Nuclear Medicine Imaging in Rheumatic Diseases

Yun Young Choi, Ji Young Kim
Department of Nuclear Medicine, Hanyang University Medical Center, Seoul, Korea

The rapid development of medical imaging technologies has greatly enhanced the utility of nuclear medicine imaging modalities over the last decade. Hybrid imaging technology merging computed tomography (CT) with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) allows superimposing the physiologic data obtained by SPECT or PET on the detailed anatomy of CT, yielding a better understanding of the disease status and improving diagnostic performance. However, the conventional whole body bone scan and three phase bone scan still have their own distinct role as diagnostic imaging, reflecting the changes of bone metabolism in benign and malignant diseases, including rheumatic diseases. A review of each nuclear medicine technique and clinical applications in various conditions of rheumatic diseases will be presented in this article. (J Rheum Dis 2017;24:4-13)

Key Words. Rheumatic diseases, Whole body bone scan, Three phase bone scan, SPECT/CT, PET/CT

INTRODUCTION

Bone is a dynamic organ, responsive to systemic and localized stress. Nuclear medicine imaging plays a crucial role in the diagnosis and management of various diseases, owing to its ability of reflecting the changes in bone physiology. Whole body bone scan using Technetium (Tc)-99m diphosphonate has been one of the most commonly performed nuclear medicine imaging procedure since the early 1970s [1-4]. Planar bone scan has many advantages in localizing active disease process, identifying increased physiologic activity, and evaluating pain, but still needs to overcome poor image resolution and lower specificity. Therefore, adding the information of perfusion status, three phase bone scan may enhance specificity in evaluation of inflammation and infection [5,6]. Single photon emission computed tomography/computed tomography (SPECT/CT) provides three-dimensional (3D) information (axial, coronal and sagittal images), and its ability to superimpose the physiologic data obtained by SPECT imaging on the detailed anatomy of CT improves the diagnostic performance [7].

The clinical use of positron emission tomography (PET)/CT with F-18 fluorodeoxyglucose (FDG) has rapidly increased particularly in oncologic diseases for a decade, and its utility in inflammatory diseases has also been proven [6,8]. F-18 sodium fluoride (NaF) is a bone imaging radiopharmaceutical, and F-18 NaF PET/CT may be useful in the metabolic evaluation of bone lesions and superimposed CT image provides precise anatomic information [9,10].

In this review article, clinical application of nuclear medicine imaging studies including conventional bone scan with blood pool images, bone SPECT/CT, and PET/CT in various conditions of rheumatic diseases will be discussed.

MAIN SUBJECTS

Whole body bone scan/three phase bone scan

1) Radiopharmaceuticals and imaging

Bone is heterogeneous calcified connective tissue consisting of about two-thirds mineral component made up
of amorphous calcium carbonate, calcium phosphate and crystalline hydroxyapatite, and one-third collagen, extracellular matrix and a variety of bone lining cells including osteoblasts, osteocytes, and osteoclasts [2]. Bone is constantly changing, with bone resorption and bone formation. Osteoblasts form an osteoid matrix which is later mineralized with hydroxyapatite crystals. Tc-99m diphosphonates makes chemical bonding (chemisorption) [11] and bind to the hydroxyapatite crystals and amorphous calcium phosphate, in proportion to local blood flow and osteoblastic activity. Tc-99m diphosphonates rapidly localize to bone, and time of imaging is about 2 ∼ 4 hours after intravenous injection of radiopharmaceuticals [12]. Three phase bone scan consists of flow, blood pool and bone phase images. The 1st phase is a radionuclide angiogram or flow study, reflects increased arterial perfusion. The 2nd phase is the soft tissue phase or blood pool phase, reflecting neovascularity (reactive granulation tissue or neoplastic angiogenesis), which may helpful to define the inflammatory activity of arthritis. The 3rd phase is the bone phase, which is taken 2 ∼ 4 hours after injection and reflects the osteoblastic activity [12-14]. Combined 2nd and 3rd phase of three phase bone scan, that is bone scan with blood pool phase (BSBP), may be useful in evaluation of rheumatic diseases, by giving informations about inflammatory activity and metabolic bone change.

Bone scan shows a higher sensitivity compared to radiographic images. Five percent change in bone turnover can be detected on bone imaging [5], while 30% ∼ 50% of mineral loss precedes radiographic changes on plain X-ray and CT images [13]. Bone uptake is increased for both osteoblastic and osteolytic process, such as tiny amount of bone destruction with osteoblastic healing process. Decreased uptake or cold defect can be caused by massive lytic process or disruption of blood flow including avascular necrosis [13].

2) Clinical applications

Rheumatoid arthritis is characterized by chronic persistent inflammatory synovitis [15]. Inflammatory neovascularization, increased capillary permeability, exudation of plasma proteins into the synovial stroma, and infiltration of cellular elements cause synovial inflammation leading to cartilage destruction, bone erosion and joint destruction [15,16]. Generally bone scan is more sensitive in reflecting disease activity than clinical and radiographic evaluation. In rheumatoid arthritis patients, BSBP seems able to provide information on periarticular bony structure as well as inflammatory synovitis through increased blood pool activity which is consistent with the pathologic features of rheumatoid arthritis [17]. In early

**Figure 1.** Early stage of rheumatoid arthritis. (A) Blood pool phase (upper row) shows increased uptake of both hands, wrists, ankles and mid-foot, and bone phase (lower row) shows increased periarticular uptake in the same joints, suggestive of active arthritis. (B) Plain radiographs of both hands and ankles show no definite abnormal findings suggesting arthritis. Combined bone scan and radiographic findings mean increased inflammatory activity without bone change, that is suggestive of early stage of inflammatory synovitis.
stage of arthritis, BSBP shows increased blood pool activity and/or increased periarticular bone uptake while plain radiography may show subtle periarticular osteoporosis (Figure 1). Even without erosive bone change, periarticular bone uptake increases due to anastomosis between epiphyseal vessels and inflamed synovial vascular network [18]. In advanced stage of arthritis or treated disease, severe joint deformity on plain radiography may show diminished radiotracer uptake on BSBP (Figure 2). Continued bone uptake after treatment could be due to persistent subclinical synovitis or to a true good clinical response with reactive osteoblastic repair [19].

Table 1. Manifestations of pathologic changes of synovial joints in rheumatoid arthritis on plain radiography and bone scan with blood pool phase (BSBP)

<table>
<thead>
<tr>
<th>Pathologic changes of synovial joint</th>
<th>Plain radiography</th>
<th>BSBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Blood phase</td>
</tr>
<tr>
<td>Normal synovial joint</td>
<td>Normal joint</td>
<td>–</td>
</tr>
<tr>
<td>Synovial inflammation, production of fluid</td>
<td>Soft tissue swelling, joint space widening</td>
<td>+</td>
</tr>
<tr>
<td>Hyperemia</td>
<td>Osteoporosis</td>
<td>++</td>
</tr>
<tr>
<td>Pannus destruction of cartilage</td>
<td>Joint space narrowing</td>
<td>+ ++</td>
</tr>
<tr>
<td>Pannus destruction of marginal bone</td>
<td>Marginal bone erosion</td>
<td>+ +</td>
</tr>
<tr>
<td>Pannus destruction of subchondral bone</td>
<td>Bone erosion, subchondral cyst</td>
<td>+ +</td>
</tr>
<tr>
<td>Fibrous and bony ankylosis</td>
<td>Bony ankylosis</td>
<td>+/−</td>
</tr>
<tr>
<td>Laxity of capsule, ligaments muscular contraction, spasm</td>
<td>Deformity, subluxation, dislocation, fracture, sclerosis</td>
<td>+/−</td>
</tr>
</tbody>
</table>

−: normal uptake, +: mildly increased uptake, ++: moderately increased uptake, +++: severely increased uptake.
tations of pathologic change of synovial joints in rheumatoid arthritis on plain radiograph and BSBP are summarized in Table 1. Tenosynovitis (Figure 3) and bursitis are similar inflammatory process occurs in the synovial lining of tendon sheaths and bursae, but usually lesser extent. Bursal involvement may occur in popliteal, olecranon, subdeltoid, and retrocalcaneal areas (Figure 4), while tenosynovitis is especially prominent in the dorsum of hand, fingers and the foot. Curvilinear increased blood pool activity along the tendon sheath or focal activity in bursa is typical on BPBS, whereas soft tissue swelling, subjacent cortical bone resorption beneath inflamed tendon sheath are characteristic radiographic findings. Focal increased blood pool and bone uptake at ligamentous and capsular attachments on BPBS could suggest possibility of enthesopathy, and clinical correlation is recommended.

In osteoarthritis, there is noninflammatory deterioration of the articular cartilage and reactive new bone formation and multiple microfractures at joint surfaces (subchondral sclerosis) and margins (formation of osteophytes), mainly in the joints with weight bearing or overuse [20]. The increased uptake is related to alterations in the rate of subchondral bone turnover and to growing and remodeling osteophytes (Figure 5). Degree of uptake is proportional to the severity of the disease [21].

Osteonecrosis is observed approximately 5% ~ 40% of patients with systemic lupus erythematosus. Although femoral head is the most common site of involvement, multiple osteonecrosis may be seen in humeral head, around both knees and ankles, appearing as multiple segmental increased uptake lesions on whole body bone scan (Figure 6) [22].

SPECT/CT

SPECT alone had been used in early 1980s, with diagnostic advantages of improved image contrast and more accurate localization of lesion compared to planar bone scan. While all overlapped layers of activity are superimposed, thereby obscuring some lesions on planar bone scan, the 3D cross sectional images of SPECT can remove

---

**Figure 3.** Tenosynovitis of tibialis posterior tendon and flexor digitorum longus tendon. (A) Blood pool phase (upper row) shows curvilinear increased uptake in left medial ankle (arrows), and bone phase (lower row) shows focal uptake in posteroinferior aspect of medial malleolus (arrow) and navicular tuberosity (arrow), suggestive of tenosynovitis of tibialis posterior tendon and flexor digitorum longus tendon. (B) Asymmetric subtle soft tissue swelling is seen in submalleolar area of left medial ankle. (C) Magnetic resonance imaging show diffuse enhancement along the tendon sheath (arrows), suggestive of tenosynovitis.

**Figure 4.** Retrocalcaneal bursitis. (A) Focal increased uptake in posterior aspect of both ankles on blood pool and bone phase, suggesting possibility of retrocalcaneal bursitis or Achilles tendinitis. (B) Diffuse infiltration in retrocalcaneal fat pad (arrows) suggests bursitis of both feet.
Figure 5. Osteoarthritis. (A) Focal increased uptake lesions in left 1st carpometacarpal joint and both 2nd ~ 5th distal interphalangeal joints of hands, superolateral aspect of right hip joint, left patellofemoral compartment and both medial compartment of knee joints. Those are characteristic findings of osteoarthritis associated with overuse or weight bearing. (B) Plain radiographs of right hip and both knees show degenerative sclerosis, joint space narrowing, and/or spur changes (arrows).

Figure 6. Multiple avascular necrosis around both knees in systemic lupus erythematosus. (A) Segmental increased uptake lesions are noted in both distal femurs and proximal tibiae (arrows), suggestive of multiple avascular necrosis. (B) Irregular calcification (arrows) and periosteal reaction (arrowheads) in both distal femurs are compatible with avascular necrosis in both distal femurs, and subtle sclerotic change is suspected in both proximal tibiae (arrows) on plain radiography. Multiple avascular necrosis may be often detected on whole body bone scan.
activity that originates from the areas surrounding the lesion of interest, then improves image contrast or lesion-to-background ratio. The hybrid SPECT/CT has further increased specificity compared with SPECT in clinical practice by conjoining the anatomical information provided by CT and permitting better characterization of equivocal lesions. It improves the accuracy of SPECT interpretation and leads to improve patient management. Bone SPECT/CT has been applied and enhanced diagnostic accuracy in various conditions including avascular

Figure 7. Conclusive diagnosis of temporomandibular (TM) joint arthritis on single photon emission computed tomography/computed tomography (SPECT/CT). (A) Planar bone scan shows suspiciously increased uptake in right TM joint area on right anterior oblique view (arrow). (B) Maximum projection image reconstructed from SPECT image shows focal intense uptake in right TM joint (arrow). (C) Focal increased uptake in right TM joint area is matched with joint space narrowing and cortical erosion on CT image.

Figure 8. Early detection of facet joint involvement in ankylosing spondylitis on single photon emission computed tomography/computed tomography. (A) There are uneven increased uptake lesions in T-L-spine on posterior whole body bone image. Lower portion of both sacroiliac (SI) joints also show mildly increased uptake. (B) Increased uptake in both SI joints, matched with joint space widening, erosion and sclerotic changes are suggestive of bilateral sacroilitis on axial image. Focal increased uptake in L-spine are located in facet joints, but without definite anatomic change on sagittal and coronal images.
necrosis of femoral heads, temporomandibular joints (Figure 7), sacroiliac joints and spines in ankylosing spondylitis (Figure 8), spondylolysis, arthropathies of appendicular bone, and musculoskeletal infection [23-25]. Compared to interpretation with planar bone scan alone, additional SPECT/CT imaging of focal abnormal uptake lesion detected on planar bone scan may enhance the diagnostic accuracy and contribute to the understanding of disease status in rheumatic diseases (Figure 9).

**PET/CT**

F18-FDG is a glucose analogue that is taken up in cells by the glucose transporters on the cell membrane and then phosphorylated to 18F-FDG-6-phosphate. Unlike glucose, it is not further metabolized and trapped in the cytosol. Thus, the amount of intracellular 18F-FDG-6-

---

**Figure 9.** Early detection of C-spine involvement of rheumatoid arthritis on single photon emission computed tomography/computed tomography. (A) Planar whole body bone scan image shows arthritis involvement of both wrists and another focal uptake lesion in right side of upper C-spine (arrow). (B) No definite abnormal findings but straightening of C-spine curvature was reported on plain radiograph. (C) Focal uptake lesion is localized in right skull base-C1 right lateral facet and C1-C2 right lateral facet (arrows), suggestive of arthritis involvement.

**Figure 10.** Characteristic entheses inflammation of polymyalgia rheumatica (PMR) detected on F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT). (A) Increased FDG uptake around both shoulders and both proximal femurs (arrows) are noted on maximum intensity projection image, suggestive of active inflammatory process. (B) Coronal and axial PET/CT images show focal increased uptake mainly in entheses (arrows), around both shoulders, hips, pubic symphysis, and ischial tuberosity, which is characteristic areas of inflammation in PMR.
phosphate is related to glycolytic activity. Tumor cells overexpress surface glucose transporters and usually have higher glycolytic activity than normal cells leading to increased 18F-FDG uptake [26]. F-18 FDG can also accumulate in neutrophils, macrophages, and activated lymphocytes. Increased FDG uptake in inflammation seems to be associated with several factors: 1) increased number of glucose transporters and an increased expression of the serum glucose transporters by activated inflammatory cells, 2) increased affinity of the glucose transporters for FDG in inflammation, probably secondary to the effects of circulating cytokines and growth factors [8,27]. FDG competes with glucose, patient preparation generally includes fasting overnight of at least 4 ~ 6 hours before injection of F-18 FDG. PET/CT imaging is performed about an hour after injection.

FDG uptake in the normal bone marrow is low, which may facilitate the distinction of inflammatory cellular infiltrates from normal marrow uptake. Degenerative bone changes usually do not show increased FDG uptake. FDG uptake normalizes fairly quickly following trauma or surgery, usually within 3 ~ 4 months. Some limited studies have been reported in rheumatic diseases in assessing disease activity in rheumatoid and psoriatic arthritis [28], and in evaluation of treatment response in rheumatoid arthritis of hands and feet [29], prediction of prognosis in large joints of rheumatoid arthritis [30,31], and in differentiation between polymyalgia rheumatica and elderly onset rheumatoid arthritis [32]. In polymyalgia rheumatica, abnormal FDG accumulation is usually found around the entheses of shoulder girdle, pelvic girdle, vertebral spinous process, and sternoclavicular joint (Figure 10). F-18 NaF is a tracer that accumulates in the bone similar to Tc-99m diphosphonate agents, proportional to regional blood flow and the rate of bone turnover. Because of its rapid renal clearance as well as fast accumulation in bone, high bone to-soft tissue contrast can be obtained within an hour after tracer injection, compared to 3 ~ 6 hours for the Tc-99m diphosphonate agents [33,34]. F-18 NaF PET/CT is emerging recently owing to the better image quality by desirable kinetics of 18F-fluoride, easy accessibility due to world-wide distribution of PET/CT scanner compared to SPECT/CT scanner, shorter imaging time with comparable radiation dose, and shorter waiting time of patients (Figure 11) [35].

**CONCLUSION**

By reflecting inflammatory activity, whole body bone scan with blood pool phase image may enhance the diagnostic performance of rheumatic diseases, especially with early synovial inflammation. In addition to the anatomic information acquired from plain radiographs, proper interpretation of BSBP may upgrade the understanding of disease status of each patient. SPECT/CT studies are gradually increasing owing to improved diagnostic accu-

---

**Figure 11.** Early arthritis involvement of multiple facet joints in ankylosing spondylitis detected on F-18 NaF positron emission tomography/computed tomography (PET/CT). (A) Multifocal increased uptake lesions are located mainly in posterior elements of C-T-L-spine on maximum intensity projections (MIP) images of PET/CT. Both sacroiliac (SI) joints are unremarkable. (B) Focal uptake lesions detected on MIP images are located in costovertebral junctions, facet joints, and enthesis of right anterior pubic body on axial PET/CT images (arrows). Both SI joints are not involved.
racy by providing detailed anatomic information in areas of physiologic/metabolic bone changes on SPECT. PET/CT imaging with F-18 FDG and F-18 NaF shows better image quality, provided more confirmative diagnostic information, and will be promising imaging modality in diagnosis and management of non-oncological skeletal diseases including rheumatic diseases.

CONFLICT OF INTEREST
No potential conflict of interest relevant to this article was reported.

REFERENCES

33. Li Y, Schiepers C, Lake R, Dadparvar S, Berenji GR. Clinical