images of patient with osteosarcoma of right tibia showing expansile heterogeneous FDG uptake the right knee region (arrow), axial CT and fused PET/CT images at the proximal shaft of right tibia showing FDG avid expansile primary (B and E). Axial CT (C and F) and fused PET/CT (D and G) images at the thoracic level showing multiple calcified masses and nodules (consistent with metastases).

tissue and bone tumors which are of mixed grade and/or cell type. In one study of soft tissue tumors, there was a statistically significant difference in SUV between benign and malignant lesions, although there was considerable overlap between the two groups and only lipomas and hemangiomas were consistently non-FDG avid.[30] Dual-time point PET imaging can be utilized to increase the accuracy of differentiating benign from malignant soft tissue lesions.[31] FDG-PET may also be used for more accurate staging of histologically confirmed tumors, in therapy response assessment to detect progression or response of disease ahead of morphological changes in the tumor and in the early detection of recurrent disease. The degree of FDG uptake by tumors pre- and post-therapy correlates well with histological response, often prior to demonstrable changes on anatomical imaging.[32] FDG-PET is also useful for the detection of tumor recurrence and has been found to be more sensitive than magnetic resonance (MR), especially when MR findings are equivocal.[33] SUV on FDG-PET is an important prognostic factor in most musculoskeletal tumors and has been shown to be a reliable independent prognostic indicator.[34,35]

Benign Tumors

Bone scan is a highly sensitive investigation for the diagnosis of osteoid osteoma. A negative bone scan virtually rules out the diagnosis of osteoid osteoma. A three-phase bone scan shows increased blood flow and blood pool and a "focal" area of intense uptake on delayed images.[36] Some surgeons have used intraoperative scintigraphic probes to localize osteoid osteoma. In addition, BS has been used for detecting recurrence after radiofrequency ablation of osteoid osteoma. Other benign lesions, which can show increased uptake, are aneurysmal bone cyst, chondroblastoma, enchondroma, etc. However, there is no specific pattern pertaining to these lesions on BS alone. With the availability of hybrid SPECT/CT, these lesions can be characterized with greater certainty by employing their CT characteristics.

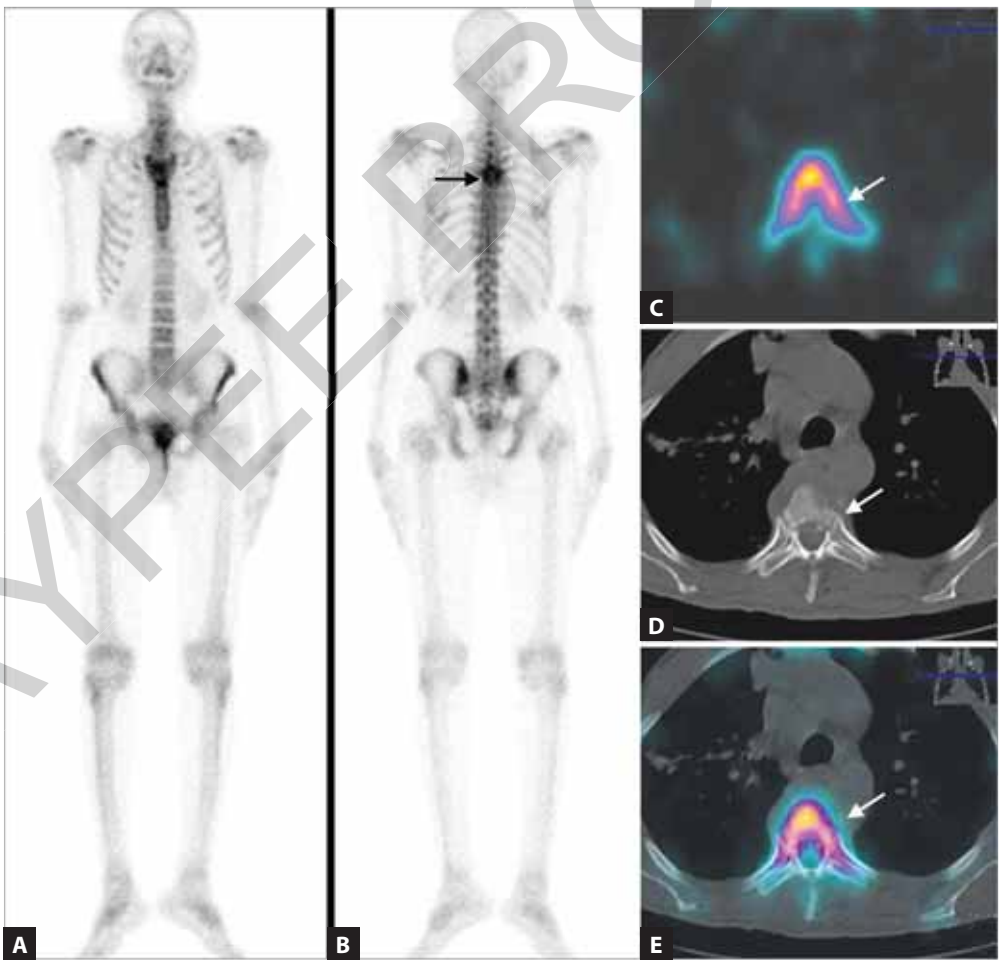
INFECTION IMAGING

Acute and Chronic Osteomyelitis

Bone scintigraphy is used as a complementary imaging procedure in the evaluation of infection. The classic findings are increased regional blood flow and blood pool with a corresponding increased uptake on delayed images. This is different from cellulitis where only increase in blood flow and blood pool in the soft tissue with no increased radiotracer uptake on delayed image is seen. ^{99m}Tc MDP has a high sensitivity (82–95%) and accuracy (90%) for detecting acute, uncomplicated osteomyelitis, becoming positive within 28–48 hours after the onset of symptoms. Compared with anatomic modalities, the radionuclide bone scan has the further advantage of detecting multiple foci of disease which can be seen especially in children. However, other conditions (e.g., fractures, neuropathic joints, and arthritis) may mimic osteomyelitis on bone

scanning alone, decreasing its specificity.[37] Although adding a fourth phase (24-hour image) is advocated to increase the specificity, with a high accuracy of 85%, the clinical results are not impressive.[38] In addition, in pediatric population, BS can show reduced radiotracer uptake, which is attributed to increased pressure on blood vessels, stripping away of periosteum via the accumulation of pus and interruption of blood supply due to plugging and thrombosis. This can lead to a false negative study. About 30% of patients with acute osteomyelitis will progress to have subacute or chronic osteomyelitis **(Figs. 7A to E)**. Bone scan remains positive for months even after successful treatment of acute osteomyelitis. It is difficult to differentiate healing from chronic active disease.[39]

Other radiotracer, such as ^{67}Ga-citrate and ^{111}In-oxine/^{99m}Tc-hexamethyl-propylene amine oxime (HMPAO)-labeled leukocyte imaging, has been extensively used in musculoskeletal infection, either alone or in combination with BS. ^{67}Ga-citrate localize to the site of infection via several pathway including increased vascular permeability at the site of infection, binding to lactoferrin and direct bacterial uptake.[40] Reported sensitivity for ^{67}Ga-citrate scintigraphy ranges from 25 to 80%, with a specificity of 67%.[41] It has proven to be extremely useful in detecting infection in the immunocompromised population. It is usually done in combination with BS for musculoskeletal infection. However, ^{67}Ga-citrate scintigraphy suffers from poor image quality, long scanning time, and significantly higher patient radiation dose leading to decline in its use with advent of better tracers. Labeled leukocytes can overcome some of the disadvantages of BS. Its uptake is dependent on the chemotaxis of labeled leukocytes at the site of infection. ^{111}In-oxine/^{99m}Tc HMPAO-labeled leukocyte imaging have shown increased specificity—upto 80–90%—compared to BS for detecting infection, particularly when complicating conditions are present. As the majority of leukocytes labeled are neutrophils, the procedure is most useful for identifying neutrophil-mediated inflammatory



Figs. 7A to E: A 35-year-old male with backache. (A and B) Planar bone scintigraphy showed increased irregular tracer uptake in D6 vertebra (arrow). SPECT (C), CT (D), and SPECT-CT (E) images showed destructive changes in D6 vertebra with increased tracer uptake along with paravertebral fluid collection (arrows). The findings were highly suspicious for tuberculosis and confirmed at histopathology.

processes, such as bacterial infections. It is less useful for those illnesses in which the predominant cellular response is other than neutrophilic, such as tuberculosis.[42] Additionally, in contrast to other locations in the skeleton, labeled leukocyte imaging is of limited value for detecting spinal osteomyelitis.[43] Also, their performance requires the withdrawal of a large amount of blood (50 cc); it is also costly, is labor intensive, and has the inherent limitations related to personnel safety, including the risks of infection and cross-contamination from handling blood products. All these factors limit their routine use. Additional use of SPECT/CT with BS, ^{67}Ga-citrate and ^{111}In-oxine/^{99m}Tc HMPAO-labeled leukocyte improves the specificity of these studies for detecting osteomyelitis.[44]

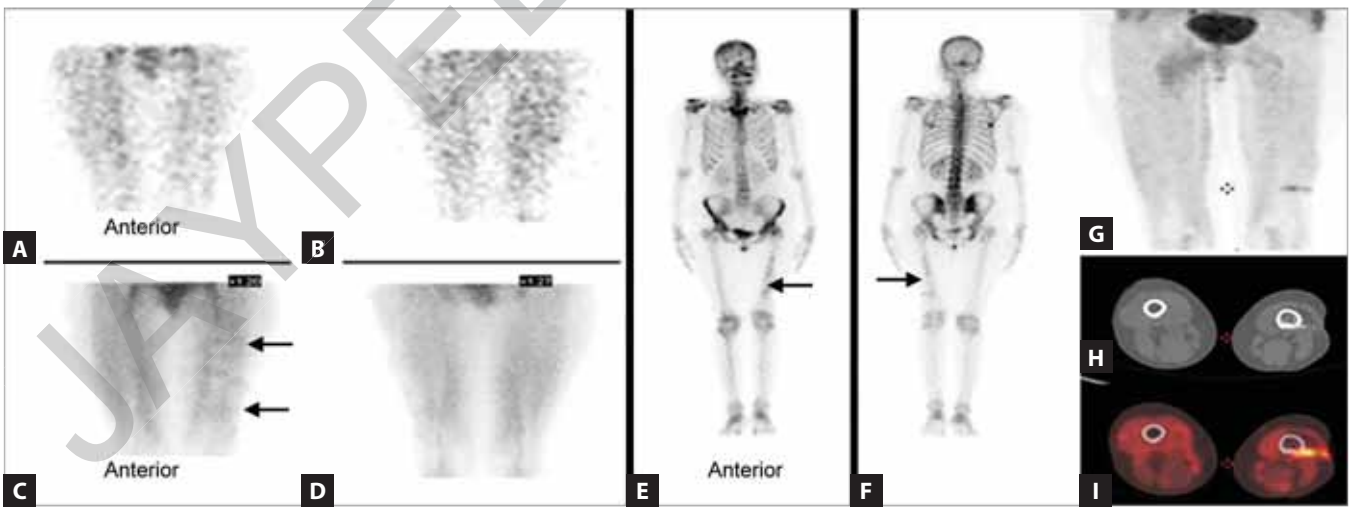
PET-CT-based radiotracers such as ^{18}F-FDG-labeled white blood cell (WBC) and plain ^{18}F-FDG are also being explored for infection imaging. These agents have shown better sensitivity and specificity than SPECT agents and are currently in use for infection imaging **(Figs. 8A to I)**.

Diabetic Foot

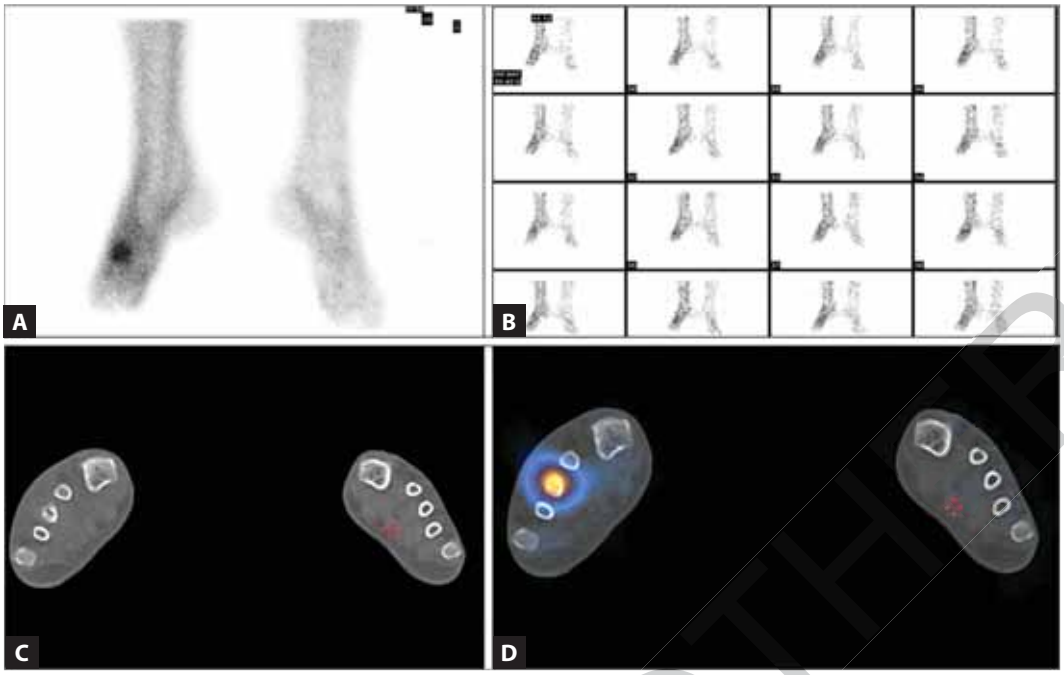
Pedal ulcers with or without osteomyelitis is a very common complication in patients with long-standing diabetes. Foot osteomyelitis frequently presents without systemic illness and with no obvious clinical symptoms or signs, besides the ulcer, and imaging studies are often needed to confirm the diagnosis. Although routinely performed, the accuracy of three-phase BS for pedal osteomyelitis is modest with large prospective study demonstrating a sensitivity of 67% and specificity of 43%.[45] With the presence of associated Charcot arthropathy, the diagnosis becomes more difficult. Addition of SPECT-CT in this scenario appears promising.[46] It can show focal bone destruction versus arthropathic changes, thereby clinching the diagnosis **(Figs. 9A to D)**. Labeled leukocyte imaging may be more sensitive for detecting clinically unsuspected pedal osteomyelitis and is useful for monitoring response to medical therapy.[47] But a major drawback is the fact that even neuropathic joints may accumulate labeled leukocyte; hence, it is not useful when both infection and Charcot joint coexist.[48]

Prosthetic Infection

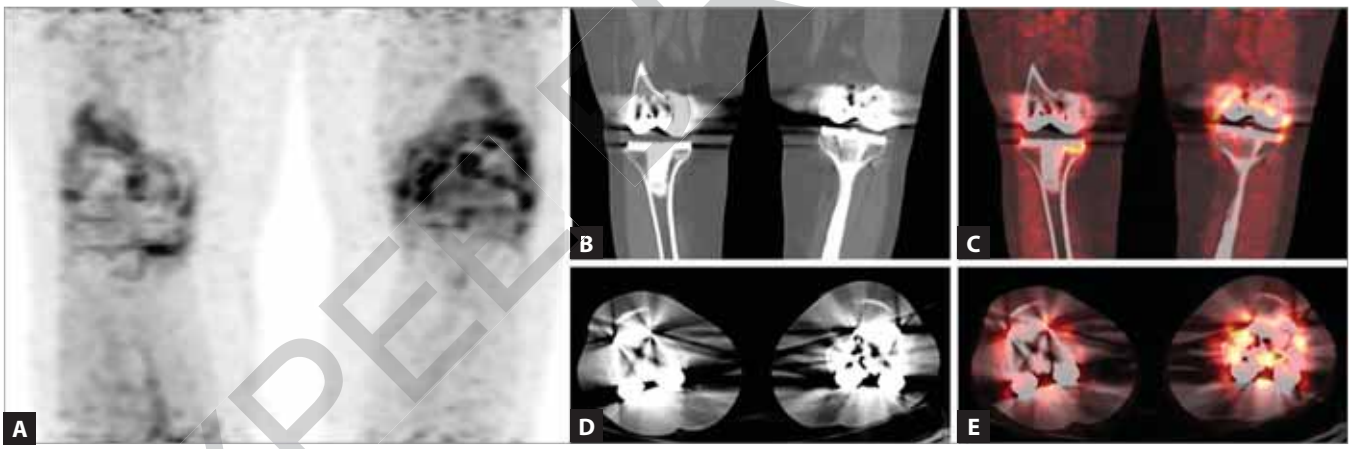
With improving surgical techniques and availability of better prosthetics, the number of patients opting for the same is increasing. Although the clinical results of joint replacement surgery are usually excellent, these implants do fail. Aseptic loosening due to mechanical factors and inflammatory reaction to prosthetic components is the most common cause for implant failure followed by infection. Infection is perhaps the most serious complication of joint arthroplasty, ranging in frequency from ~1–2% for primary implants to ~3–5% for revision implants.[49] Because their treatments are so different, the importance of distinguishing infection from aseptic loosening of prosthesis cannot be overemphasized. Although BS is sensitive for detecting complications of prosthetic surgery, it cannot reliably distinguish among the causes for failure. Although routinely advocated, periprosthetic uptake patterns are not too useful for differentiating infection from aseptic loosening.[50] Addition of ^{67}Ga-citrate scintigraphy to BS only provides



Figs. 8A to I: ^{99m}Tc MDP three-phase bone scintigraphy images (Flow A and B, soft tissue/blood pool phase—C and D, delayed phase E and F) and ^{18}F-FDG-PET/CT images (images G to I) of a 37-year-old female with chronic osteomyelitis of left femur. The flow phase images were within normal limits; however, pool showed mild increased radiotracer accumulation in the mid and distal thigh region and delayed phase images showed mild tracer uptake in the mid and distal shaft of femur. FDG-PET/CT was done to rule out infection which showed small area of increased radiotracer uptake in the cortex of distal shaft of femur with calcific changes and increased uptake in the adjacent bone suggestive of residual infection which was confirmed by biopsy culture.



Figs. 9A to D: 35-year-old male, known case of diabetic mellitus, having foot ulcer, referred for bone scan to differentiate between cellulitis and osteomyelitis. Blood pool (A) and blood flow (B) images show focal area of increased radiotracer uptake in distal foot region. Axial CT (C) and fused SPECT-CT (D) images showing involvement of right third metatarsal bone—consistent with osteomyelitis.



Figs. 10A to E: ^{18}F-FDG WBC PET/CT maximum intensity projection image of both knee joint showing increased FDG-labeled WBC accumulation around the prosthesis of left knee joint. Corresponding coronal (A) and axial images of CT (B and D) and fused PET/CT (C and E) show periprosthetic accumulation of labeled WBCs consistent with culture positive prosthetic infection.

moderate improvement in accuracy.[51] Labeled leukocyte scintigraphy though theoretically presents the advantage of differentiating aseptic loosening from infection, the actual results has been variable.[52,53] Poor sensitivity is ascribed to the chronicity of the process, whereas poor specificity is ascribed to nonspecific inflammation. Addition of BS or marrow scintigraphy might improve the specificity of this test, though there is no general consensus.[54] ^{18}F-FDG-labeled WBC scan and F-18 FDG-PET-CT are also used in these days for distinguishing aseptic and septic loosening **(Figs. 10A to E)**.

FDG-PET-CT for Musculoskeletal Infection

Experimental studies have shown that mononuclear cells and neutrophilic granulocytes have increased FDG uptake when activated during the so-called respiratory burst, which they experience while fighting an infection.[55] This forms the basis for its use in musculoskeletal infections. It provides better resolution and shorter test duration compared to conventional radionuclide procedures, albeit with higher cost and radiation exposure. It should also be remembered that FDG is not specific for

infection, and increased FDG uptake also is observed in inflammatory arthritis, osteoarthritis, fractures, normally healing bone, and degenerative changes.[56] For acute and subacute bone and soft tissue infections, sensitivities of 98% and specificities from 75 to 99% have been reported with FDG-PET.[57] It is especially useful in cases of chronic infections where BS has major limitations. It has been shown to be superior to labeled leukocyte imaging for chronic musculoskeletal infections.[58] Its specificity is higher, if recently (<4 months) traumatized or operated bone is excluded. Though initial results were excellent, FDG-PET-CT appears to be less useful for diabetic foot infection.[59] It is inferior to labeled leukocyte imaging for this purpose. Moreover, altered glucose and insulin dynamics in these patients makes FDG technically challenging. Regarding FDG-PET in patients with suspicion of joint prosthesis infection; initial studies showed promising results and reported sensitivities of 90% and specificities of 89% in the diagnosis of infected lower limb prostheses.[60] Accuracy of FDG-PET was 96% for hip prostheses, 81% for knee prostheses, and 100% for other orthopedic devices. However, when associated with loosening, FDG-PET cannot differentiate between septic and aseptic loosening, as both conditions can cause increased FDG uptake.[61] The reason for the increased FDG uptake around the prosthesis in aseptic loosening is likely an inflammatory immune reaction to the prosthetic material. In a large series, the accuracy of FDG-PET for diagnosing infection of the failed prosthetic joint was low, and varied between 47 and 71% depending on different criteria used to evaluate the images.[62] In fact, it was inferior to combined labeled leukocyte/marrow imaging in this series. It should be remembered that image interpretation in patients with prosthetic devices can be affected by attenuation-correction-induced artifacts. Therefore, it is necessary to examine the nonattenuation corrected scans because they show less prominent reconstruction artifacts.[63]

MUSCULOSKELETAL TRAUMA

Stress Fractures

Stress fractures are two types: (1) Fatigue fractures, which are caused by repeated abnormal stress on normal bones, bone scan shows fusiform increased radiotracer uptake involving the posterior tibial cortex and (2) insufficiency fractures resulting from normal stress on abnormal bone. The latter is seen in patients with underlying bone disease such as osteoporosis, osteomalacia, Paget's disease, and fibrous dysplasia. Because clinical assessment usually is not definitive in these injuries, diagnostic imaging is often required. Plain-film radiography is usually the first examination performed when a stress fracture is suspected. Unfortunately, sensitivity of this method for stress fracture may be as low as 15%.[64] BS, however, is extremely sensitive in detecting stress fractures because it assesses bone metabolism rather than bone anatomy **(Figs. 11A to C)**. In fact for stress fracture at certain sites such as metatarsal bones, it is considered to be the reference method. Sacral insufficiency fractures have a classic appearance on BS, highly specific pattern of horizontal uptake in the body of the sacrum and vertical uptake in the alae, resulting in the "Honda" or "H" sign.[36] Addition of SPECT/CT is likely to improve the accuracy of BS, especially by improving the anatomical localization.

Shin Splints

The clinical entity shin splints is characterized by exercise-induced pain and tenderness on palpation along the posteromedial border of tibia. It results generally from unaccustomed biomechanical stress on the tibia. Shin splints are not fractures and can be distinguished from stress fractures by their linear activity rather than round or fusiform activity.[65] In addition, blood flow and blood pool images are almost always normal. Delayed images of BS demonstrate involvement of the posterior tibial cortex, longitudinally oriented uptake involving one-third of the length of the bone **(Figs. 12A to G)**.

Fractures in Childhood

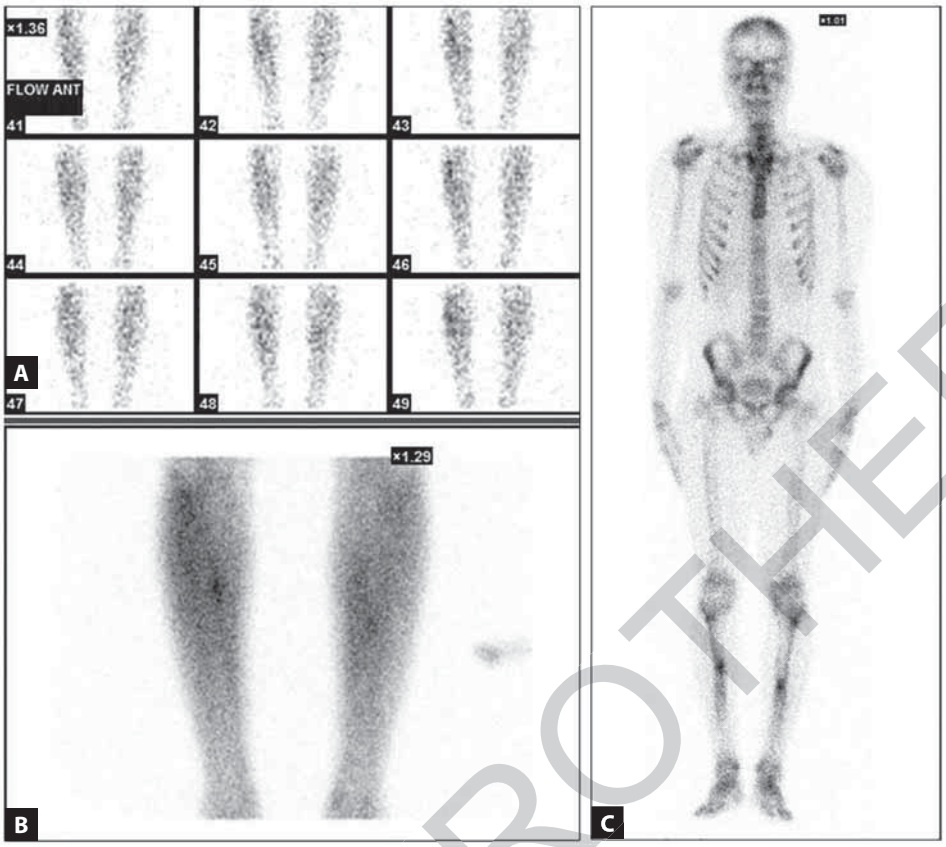
Very young children may present with failure to move a limb or joint. A history may not be available, especially in preschool children. Bone scans can identify unsuspected sites of fractures in such children. In addition, it can be useful to identify child abuse in children at risk. Radiological skeletal survey and whole-body scintigraphy does offer complementary information that is not available from either study alone.[66] More than 50% of such cases demonstrate diaphyseal injuries.[67] Rarely, fracture of the first rib may be the sole manifestation of abuse. Of course, knowledge of normal BS appearance for the age of child is essential for interpreting such a study.

Sport Injuries

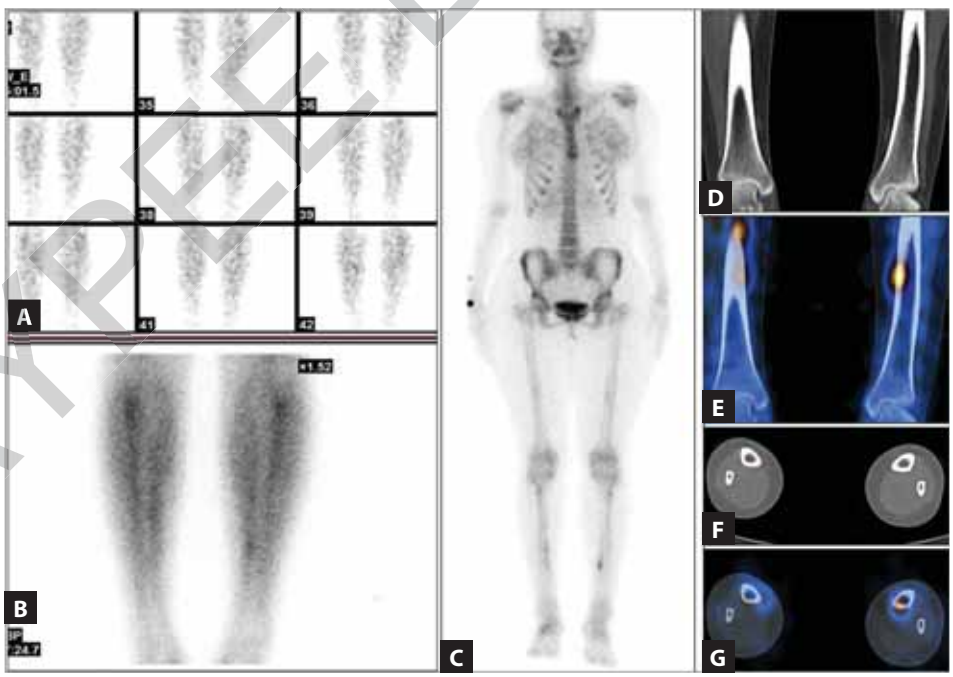
The blood pool phase of BS is very important in detection of soft tissue injuries. Hyperemia is evident in the affected structure with delayed uptake apparent only if there is necrosis/calcification or close apposition of adjacent bony structures, as with tendonitis of the extensor and abductor pollicis tendons and the adjacent radius or tibialis posterior tendonitis and the medial malleolus. SPECT/CT adds by anatomically localizing the site of involvement. It can in addition guide the site of injection, when required.

METABOLIC BONE DISEASE IMAGING

Metabolic bone disorders represent a heterogeneous group of skeletal pathologies that can lead to global or focal

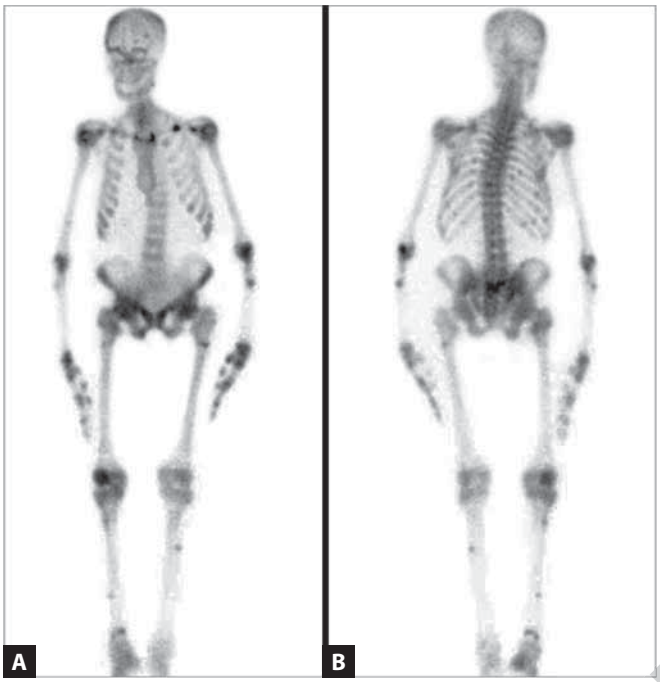


Figs. 11A to C: A 25-year-old active male complain of pain in bilateral leg, bone scan showed focal area of increased radiotracer in bilateral tibial region in flow (A), pool (B), and delayed static (C) images suggestive of bilateral stress fractures.



Figs. 12A to G: An 18-year-old sports female complains of pain in both legs. Flow (A) and pool (B) images show mild increased radiotracer uptake along the posterolateral border, also noted increased radiotracer along the posterolateral border in delayed static images (C) in addition to focal uptake. CT (D) and fused (E) coronal images, no changes noted on CT images; however, linear uptake noted in the right tibia and focal uptake in mid shaft of the left tibia. Transaxial CT (F) and fused (G) images, on CT, there is no change noted; however, focal uptake noted along the medial boarder of both tibia.

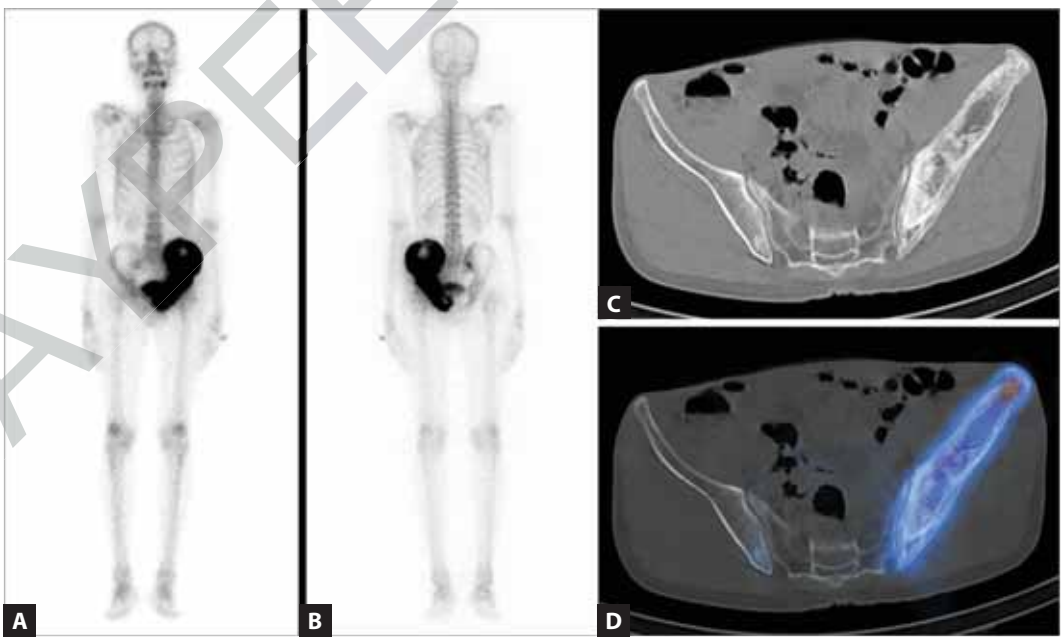
changes in bone metabolism. The superior sensitivity of BS can be valuable for diagnosis, detection of complications, and monitoring of treatment response **(Figs. 13A and B)**. The continuous improvement in gamma camera hardware and software with the addition of SPECT, and more recently, hybrid SPECT/CT, has maintained a role for nuclear medicine methods in bone disease despite the improvements seen in morphologic imaging techniques.



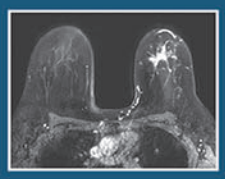
Figs. 13A and B: A 29-year-old female presented with multifocal body ache. Biochemical evaluation showed decreased serum calcium. (A and B) Planar bone scintigraphy images showed classical features of metabolic bone disease-increased bone to soft tissue activity, hot calvarium, tie sternum, nonvisualization of kidneys, and multiple pseudofractures classical for osteomalacia.

Paget's Disease

The initial step in Paget's disease is increased osteoclastic resorption, followed by compensatory osteoblastic activity and increased bone formation. Most patients with Paget's disease have polyostotic disease. Bone scans are a convenient way to evaluate the whole skeleton and has shown a greater sensitivity for detecting affected sites in symptomatic patients in comparison with radiographic skeletal surveys.[68] Characteristically, affected bones show intensely increased activity, extending from the end of a bone and spreading either proximally or distally, often showing a "V"-shaped leading edge **(Figs. 14A to D)**. Many different patterns describing vertebral uptake have been reported as being specific for pagetic involvement, including clover, heart, and Mickey Mouse signs.[69] Apart from localizing the sites of multifocal involvement, another important use of BS is monitoring response to therapy (bisphosphonates). For this purpose, BS is better than measurement of serum alkaline phosphatase alone. The bone scan appearances can be unusual after successful bisphosphonate treatment, resultant heterogeneous uptake sometimes mimicking metastatic disease. As ^{18}F-fluoride PET is better suited to assess bone mineral kinetics, it has also been used to monitor response to bisphosphonate therapy.[70]



Figs. 14A to D: A 57-year-old female complains of pain in the left hip. Anterior (A) and posterior (B) images show intense radiotracer uptake in the left iliac bone in delayed static images. Transaxial CT (C) and fused (D) images, on CT, there is lytic and sclerotic changes in left iliac bone noted. There is no other lesion in the rest of whole body bone scan.



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