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Nuclear Medicine in Musculoskeletal Disorders: Clinical Approach

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1. Introduction

Nuclear medicine supplies with functional perspective in the diagnosis of different pathologies of the musculoskeletal system. Bone scintigraphy is one of the most used nuclear medicine techniques in our clinical practice for location, evaluation and diagnosis of these pathologies because of its high sensitivity. This technique identifies functional changes before structural lesions have been established. For the study of musculoskeletal disorders, the usage of three-phase bone scintigraphy is applied more often than conventional bone scintigraphy. However, due to its low specificity, it has been replaced by other techniques such as magnetic resonance imaging (MRI) in the evaluation of localized lesions. New techniques in nuclear medicine which provide precision with high sensitivity are currently available, such as single-photon emission computed tomography (SPECT), useful in the evaluation of lumbar and hip pathology, or the presence of inflammation in small joints (hands and feet), and positron emission tomography (PET), which provides a metabolic imaging. Several radionuclides can be used in the scintigraphic evaluation, although the most commonly used for bone scintigraphy are labelled with technetium 99-m (99mTc), standing out diphosphonate compounds such as methylene diphosphonate (MDP). This radiopharmaceutical (Tc-99m-MDP) is used for studying metabolic bone diseases like Paget´s disease, transient osteoporosis and reflex sympathetic dystrophy. And it is also useful in the location of polytopic forms of avascular osteonecrosis, in the study of hidden painful radiologic bone lesions such as osteoid osteoma or others bone tumours, in the evaluation of soft-tissue lesions, and in the assessment of spread pattern of bone metastases. Furthermore, this radionuclide may locate bone fractures, identify the cause of pain in patients with chronic pain after arthroplasty, show the evolution of heterotopic ossification and provide information about musculoskeletal system infections (in combination with other radionuclides) and paediatric diseases. Other radionuclides commonly used in the evaluation of infectious or inflammatory processes in the musculoskeletal system are gallium citrate and indium 111-labelled leukocytes, since the latter increases the specificity of technetium radiotracer. Local treatments can be applied by radio isotopic techniques. One of these is radiosynoviorthesis, used in the treatment of patients with persistent monoarthritis in different stages (from inflammatory poliarthritis to pigmentary villonodular sinovitis).

The objective of this chapter is to make a simple but detailed review of the main nuclear medicine clinical applications in the appraisal and management of musculoskeletal problems.

2. Normal bone scintigraphy

Bone scan is a diagnostic technique used to assess the presence of anomalies in the distribution pattern of bone formation. It has high sensitivity, but specificity is frequently variable or limited. Three-phase bone scintigraphy is currently the most used technique because it allows evaluating the degree of hyperemia (flow phase), increased of articular permeability (blood pool phase) and the presence of alterations in bone remodeling (bone tissue phase). Traditional technique is based on the biological properties of bisphosphonates marked with 99mTc, usually MDP, when they are integrated into the bone metabolism after intravenous administration. Typically, 30% of the injected dose of Tc-99m-MDP remains in the skeleton, and most of bone uptake occurs in the first hour. The remainder is eliminated from the tissues and blood by the kidneys and imaging is obtained 3 – 4 hours later. In general, uptake of the tracer depends on local blood flow, osteoblastic activity and extraction efficiency. Normal scintigraphy imaging depends on technical equipment and employees, but it is also significantly influenced by other factors such as age and constitution of the patient, intake of drugs, degree of hydration, renal function and/or the presence of impaired circulation. Therefore a whole body study is recommended, with anterior and posterior screenings that allows assessing the symmetry or asymmetry in the distribution of the drug. However, a located study may be sufficient in some cases, since provides greater image quality and requires less time and is less expensive. In other patients, especially when a spine study is necessary or avascular osteonecrosis located in the hip or knee is suspected, it will require a SPECT, that is more sensitive for detecting abnormalities and provides, combined with tomography, three-dimensional images.

It is necessary to have knowledge of normal variants and patterns of abnormality to minimize misinterpretation. Whole body bone scan shows normal variations in the uptake of the radiotracer, as this is higher in areas with high bone remodeling. The age of the patient has a fundamental role in the appearance of the scan, especially during the growth period and in the elderly. In children, as they have a growing skeleton, there is a diffuse bone uptake and a striking uptake at the growth plates of bones, especially in metaphyseal-epiphyseal areas of long bones and cranial sutures. This decreases over the years until complete fusion of the epiphyses takes place. On the other hand, bone scan images are often of poor quality in old people. Aging may be reflected in scintigraphic images by a diffuse reduction of bone uptake of the radioisotope, although diffuse uptake at the dome or symmetrical uptake in the peripheral joints (secondary to osteoarthritis) may be present. Associated degenerative processes may lead to increased uptake in the involved joints. Obese people also get lower quality images. In addition, insufficient hydration and/or renal failure hamper the radiopharmaceutical removal of soft tissues and modify the end result.

The sternum and the sacroiliacs joints are normal uptake areas in scintigraphic studies (**Fig. 1**). Other areas that may appear as normal increased uptake (**table 1**) are forewings of the iliac bone, coracoid process, tip of the scapula and, sometimes, costochondral junction, lower portion of the cervical spine, kneecaps and some muscle attachments. Thoracic kyphosis and lumbar lordosis may cause the parts of the column that are farther away, appear as less warm. In patients with scoliosis, concave side usually appears hotter than the convex. There is also a physiological uptake located at renal pelvis and the bladder, since radiotracers are eliminated by the kidneys (Murray, 1998; Schneider, 2006).

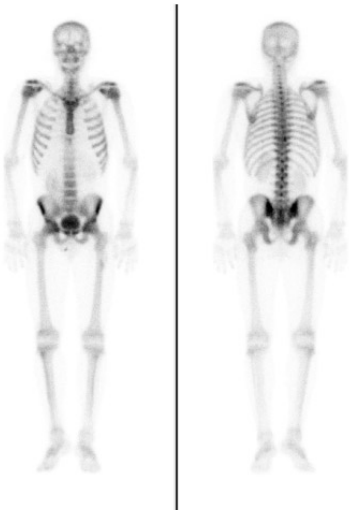


Fig. 1. Normal bone scintigraphy.

Head and neck:	Skull sutures, pterion, occipital protuberance, angle of mandible, hyperostosis frontalis, sinuses (ethmoidal and maxillary), dental disease and microcalcification of thyroid cartilage
Thorax:	Sternoclavicular joint, acromioclavicular joint, sternal foramina, costochondral uptake, manubrium sternum/xiphisternum, tip of scapulae, symmetrical muscle insertion in the posterior ribs of paraspinal muscles (stippled appearance)
Abdomen and pelvis:	Kidney, bladder, bladder diverticulae, pelvic diastasis (post partum women)
Long bones:	Deltoid tuberosity/deltoid insertion, trochanteric bursitis

Table 1. Normal Variants of uptake on 99mTc-MDP Bone Scan.

Many causes may lead to false pathologic imaging or pitfalls (Naddaf et al., 2004). Bladder diverticula or bladder image over pubic bones, urine leakage or urinary retention and patient rotation are some common examples. Artifacts on bone scintigraphy can be technical or patient-related (**Table 2**). The technical artifacts include equipment, radiopharmaceutical, and image processing-related problems. Equipment-related artifacts may be due to inadequate quality-control procedures and calibration. Faulty radiopharmaceutical preparation alters biodistribution and can compromise the diagnostic quality of the images. Increased tracer uptake in the stomach, thyroid, and salivary glands can be seen if there is free pertechnetate, in the radiopharmaceutical. A number of factors, for example, presence of reduced aluminum ions, if the radiopharmaceutical is left unused for a long time, inappropriately high pH and addition of dextrose solutions, may affect uptake of radioactivity in bone.

Finally, the most common artifact on the bone scan is due to extravasation at the site of injection, that may occasionally cause confusion with a bone abnormality, and it is therefore important to document the site of injection in all patients. Further, ipsilateral lymph node(s) may be seen due to extravasation of radiotracer and can on occasion cause confusion,

Radiopharmaceutical:	Free pertechnetate (stomach, thyroid, salivary glands)
Technical:	Injection site, lymph node (radiotracer extravasations), injection into central venous catheter, arterial injection
Patient:	Urine contamination, patient motion, breast prosthesis, metallic prosthesis (elbow, shoulder, knee and hip)
Metallic:	Belt buckle, medallion, jewellery, pace maker
Instrumentation:	Photomultiplier tube, cobalt peak, image contrast
Treatment:	Postradiotherapy

Table 2. Common Artifacts in Bone Scintigraphy.

particularly if overlying the scapula or a rib (Gnanasegaran et al., 2009). Photon-deficient areas commonly seen on the bone scan are due to metallic objects. Patients should be asked to remove metallic objects wherever possible before performing the scan. Urinary contamination is a common problem, which may simulate focal lesions, especially if close to or overlying the bone. It is useful to remove the clothing or to wash the skin and reimage the patient around the region of interest to avoid any confusion. The patient should void before the study and rarely delayed imaging or bladder catheterization may be required. Further, radioactive urine in the bladder is a frequent cause of artifact in patients evaluated with SPECT for pelvic metastases (prostate cancer) or low-back pain. Increased radioactive urine in the bladder can cause streak artifacts on the reconstructed images and overlap bony structures. Further, intense tracer retention in the bladder is reported to cause pixel overload, resulting in a relatively cold area close to the region of interest of the femoral heads, which hinders its interpretation.

3. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disease of unknown origin, with an overall prevalence of 1%. It mainly affects joints with symmetrical and polyarticular pattern and may lead up to progressive structural damage, functional disability and extra–articular complications. It can affect many organ systems and it is also associated with a higher prevalence of other diseases such as infections, neoplasms and cardiovascular disease. It has been shown that 50% of patients with RA are disabled within 10 years of onset of disease and survival is reduced (Malviya et al., 2010; as cited in Solomon et al., 2003, Wolfe et al., 1994, 2002, 2003).

Conventional radiology is the most wide-spread technique for the appraisal of RA, since it allows the evaluation of the presence or absence of erosions, joint space narrowing or articular osteopenia, but only when symptoms have been present for several months or years. The importance of early diagnosis in patients with RA, based on the possibility of modifying the prognosis with an early treatment, has led to the introduction of new techniques that identify the characteristic changes in an accurate and reliable way. MRI and High-Frequency Ultrasonography (US) have shown their reliability for detecting early bony, vascular and soft tissue changes in patients with RA and are the techniques most commonly used with this aim. Nuclear medicine techniques, such as imaging with nanocolloids, PET or three-phase bone scintigraphy may also be useful in this field. Three-phase bone scintigraphy is still used in clinical practice in patients with RA because it allows the detection of changes (hyperemia, increased permeability, altered bone metabolism) before the structural lesions appear, and may display the pattern of joint involvement and even predict the development of erosions (Colamussi et al., 2004; as cited in Mottonen et al.,

1988). The intensity of uptake on scintigraphy is correlated to some clinical and laboratory indexes of disease activity (De Leonardis et al., 2008; as cited in Park et al., 1977) and the monitoring during treatment can evaluate the effectiveness of it (De Leonardis et al., 2008; as cited in Palmer et al., 1993; Elzinga et al., 2010). It is also a useful technique when an additional pathology (eg, osteonecrosis, stress fractures or metastatis) is suspected. Furthermore, in patients with nonspecific polyarthralgia, normal bone scan excludes the presence of active arthritis (Colamussi et al., 2004; as cited in Shearman et al., 1982). It is a sensitive tool but not highly specific, and may be altered in other diseases such as osteoarthritis. Nevertheless, planar bone scintigraphy is clearly less sensitive than SPECT in the evaluation of early stages of this disease or mild abnormalities. Multipinhole SPECT of the hands has been used to identify patients with minimal changes in bone metabolism (Gotthardt et al., 2010). This technique proven to equal MRI in sensitivity and also detected increased bone metabolism in two patients in whom MRI had negative results, demonstrating that multipinhole SPECT may be even more sensitive than MRI in some cases (Gotthardt et al., 2010; as cited in Ostendorf et al., 2010). PET may also be used for imaging of synovial inflammation. The most commonly used radiotracer in clinical PET scanning is fluorodeoxyglucose (18F-FDG), and since inflammation is a glucose-avid oxidative process, 18F-FDG-PET allows a quantitative measurement of the uptake of tracer concentration with a positive correlation with the degree of joint inflammation in patients with RA. Recently, it has been demonstrated its correlation with parameters of disease activity (swelling, tenderness, serum markers) and findings from gold standard techniques such as US and MRI. This quantitative assessment could be useful for evaluating the therapeutic effectiveness. Besides 18F-FDG, tracers such as 11C-choline may be used for measurement of cell proliferation and evaluation of synovitis with high accuracy (Gotthardt et al., 2010; as cited in Roivainen, 2003). Other techniques, including the imaging of sinovitis with 99mTc-nanocolloids, have shown high sensitivity and specificity in this field. Thus, nuclear medicine techniques, especially PET and multipinhole SPECT of small joints, may play a role in identifying RA at an early stage, but the usefulness of these techniques compared with MRI and US needs to be proven in RA imaging. Currently, US and MRI are the techniques of choice for serial assessments of patients with RA due to practical reasons and the required exposure of the patient to radiation in the nuclear medicine studies. Large systematic prospective studies on the efficient use of imaging modalities to assess the efficacy of treatment in early RA are lacking. Nevertheless, new imaging modalities are assuming an important role in the investigation and management of RA. Tagging important cellular and protein mediator may allow us improving the knowledge of RA pathophysiology. In recent years, the use of labelled immunoglobulins (Igs) that head for areas of inflammation and where they stay accumulated (aspecific polyclonal IgG-type antibodies labelled in most cases with Tc-99m), has been developed (**Table 3**).

mAbs	Type	Class	Isotope	Target
Infliximab (Remicade)	Chimeric	IgG1	99mTc	TNF-α
Adalimumab (Humira)	Fully human	IgG1	99mTc	TNF-α
Rituximab (Rituxan/Mabthera)	Chimeric	IgG1	99mTc	CD20
MAX.16H5	Murine	IgG1	99mTc	CD4
1.2B6	Murine	IgG1	111In	E-selectin
OKT-3 (Muromonab)	Murine	IgG2	99mTc	CD3

Table 3. Molecular imaging of RA by radiolabelled monoclonal antibody (mAbs).

The immunoscintigraphy has proven to be more sensitive than clinical examination for identifying synovitis and have a high positive predictive value for the onset of RA in patients with nonspecific arthropathy, and its usefulness for monitoring and assessing treatment response (Colamussi et al., 2004; as cited in De Bois et al., 1995a, 1995b, 1996). It can also be used to detect infection, although the preferred technique in these cases is labelled leukocyte scintigraphy, in which two tracers are often used: 99mTc-HMPAO or 111In-oxine (De Gersem & Jamar, 2010). Labelled leukocyte scintigraphy is also useful in assessing therapeutic response in RA patients and it has been correlated with other indices of activity in this disease (Collamussi et al., 2004; as cited in Al-Janabi et al., 1988). However, immunoscintigraphy seems to be more accurate than labelled leukocyte scintigraphy for the identification of synovitis in RA (Collamussi et al., 2004; as cited in Liberatore et al., 1992).
Other molecules and receptors (e.g. 64Cu-labelled anti-GPI, 68Ga-labelled annexin V or 123I-antileukoproteinase) are being identified as therapeutic targets and used to develop new radiopharmaceuticals which accumulate in areas of inflammation where they can be located and quantified. Their study and description will allow improving the understanding of the complex pathophysiology of RA and detecting changes in very early stages of this disease and will give us the possibility of a pre-therapy scintigraphic approach with radiolabelled monoclonal antibodies that will let us evaluate the presence of target molecules in the inflammatory lesion, thus helping in the selection of the most efficient therapy and predicting therapy response (Glaudemans et al., 2010; Malviya et al., 2010). But currently, these techniques are not used in clinical practice and remain like a research tool inside selected laboratories. Bioluminescence and fluorescence reflectance imaging are other approaches that allow imaging, and potentially the delivery of therapeutic agents at a molecular level (McQueen & Ostergaard, 2007).

4. Sacroilitis

Sacroiliac joint involvement is a common finding in the spondyloarthropathies (SpA) group and it is an important parameter included in the diagnostic criteria. Conventional radiology is essential in the evaluation of the sacroiliac joints, but it does not detect early abnormalities and, therefore, the use of other complementary techniques currently available, such as CT, MRI, US, and bone scintigraphy, is necessary to avoid delaying the diagnosis.
Until only a few years ago, bone scintigraphy was the gold standard technique for early diagnosis of inflammatory processes at this joint. The assessment of sacroilitis by scintigraphy is based on the quantification of radiotracer uptake in the sacrum and sacroiliac joints. This technique can help to differentiate between degenerative and inflammatory disorders in patients with nonespecific radiological changes. Both conventional bone scintigraphy and SPECT mode are sensitive techniques for early detection of SpA in patients with low back pain and who still do not have typical radiological changes, because the uptake of radiopharmaceutical at sacroiliac joints is produced before structural damage happens. However, in the sclerotic phase of evolved SpA, scintigraphy frequently does not detect any abnormalities. MRI, more sensitive in detecting early changes and more specific, has shifted to the bone scan. In this regard, a published review (Schneider, 2006; Song et al., 2008) realized with the aim to assess the diagnostic value of scintigraphy for detecting sacroilitis in patients with established and/or probable ankylosing spondylitis, has proven limited value of scintigraphy both in the early detection of sacroilitis and in patients with established ankylosing spondylitis. In patients with SpA and gastrointestinal symptoms but

negative endoscopic or radiological test results, abdominal scintigraphy with labelled leukocytes can be used to assess the abdominal involvement (Colamussi et al., 2004; as cited in Elkayam et al., 2002).

5. Infection

In the setting of infection four entities can be established: osteomyelitis, septic arthritis, soft tissues infections and joint replacement infection.

5.1 Osteomyelitis

Osteomyelitis is defined by infection localized to bone. It can occur as a result of hematogenous seeding, contiguous spread of infection to bone from adjacent soft tissues and joints, or direct inoculation of infection into the bone as a result of trauma or surgery (Lalani, 2011). Three-phase bone scan with 99mTc-hydroxymethylene diphosphonate or Tc-99m-MDP has long been used as the standard method for the detection of osteomyelitis (Gotthard et al., 2010), and positive focally increased uptake on all three phases (**Fig. 2**) is usually seen (Love et al., 2003).

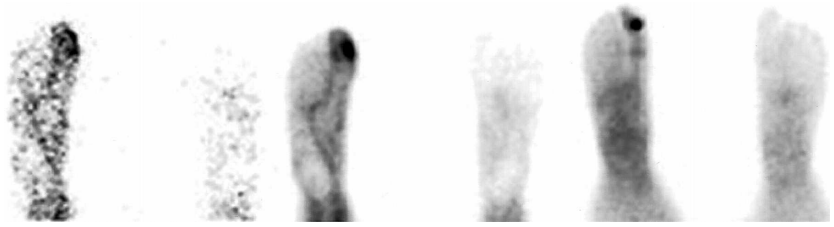


Fig. 2. Three-phase bone scan: Focally increased uptake on all three phases in a patient with osteomyelitis of the right great toe.

In contrast, in the setting of cellulitis there is increased activity only in the first two phases and normal or mild diffuse increased activity in the third phase (Brown et al., 1993; Horwich, 2011). Radiographic studies do not show any change for at least 1- 2 weeks after initial infection, contrary to the three-phase bone scan where imaging of the infection can be seen in the first 24 - 48 hours of the infection (Díaz & De haro, 2005). Bone scintigraphy has a high sensitivity exceeding 80% and a limited specificity reaching up to 50% (Gotthard et al., 2010, as cited in Hakim et al., 2006; Palestro et al., 2002). The limited specificity can be explained by uptake of the radiopharmaceutical at all sites of increased bone metabolism irrespective of the underlying cause. Other conditions such as tumors, fractures, joint neuropathy may mimic osteomyelitis at three-phase bone scintigraphy. To improve specificity, complementary imaging with gallium-67 (67Ga) citrate (for spinal infection) or indium-111-labelled autologous leukocytes (for the appendicular skeleton) is often performed (Love et al., 2003).

Gallium scans utilize the affinity of gallium-67 to acute phase reactants (lactoferrin, transferrin, and others) to demonstrate areas of inflammation that may be related to infection (Horwich, 2011). Intense uptake on 67Ga bone scintigraphy in two adjacent vertebrae with loss of the disc space is highly suggestive of spinal osteomyelitis (Palestro & Torres, 1997). This method is quite sensitive and more specific than three-phase bone scan (Horwich, 2011; as cited in Palestro, 1991; Tumeh, 1986). It is typically performed 24 hours following inyection and therefore should be reserved for patients who are clinically stable and do not require prompt

imaging results for urgent management decisions. Gallium not only enhances the specificity of the diagnosis but provides information about surrounding soft tissue infection (Palestro & Torres, 1997). If gallium scan is negative, it effectively excludes the diagnosis of osteomyelitis (Horwich, 2011; as cited in Pineda, 2006). A gallium scan can be performed concurrently with a technetium labelled three-phase bone scan, and the information gathered may be more useful than that of either examination alone (Horwich, 2011; as cited in Tumed, 1986). Both radionuclides can be injected at the same time and the scintigraphic images can be obtained three to four hours after injection, while gallium images will be obtained up to 24 hours later (Horwich, 2011). This combination is probably the best nuclear medicine tool for the evaluation of vertebral osteomyelitis (Palestro & Torres, 1997).

Labelled leukocyte imaging is a good alternative in the evaluation of osteomyleitis, but is of little value in vertebral osteomyelitis because this entity often presents as a non specific photopenic defect (Gotthard et al., 2010; as cited in Van Der Bruggen et al., 2010). But, in the diabetic foot diagnosis, labelled leukocyte imaging alone is sufficient to determine the presence of osteomyelitis in the forefoot. In the midfoot and hindfoot it may be necessary to combine leukocyte scintigraphy with others radiotracers to precisely localize the infection (Palestro & Torres, 1997). The combined imaging approach of 99mTc-colloid bone marrow/labelled-leukocyte scanning enhances the sensitivity and specificity above 90%, avoiding the problem of physiologic uptake into bone marrow. Because in osteomyelitis bone marrow is replaced by the infectious process, bone marrow imaging will be negative whereas leukocyte scanning in the same location will be positive (Gotthardt et al., 2010, as cited in Palestro et al., 2006).

In chronic osteomyelitis the specificity of Tc-99m-MDP bone scans is very low even with active exacerbation because positive uptake also occurs with the healing process (El-Maghraby et al., 2006). Other false negative results are possible in areas of relative ischemia, since radiotracer may not be adequately delivered to the target site (Horwich, 2011). 67Ga combined with Tc-99m-MDP allows identification of active chronic osteomyelitis. Discordance between 67Ga and Tc-99m-MDP with more intense 67Ga or different distribution is highly specific at 80-100% (El-Maghraby et al., 2006). 18F-FDG-PET is a promising modality for imaging musculoskeletal infection and might play an important role in the evaluation of chronic osteomyelitis and spinal infection (Strobel & Stumpe, 2007). The specificity for spinal infection drops only if patients underwent surgery less than 6 months before PET and if osteosynthetic material is present (Gotthardt et al., 2010; as cited in De Winter et al., 2003). However, because MRI may not be an option in patients with metallic implants in situ, PET currently is the most sensitive imaging modality in the evaluation of such patients (Gotthardt et al., 2010; as cited in De Winter et al., 2003). Furthermore, in cases of severe defenerative disk disease with oedema-like changes in the endplates and the adjacent discs, MRI can give false-positive results (Gotthardt et al., 2010; as cited in Palestro et al., 2006). Other tracers for diagnosing spinal osteomyelitis are also under investigation, including radiolabelled antibiotics and antifungical tracers (Gemmel et al., 2006).

5.2 Septic arthritis

Septic arthritis is the infection of the synovial tissues. It often occurs as a result of hematogenous seeding and less often by direct inoculation as a result of trauma or surgery (Díaz & De haro, 2005). Although it may occur at any age, it is most common in children under 3 years. Over 90% of cases are mono-articular (El-Maghraby et al., 2006). The most commonly involved joints are the hips and the knees (Díaz & De haro, 2005). Despite MRI

and nuclear medicine methods are used for the diagnosis or a preliminary investigation of infectious arthritis, the definitive diagnostic test is the identification of bacteria in the synovial fluid aspiration (Díaz & De haro 2005). Though, some joints are difficult to examine. As in the osteomyelitis, there is an increased uptake on all three phases of three-phase bone scan (El-Maghraby et al., 2006). The hallmark of septic arthritis is symmetrical uptake in both sides of the joint (Díaz & De haro, 2005). However, a positive scintigraphy has a low specificity. The differential diagnosis is made more accurate when the osteoarticular scintigraphy is combined with gallium citrate or more commonly radiolabelled leukocyte or immunoglobulins. In the presence of septic arthritis, these agents demonstrate activity patterns of diffuse nature in the soft tissue in and around the joint with no focal abnormality in bone. However, this can be difficult to ascertain without demonstration of exactly where bone lies in relation to the soft tissue infection and may need combined imaging. Rosenthall et al have shown that a combined study does raise the sensitivity for the detection of septic arthritis from 54% with TC-99m-MDP alone to 84% for combined 67Ga/Tc-99m-MDP scanning (El-Maghraby et al., 2006; as cited in Rosenthall et al., 1982). Another combination is the labelled leukocytes/Tc-99m-MDP combined study, which is reported to be more specific than a 67Ga/Tc-99m-MDP study and produces fewer equivocal results (El-Maghraby et al., 2006; as cited in Tehranzadeh et al., 2001; Chengazi & O'Mara, 2003). For disc space infections, although the bone scan is often positive, gallium scintigraphy is the preferred method. Indium-111(111In)-leukocytes have been shown to be of limited value in the diagnosis of disc space infection; although some authors feel that the labelled white cell scan can be of benefit especially if the cold (photon deficient) lesions are considered diagnostic of disc space infection (Brown et al., 1993).

5.3 Cellulitis

Cellulitis is a soft tissue infection. The scan shows intense uptake in the first two phases of the study with diffuse extra-osseous activity, while the final image is normal after 2-4 hours. The presence of other processes that stimulate osteoblastic reaction, as in cases of suspected osteomyelitis in areas with trauma, surgery or arthritis, complicates the interpretation of the scintigraphic image which is completely non specific. Combined studies with different radiotracers such as 67Ga, 111In-leukocytes or 99mTc-HM-PAO improve the sensitivity and specificity, although MRI remains as gold standard technique (Díaz & De Haro, 2005).

5.4 Painful joint replacement

Prosthetic joint replacement is a common procedure and most patients have excellent results, but 20% of them develop pain during the follow-up. It may be secondary to infection, aseptic loosening or heterotopic bone formation (El-Maghraby et al., 2006). Differentiate betweeen loosening and infection is often a difficult problem, especially because clinical signs and symptoms, laboratory tests and radiographies are insensitive, nonspecific, or both. Cross-sectional imaging modalities are hampered by artifacts produced by the prosthetic devices. Radionuclide imaging is not affected by the presence of metallic hardware and is therefore useful for evaluating the painful prosthesis (Love et al., 2001). Negative scintigraphic study rules out septic or aseptic loosening. Both conditions, however, may show increased tracer uptake in bone scans, but the pattern and site of uptake may help to differentiate each other. In aseptic loosening, focal localized uptake at the tips is seen, whereas in the infection diffuse intense uptake will be seen in the three phases of bone scan. The sensitivity for bone scan in infection is relatively high, ranging from 70% to 100% but the specificity is variable ranging

from 20% to 90% and the reported accuracy is around 50-70% (El-Maghraby et al., 2006; as cited in Rosenthall et al., 1982, Turpin & Lambert, 2001, Wilson, 2004). The combination of 67Ga-citrate and Tc-99m-MDP bone scans has better results, with accuracy around 70-80% (El-Maghraby et al., 2006). But lower results for this combination has also been reported because the uptake of both tracers can be found not only in infection, but also in the postoperative patient, in heterotopic bone formation, and loosening or inflammatory reaction to cement fixators (El-Maghraby et al., 2006; as cited in Turpin & Lambert, 2001).

Labelled leukocyte imaging is, at least theoretically, the ideal technique for diagnosing the infected prosthesis because in general, white cells do not accumulate at sites of increased bone mineral turnover in the absence of infection (Palestro, 1998). However, labelled-leukocytes yield false positive results due to reactive or displaced bone marrow as a result of surgery are present up to more than 24 months after implantation (El-Maghraby et al., 2006; as cited in Oswald et al., 1990). Labelled leukocytes accumulate not only in infection but in the bone marrow as well. This problem has been overcome by the addition of complementary bone marrow imaging, which is usually performed with Tc-99m sulfur colloid. Both, labelled leukocytes and sulfur colloid accumulate in the bone marrow, but only labelled leukocytes accumulate in infection. In contrast to the results reported for labelled leukocyte imaging alone, the results of combined leukocyte-marrow imaging of prosthetic joints have been uniformly excellent, with an accuracy of 90% or greater (Love et al., 2001; as cited in Palestro 1990, 1991) and has become the method of choice to evaluate surgical prostheses (El-Maghraby et al., 2006; as cited in Love et al., 2001; Turpin & Lambert, 2001). Although extremely accurate, leukocyte-marrow scintigraphy is hampered by significant limitations. The in vitro labelling process is labor intensive, is not always available, and requires direct contact with blood products. The need for marrow imaging adds to the complexity and cost of the study and is an additional inconvenience to patients, many of whom are elderly and debilitated (Love et al., 2001). In an effort to maintain the accuracy of the study while reducing or eliminating the disadvantages, several methods of labelling leukocytes in vivo have been investigated, but their role in prosthetic joint infection has not been established.

FDG-PET has been extensively investigated, the high-resolution tomographic images, availability of the agent, and rapid completion of the procedure are all desirable traits. Published results to date, however, are inconclusive in this setting (Love et al., 2009; as cited in Chacko et al., 2002; Joseph et al., 2001; Love et al., 2004; Manthey et al., 2002; Pill et al., 2006; Reinartz et al., 2005; Stumpe et al., 2004; Zhuang et al, 2001).

6. Avascular osteonecrosis

Osteonecrosis, also known as aseptic necrosis, avascular necrosis, ischemic necrosis, and osteochondritis dissecans, is a pathological process that has been associated with numerous conditions and therapeutic interventions. The exact prevalence of osteonecrosis is unknown. In the United States, there are an estimated 10,000 to 20,000 new patients diagnosed per year, and osteonecrosis is the underlying diagnosis in approximately 10 percent of all total hip replacements. The male-to-female ratio of this disorder is 8:1, but varies with different comorbidities (Jones, 2011). The mechanisms by which this disorder develops are not fully understood. Compromise of the bone vasculature leading to the death of bone and marrow cells (bone marrow infarction) appear to be common to most proposed etiologies. The process is most often progressive, resulting in joint destruction within three to five years if left untreated. A variety of traumatic and nontraumatic factors contribute to the etiology of

osteonecrosis. Glucocorticoid use and excessive alcohol intake are reported to be associated with more than 90% of the cases. Osteonecrosis usually occurs in the anterolateral femoral head, although it may also affect the femoral condyles, humeral heads, proximal tibia, vertebrae, and small bones of the hand and foot. Many patients have bilateral involvement at the time of diagnosis, including disease of the hips, knees, and shoulders. The most common presenting symptom of osteonecrosis is pain and patients may have eventually limitation on range of motion. A limp may be present late in the course of lower extremity disease. A small proportion of patients are asymptomatic. In these cases the diagnosis is usually incidental. Asymptomatic involvement contralateral to a symptomatic site is frequently noted.

There is no pathognomonic feature of osteonecrosis. A clinical diagnosis is appropriately made in a symptomatic patient when imaging findings are compatible with this disease and other causes of pain and bony abnormalities are either unlikely or have been excluded by appropriate testing. The evaluation for suspected osteonecrosis should begin with plain film radiography, althought it can remain normal for months after symptoms of osteonecrosis begin. Features of osteonecrosis on plain film radiographs, radionuclide scans (**Fig. 3**), and MRI are helpful diagnostically and provide the basis for classification and staging systems. Early diagnosis of osteonecrosis is crucial: the earlier the stage of the lesion at the time of diagnosis, the better the prognosis. Clinically, early diagnosis and treatment of osteonecrosis might prevent unnecessary surgery (Pape et al., 2004). Therefore, early diagnosis and location of osteonecrosis have prognostic value and determine the therapeutic alternatives.

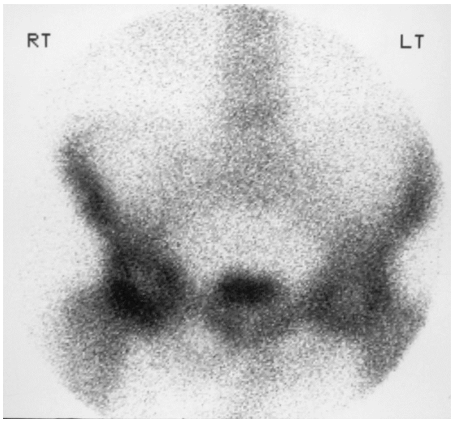


Fig. 3. Radionuclide bone scan of the pelvis in a 68-year-old man with hip pain. Bilateral central area of diminished uptake surrounded by a zone of increased uptake in the femoral head consistent with avascular necrosis.

Currently, MRI is the technique of choice for the diagnosis of avascular osteonecrosis in the early stages. This technique has been proven to be a highly accurate method both for early diagnosis (changes can be seen early in the course of disease when other studies are negative) and for staging of the disease (Malizos et al., 2007). MRI is far more sensitive than plain radiographs or bone scanning, with an overall reported sensitivity of 91% (Jones, 2011; as cited in Chang et al., 1993). Nevertheless, 99mTc bone scintigraphy also plays an important role in the early diagnosis of avascular necrosis and whole body bone scan is useful in patients with suspected polytopic osteonecrosis. The characteristic distribution of the radiopharmaceutical

in the affected area (cold area surrounded by a hyperfixation rim) enables early diagnosis, before the appearance of anatomical changes, which only show up later with radiography (Jones, 2011; as cited in Feggi et al., 1987 and Maillefert et al., 1997). The presence of this tipical pattern may increase the diagnostic accuracy to distinguish between osteonecrosis and transient osteoporosis, which usually has a diffuse pattern of tracer uptake, with no cold area. The accuracy of scintigraphy can be improved by using SPECT in patients with suspected avascular necrosis of the femoral head but have concomitant changes that may show up as false positives, such as severe acetabular osteoarthritis (Jones, 2011; as cited in Collier et al., 1985). It also may help us to avoid overlooking a subchondral fracture.

6.1 Transient osteoporosis

Transient osteoporosis of the hip, also called transient marrow edema syndrome, is characterized by the presence of intense radionuclide uptake in the femoral head, which may extend to the femoral neck, to the intertrochanteric region, or to proximal femoral diaphyseal region. It is also typical to find hyperactivity at the images of flow phase and blood pool phase. Ischemia of the femoral head, that has not caused necrosis, has been suggested as a possible cause of this process. The reactive hyperemic response to this ischemic phenomenon, with a repair process, would explain scintigraphic changes. Insufficiency fractures in this location can provide similar scintigraphic imaging (Schneider, 2006).

7. Reflex sympathetic dystrophy

Reflex sympathetic dystrophy (RSD) is a complex physiologic response of the body to an external stimulus resulting in pain sympathetically mediated, usually nonanatomic pattern, which is out of proportion to the inciting event or expected healing response (Fournier & Holder 1998). It is a syndrome affecting an extremity after a minor trauma or surgery, but the particular mechanism remains uncertain. The diagnosis of RSD relies on clinical evaluation, scintigraphy or MR imaging, and routine radiographs. In the spontaneous course of this syndrome three phases can be distinguished: Stage I is the warm or hypertrophic phase, stage II is called the cold or atrophic phase and the third stage corresponds to stabilization or, in rare instances, to healing (Driessens et al., 1999; Ornetti & Maillefert, 2004).

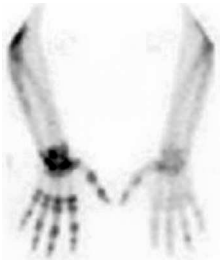


Fig. 4. Bone scanning: Diffusely increased uptake in the distal right upper extremity in reflex sympathetic dystrophy.

Three-phase scintigraphy has been widely utilized in both the diagnosis and monitoring of treatment (Murray, 1998). Scintigraphy imaging (**Fig. 4**) shows increased perfusion during the angiographic and vascular pool phases and widespread increases in radiophosphonate bone uptake in the late stage (Colamussi et al., 2004). The highest diagnostic accuracy is

provided by the combination of three signs: Increase activity ratio in the blood pool phase performed at 5-15 min, diffuse uptake in the carpus o tarsus and periarticular uptake in all the small joints (Murray, 1998). Decreased radiotracer accumulation has also been described, especially in children and adolescents (Driessens et al., 1999; Love et al., 2003). Bone scintigraphy is of major importance for the diagnosis in order to clearly differentiate from other conditions which are incorrectly diagnosed and treated as RSD. If the bone scan is not suggestive of RSD, the clinical picture, radiological examination and vascular scan may lead to the correct diagnosis. This may be a pseudodystrophy, in which a hypovascularization is found right from the start, while in true RSD there is initially a hypervascularization. Other conditions which may be confused with RSD are causalgia, neurotic compulsive postures, hysterical conversion, malingering and even self-mutilation (Driessens et al., 1999). Bone scintigraphy has a high sensitivity in the initial stage of Sudeck's syndrome, but after 26 weeks, it loses accuracy (Benning & Steinert, 1988; Lee & Weeks, 1995).

8. Metabolic bone disorders

8.1 Osteoporosis

Osteoporosis is defined as a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue, with an increase in bone fragility and susceptibility to fractures. Despite an increase in bone turnover that is usually present in osteoporosis, the bone scan has no role in the diagnosis of uncomplicated osteoporosis, but the Tc-99m-MDP bone scan is most often used in established osteoporosis to diagnose fractures, particularly at sites that are difficult to image with plain film radiography (eg, sacrum, ribs), and may be particularly useful in the diagnosis and timing of vertebral fractures. It also has an important role in assessing suspected fractures where radiography is unhelpful, either because of poor sensitivity related to the anatomical site of the fracture (eg, sacrum **Fig. 5**) or because adequate views are not obtainable because of the patient's discomfort (Fogelman & Cook, 2003). The characteristic appearance of these fractures is discussed elsewhere in this chapter. If a patient complains of back pain with multiple previous vertebral fractures noted on

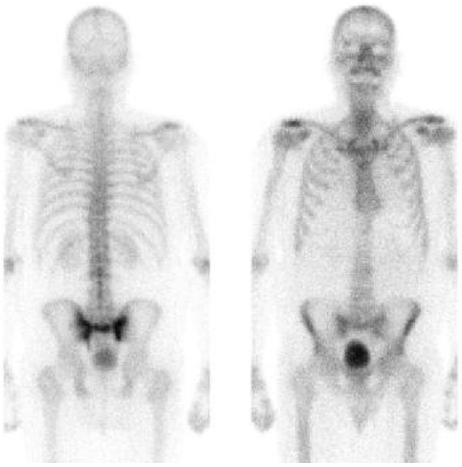


Fig. 5. Posterior and anterior Tc-99m-MDP bone scan showing a typical "H-shaped" pattern in the sacrum, indicating a sacral insufficiency fracture.

radiographs, and the bone scan is normal, then this essentially excludes recent fracture as the cause of symptoms and other causes of pain should then be considered.

8.2 Paget

Paget's disease is a localized disease of bone remodeling characterized by an increased bone resorption mediated by osteoclasts and a compensatory increase in bone formation. The result is a disorganized mosaic of woven and lamellar bone at affected skeletal sites. This structural change produces bone that is expanded in size, less compact, more vascular and more susceptible to deformity and fracture than in normal bone. It can affect any bone, but is more common in skull, hip, pelvis, legs and back. Paget's disease may be monostotic, but the majority of patients have a polyostotic disease (80-90%). Most patients are asymptomatic, but they can experience a variety of symptoms such as bone pain, bone deformity, secondary arthritic problems, excessive warmth over bone area and different neurological complications caused by compression of adjacent neural tissues.

Bone scintigraphy, combined with radiology, is the technique of choice for assessing the location and extent of the pagetic bone lesions. It allows of evaluating the entire skeleton and is more sensitive than radiography in identifying metabolically active lesions (Fogelman & Carr, 1980): there is no radiological correspondence over 10% of scintigraphic hot spots (Devogelaer & De Deuxchaisnes, 2003). Symptomatic lesions are usually characterized by an increased uptake. Characteristically, affected bones show a striking increase in metabolic activity that starts at one edge of the bone and extends distally or proximally, often showing a "V" or "flame – shaped" leading edge. Both osteolytic and osteoblastic lesions are associated with and increase in radiotracer uptake on bone scan (**Fig. 6**). Scintigraphic pagetic bone features are usually characteristic, presenting as "hot spots". Whole bone may be affected, especially at pelvis, scapula and vertebrae. Abnormal tracer accumulation throughout the vertebra, affecting the body and posterior elements, is the characteristic finding in this localization. The skull may show a different pattern with a ring of increased activity only in the margins of the lesion (Fogelman & Cook, 2003). The intensity of radiactive tracer uptake, usually Tc-99m-MDP, depends on the metabolic activity of Paget's disease. In later stages, the disease may go into a period of inactivity and bone scan shows little or no uptake. Therefore, bone scintigraphy is complementary to the use of biochemical markers (e.g. serum alkaline phosphatase, urine hydroxyproline) for the assessment of bone turnover and may be useful in assessing therapeutic efficacy, since a good correlation between bone scintigraphy uptake and clinical and biochemical markers has been found (Cook et al., 2010). Cases of scintigraphic evidence of pagetic activity in the setting of normal serum alkaline phosphatase have been reported. In these cases, bone scintigraphy is the main technique in the evaluation of the effectiveness of the treatment. Bone scan can be performed 3-6 months after treatment with bisphosphonates, although scintigraphic images may respond in a heterogeneous way (after intravenous bisphosphonate therapy, some bones may become normal, most bones show some improvement, and a small proportion remain unchanged), and even lead to infrequent images that sometimes mimic those of bone metastases. In these cases, knowing the medical history of the patient is essential (Fogelman & Cook, 2003). The superior quantitative accuracy of PET using 18F-fluoride ion has been described in the evaluation of pagetic bone (Cook et al., 2002), and this method has also been described to measure response to bisphosphonate treatment. An increase in 18F-FDG uptake has also been reported in pagetic bone (Cook et al., 2010; as cited in Cook et al., 1997), correlating also with disease activity. Bone scintigraphy can also identify complications (**Fig.**

6) of Paget's disease like fractures (shown as a linear area of increased activity perpendicular to the cortex) or sarcomatous degeneration. The latter should be suspected in patients with persistent pain. The most common scintigraphic sign in the setting of sarcomatous degeneration is a cold area inside an area of increased uptake. The scan may also show heterogeneous and irregular uptake in the study area or adjacent soft-tissue uptake. The evaluation of the lesion should always be completed with x-ray and, even if doubts persist, with an MRI, which could allow a more precise diagnosis (Fransen et al., 1998).

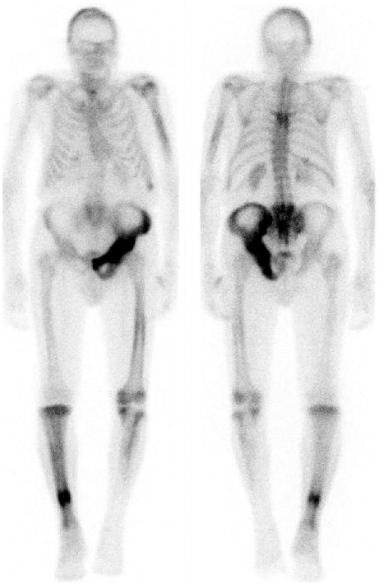


Fig. 6. A Tc-99m-MDP bone scan showing Paget's disease affecting the left humerus, mid-thoracic and lower lumbar spine, sacrum, right 11th rib, left pelvis, left femur and tibia, and the right tibia. Focal linear activity in the right tibia indicates an incremental fracture

8.3 Hyperparathyroidism

Most cases of primary hyperparathyroidism are asymptomatic and are unlikely to be associated with changes on bone scintigraphy. The diagnosis is made biochemically and the use of bone scintigraphy does not make sense with this goal. But bone scan may be useful to differentiate the causes of hypercalcemia, in particular, hyperparathyroidism vs malignancy, so that typical features of metabolic bone disorders may be recognized. There is increased skeletal turnover in hyperparathyroidism, commonly seen as part of renal osteodystrophy, and in the more severe cases, this will be evident scintigraphically. A bone scan may show several features in hyperparathyroidism, but the most important is the generalized increased uptake throughout the skeleton that may be identified because of increased contrast between bone and soft tissues. This is commonly termed the metabolic superscan to differentiate from superscans caused by widespread bone metastases. Other typical features that have been described in this context include a prominent calvarium and mandible, beading of the costochondral junctions, and a "tie" sternum (Fogelman & Carr, 1980). Severe forms of hyperparathyroidism may be associated with uptake of bone radiopharmaceuticals

into soft tissue, related with ectopic calcification. Focal skeletal abnormalities may represent associated Brown tumors, although these are relatively uncommon.

8.4 Renal osteodystrophy

Renal osteodystrophy is secondary to a combination of bone disorders as a consequence of chronic renal dysfunction, and often shows the most severe cases of metabolic bone disease. It may include osteoporosis, osteomalacia, adynamic bone, and secondary hyperparathyroidism in varying degrees. The most frequent bone scan imagings are similar to a superscan from other metabolic bone disorders, and uptake of diphosphonate in areas of ectopic calcification also may be seen. A lack of bladder activity (secondary to the renal failure) may help in identification and differentiating this type of scintigraphic pattern from others. Aluminum toxicity from hemodialysis, rarely seen now, causes a poor quality bone scan with reduced skeletal uptake and increased soft-tissue activity, as aluminum blocks mineralization and hence the uptake of tracer, resulting in a pattern applicable to all forms of adynamic bone disease. Quantitative measurements of bone metabolism in renal osteodystrophy using 18F-fluoride have been compared with bone histomorphometry and have shown a close relationship between the net plasma clearance of 18F-fluoride to bone mineral and the histomorphometric indices of bone formation. The method was able to differentiate low turnover from high turnover states of renal osteodystrophy (Cook et al., 2010; as cited in Messa et al., 1993).

8.5 Osteomalacia

Patients with osteomalacia usually demonstrate similar features of a bone scan as described in hyperparathyroidism, although in the early stages of the disease it may appear normal (Cook et al., 2010). The reason that osteomalacia shows these features is not fully understood. Tracer avidity may reflect diffuse uptake in osteoid, although more likely, it is due to the degree of secondary hyperparathyroidism that is present. In addition, the presence of focal lesions may represent pseudofractures or true fractures. Pseudofractures are characteristically found in the ribs, the lateral border of the scapula, the pubic rami, and the medial femoral cortices. Although osteomalacia is usually a biochemical and/or histologic diagnosis, the typical bone scan features can be helpful in suggesting the diagnosis. The detection of pseudofracutures with this technique is more sensitive than that with radiography (Cook et al., 2010; as cited in Fogelman et al., 1977, 1978).

9. Bone tumors

For the diagnosis study of primary bone tumors prevails the importance of the morphological study to characterize the lesion and, in many cases, the initial plain films guides the diagnosis. In these cases, the usefulness of bone scintigraphy is lesser, but may be useful for detecting a lesion that is difficult to assess radiologically because of its location, and supporting the suspicion about the benignity or malignancy of the lesion. Characteristic patterns of uptake have been described in some primary bone tumors, but they are not reliable enough, given that there is an overlap in the scintigraphic characteristics of the benign and malignant bone lesions. The differential diagnosis of a solitary bone lesion usually depends more on morphologic imaging techniques, including radiographs, CT, and MRI, and on expert histologic analysis. In contrast, a larger role is developing for 18F-FDG-PET/CT for staging and response assessment of several bone tumors. Three-phase bone

scintigraphy offers information about the vascularity of the bone lesion: Malignant tumors tend to be more vascularized and be uptake in all three phases of the scan, while benign bone tumors often do not show changes in the first two phases of the scintigraphy. Normal uptake, even in the third stage, is a sign for the mildness of the bone lesion. Osteoid osteoma is a benign bone tumor that constitutes an exception to this statement: It is highly vascular and provides uptake images in all three phases of the scan. In fact, a normal bone scan excludes its diagnosis. Aneurysmal bone cyst may show similar features. In patients with a benign tumor and a bone scan showing intense uptake, a fracture should be suspected.

9.1 Benign bone tumors and tumor- like disorders

In benign bone tumors, the uptake of radiopharmaceuticals (e.g. 99mTc) varies by type of tumor and may be normal, mild or severe. Bone scintigraphy is useful for the diagnosis of osteoid osteoma, especially when it is located at the spine, pelvis or hip, where radiological studies are usually not diagnosed. The typical scintigraphic finding is a round focal uptake lesion. CT is always necessary to confirm the diagnosis and surgical treatment. Most enchondromas appear like hot spots at bone scan study. This technique can locate these tumors in multiple enchondromatosis, but it can not differentiate between enchondroma and chondrosarcoma. The scintigraphic feature of the giant cell tumor is increased tracer uptake in all phases of this study, and the image of donut of the lesion, with a rim of uptake surrounding a central area of low uptake. Nevertheless, this image may also appear in other bone tumors. In fibrous displasia, characterized by replacement of normal bone tissue by abnormal fibro-osseous tissue with a high bone turnover, bone scan also display areas of increased uptake. In other bone lesions such as Langerhans cell histiocytosis, hemangiomas and aneurysmal bone cysts, the sensitivity of this technique is variable (Schneider, 2006).

9.2 Soft tissue tumors and primary malignant bone tumors

Musculoskeletal sarcomas represent a heterogeneous group of malignancies involving bone and soft tissue. Multiple myeloma is the most common primary malignancy of bone in adults, with an incidence of 3 per 100,000 in the USA. It may affect any bone with hematopoietic red marrow. Patients affected are usually over 50 years of age with the most common age group being between 60 and 65 years of age. Excluding myeloma and lymphoma, malignant primary bone tumors constitute only 0.2% of all malignancies in adults and approximately 5% of childhood malignancies, and, excluding mieloma in adults, the overwhelming majority of cases consist of osteosarcoma or Ewings' sarcoma (Green, 2009). Both are more common in the pediatric than the adult population. Osteosarcoma is the most frequent primary bone malignancy in children and second in adults following multiple myeloma. The Ewing's sarcoma family of tumors is the second most frequent primary bone malignancy in children and young adults and it is the most lethal bone tumor. The most common presenting symptom for primary bone tumors is a painful swelling arising in the bone. The presentation may be similar to acute or chronic osteomyelitis with systemic symptoms of fever, malaise, weight loss, and leukocytosis. Approximatly 15% of patients have clinically evident metastasic disease at diagnosis. Metastatic spread is mainly hematogenous, and the lungs are the most common site of metastases, followed by bone and bone marrow. Anatomic imaging techniques including radiography, US, CT and MRI, currently play a dominant role in the evaluation of suspected and known sarcomas of both soft tissue and bone. Nuclear medicine techniques such as scintigraphy, Thallium-201, and 67Ga imaging have all been used in the assessment of primary bone tumors. However, PET

is becoming the most imporant modality for assessing biologic characteristics of the tumor, for primary staging, and for determining response to treatment. Although imaging studies may be highly suggestive of the diagnosis, they cannot reliably differentiate among the various types of malignant bone tumors, and even among malignant and benign conditions. Histopathologic confirmation, therefore, is required. The sites for biopsy are critical for accurate histological diagnosis and staging because biopsy of a small site may not represent the overall character of the tumor, missing high-grade areas, and non-diagnostic biopsies may also occur (Howman-Giles et al., 2006).

The diagnosis of indeterminate bone lesions is limited with 18F-FDG-PET, but in general the greater the level of uptake, the more likely a lesion is malignant in nature. However, it has been reported that some giant cell tumors and fibrous dysplasia may show uptake equivalent to osteosarcomas and that some other benign bone lesions may show high 18F-FDG accumulation (Aoki et al., 2001). Despite this, 18F-FDG-PET has a high specificity for excluding malignant bone tumors (Cook et al., 2010). Recently, dual time point imaging and calculation of a retention index for 18F-FDG have shown improved discrimination of benign and malignant bone lesions compared with static measures, but that some overlap was still present (Tian et al., 2009). Lodge et al observed difference in time-activity curves between benign and low-grade malignant tumors that show peak activity within the first 30 minutes post-injection and high-grade sarcomas, which reach peak activity 4 hours after injection. This quantitative approach cannot separate low-grade sarcomas from benign lesions. MRI is the modality of choice to define the extension of tumors to surrounding soft tissue as well as to estimate the local tumor infiltration into bone marrow. However, in the pediatric population, 18F-FDG-PET is valuable for detection of skip metastases in cases of equivocal MRI findings due to the physiological red blood marrow in long bones (Even-Sapir, 2007; as cited in Wuisman P, Enneking WF, 1990). With the new hybrid imaging, it is now possible to take advantage of the metabolic and morphologic information from 18F-FDG-PET/CT to enhance discrimination between benign and malignant bone lesions by dedicated interpretation of the CT characteristics (Strobel et al., 2008). 18F-FDG-PET data can also assist in optimizing the biopsy site of heterogeneous masses by guiding sampling to active tumor sites and avoiding errors due to biopsy of necrotic tumor areas (Even-Sapir, 2007; as cited in Pezeshk et al., 2006). In general, 18F-FDG-PET or PET/CT would appear to have a complementary role to conventional staging procedures (Cook et al., 2010; as cited in Kleis et al., 2009, Kneisl et al., 2006 and Völker et al., 2007). After a diagnosis of a malignant primary bone lesion is made, the use of bone scintigraphy to define the extent of tumor before surgical resection is controversial: good correlation between increased bone tracer uptake and true anatomical extent that has been reported (Cook et al., 2010; as cited in Goldmann et al., 1975, McKillop et al., 1981, and Papanicolou et al., 1982), has not been supported by other studies (Chew & Hudson, 1982). These discrepancies may be due to peritumoral reactive changes overestimating extent or underestimations due to inability to detect marrow and soft-tissue involvement. For these reasons, MRI is the most accurate noninvasive assessment of tumor extent. On the other hand, several studies have reported the ability of bone scintigraphy to predict histological response to preoperative chemotherapy in patients with primary malignant bone tumors. Ozcan et al have reported a study of 27 patients with osteosarcoma, Ewing's sarcoma, and malignant fibrous histiocytoma, which has displayed a reduction in hyperemia and extension as the most notable findings on three-phase bone scintigraphy. A reduction in tumor blood flow of 58.7% was found in 15 responding patients compared with 19.9% in the nonresponders. A higher accuracy in assessing response was possible using all

the information from three-phase scintigraphy (88%), compared with static imaging alone (74%) where the blood flow and blood pool images showed a reduction in vascularity and extension. These are consisting features with the results published in previous studies (Cook et al., 2010; as cited in Knop et al., 1990, and Sommer et al., 1987). The sensitivity of 18F-FDG-PET in staging primary bone tumors appears to vary between different tumor types and location of metastases. Spiral CT is the modality of choice for detection of relatively small lung metastases. Franzius et al compared the detection lung metastases of sarcoma by CT and 18F-FDG-PET, showing a higher sensitivity for the former modality especially in lesions <9 mm. 18F-FDG-PET may, however, assist in differentiating nonspecific lung nodules from metastases detected by CT in case of larger lung lesions, within the size range of PET resolution. 18F-FDG-PET may also identify unexpected extra pulmonary metastases. Serial 18F-FDG-PET assessment of primary bone tumors (predominantly osteosarcomas, Ewing's sarcomas, or both) is a good non-invasive method to predict pathologic neoadjuvant chemotherapy response (Cook et al., 2010; Even-Sapir, 2007). Another earlier study also showed a correlation with pathologic response but described high 18F-FDG uptake in granulation and/or fibrotic tissue and in the fibrous pseudocapsule of treated tumors (Cook et al., 2010; as cited in Jones et al., 1996).

Multiple myeloma hardly triggers osteoblastic reaction and therefore scintigraphy is less sensitive than plain radiography and CT. FDG-PET indicates active myeloma and CT shows bone destruction. Therefore hybrid whole-body PET/CT is an excellent method to evaluate myeloma. Currently whole-body and spinal MRI and PET/CT are considered the imaging techniques of choice for initial evaluation and follow-up of these patients. Durie et al assessed the role of 18F-FDG-PET in 66 patients with multiple myeloma and monoclonal gammopathy of undetermined significance. Their results suggested that a positive 18F-FDG-PET reliably indicates the presence of active myeloma, whereas a negative study strongly supports the diagnosis of monoclonal gammopathy of undetermined significance. 18F-FDG-PET has also been reported to identify unexpected medullar and extramedullar sites of myelomatous disease not appreciated on X-ray, CT, or scintigraphy (Even-Sapir, 2007). In a recent report on 28 patients with multiple myeloma, 18F-FDG-PET/CT and MRI of the spine were shown to have complementary roles. Although the former modality detected more lesions, all of which were located outside the field of view of MRI, the latter modality was found superior for diagnosing an infiltrative pattern in the spine (Nanni et al., 2006). In another recent report, 18F-FDG-PET was found to be valuable in detecting infection in patients with multiple myeloma (Even-Sapir, 2007).

Osteosarcoma represents only 0.1% of all tumors, but it is the second most frequent malignant primary bone tumor after myeloma. The diagnosis of osteosarcoma is based on characteristic histologic features in combination with typical radiographic findings. MRI of the entire suspected bone is performed to define the degree of penetration of the tumor surrounding soft tissue as well as to estimate the local tumor infiltration into bone marrow. Furthermore, CT of the chest and conventional bone scan are necessary for early detection of metastases. MRI and scintigraphy are also used to distinguish postoperative changes from residual or recurrent tumor tissue after local surgical treatment. Because osteosarcoma metastases usually incorporate bisphosphonates, bone scanning can be used for follow-up examinations to detect both osseous and nonosseous metastases. High-resolution CT has been shown to be superior to 18F-FDG-PET for detecting lung metastases. Data on the benefit of 18F-FDG-PET for detecting skeletal metastases in osteosarcoma patients are still very sparse, but successful detection of all sites of bone involvement by 18F-FDG-PET has

been reported recently (Even-Sapir, 2007; as cited in Franzius et al., 2002). Nevertheless, in children there may be an exception for primary staging, where there may be an indication for 18F-FDG-PET to detect intraosseous skip metastases in cases of unequivocal MRI findings, although no data are yet available to support this hypothesis. PET scans will not obviate the need for biopsy and tissue diagnosis in soft-tissue and bone masses, but it is remarkably helpful to guide biopsy. Non-PET–guided biopsy might miss the most biologically significant region, resulting in a false low pre-therapeutic tumor grading. 18F-FDG-PET imaging data has shown reliability for prediction of tumor response to preoperative, neoadjuvant chemotherapy. On the other hand, for differentiation between benign residual mass lesions caused by post-therapeutic tissue changes and residual tumor tissue or local relapse, 18F-FDG PET is considered to be highly sensitive and more accurate than CT or MRI (Brenner et al., 2003). A high baseline uptake of 18F-FDG in osteosarcoma has been reported as showing an inverse correlation with prognostic indicators and is associated with a poor outcome with similar results for patients with high post-treatment FDG activity (Cook et al., 2010; as cited in Costelloe et al., 2009; Franzius et al., 2002).

Ewing's sarcoma is a highly malignant primary bone tumor that is being derived from red bone marrow. It accounts for approximately 5% of biopsy-analyzed bone tumors and approximately 33% of primary bone tumors. No single morphologic or functional imaging method provides findings for a specific diagnosis of Ewing's sarcoma, but the results do contribute to tumor staging. Because the clinical symptoms of Ewing's sarcoma are nonspecific and because they frequently suggest osteomyelitis, an initial conventional radiographic and/or MRI examination is performed. With static bone scintigraphy, Ewing's sarcoma is usually depicted as a focal area of increased radionuclide activity. Whole-body bone scans can provide information about the primary lesion and depict skip lesions. Also, bone scintigraphy can be used to localize distant metastases during tumor staging. Three-phase dynamic bone scintigraphy can help in the assessment of treatment effects, with a reported accuracy of 88%. In cases that respond to treatment, a reduction of both flow and tracer uptake can be observed. 18F-FDG-PET may help to detect lesions that are not shown on conventional bone scans. It is the most sensitive modality for therapeutic follow-up, and this modality can reveal early changes in tumor metabolism, which is an indicator of the therapeutic effect.

Regarding the lymphomatous disease, primary skeletal involvement occurs in 3 to 5% of patients with non-Hodgkin's lymphoma, and secondary bone involvement occurs in up to 25% of patients. Moog et al have reported 18F-FDG-PET to be more sensitive and specific than Tc-99m-MDP bone scintigraphy for detection of osseous involvement by lymphoma. Early bone involvement may present as abnormal on 18F-FDG-PET with normal CT appearance, since detection of malignant bone involvement on CT depends on the presence of a considerable amount of bone destruction.

9.3 Metastases

Bone metastasis is the most common malignant bone tumor. It affects two thirds of cancer patients, and tumors that most often lead to metastases are breast, lung and prostate neoplasms. Bone involvement by cancer occurs most commonly by hematogenous spread, although tumor may occasionally extend directly from the soft tissue to the adjacent bone. The vast majority of bone metastases initiate as intramedullary lesions. The normal bone undergoes constant remodeling, maintaining a balance between osteoclastic (resorptive) and osteoblastic activity. As the metastatic lesion enlarges within the marrow, the surrounding bone undergoes osteoclastic and osteoblastic reactive changes. Based on the balance

between the osteoclastic and osteoblastic processes, the radiographic appearance of a bone metastasis may be lytic, sclerotic (blastic), or mixed. The osteoblastic component of the metastasis represents reaction of normal bone to the metastatic process. The incidence of lytic, blastic, and mixed types of bone metastases is different in various tumor types. Lytic lesions may be seen in almost all tumor types. Bone metastases of bladder, kidney, and thyroid cancer and lesions of multiple myeloma are invariably lytic. Blastic lesions are frequently seen in prostate and breast cancer, occasionally in lung, stomach, pancreas, and cervix carcinomas, and infrequently in colorectal cancer (Beheshti et al., 2009; Even-Sapir, 2005). The most frequent distribution of metastasis in the human skeleton is usually 80% in the axial skeleton and ribs, 10% skull and 10% in long bones. Approximately 40% of patients with metastases have no pain at diagnosis (Diaz & De Haro, 2005). Symptoms occur mainly when the lesion increases in size, causing extensive bone destruction, which may lead to collapse or fracture, or in the presence of accompanying complications, such as spinal cord compression or nerve root invasion.

Bone scan is the primary tool for screening or monitoring bone metastases due to its high sensitivity, versus plain radiography (Brown, 1993), and plays an integral part in tumor staging and management, since early detection of skeletal metastases optimizes management (Even-Sapir, 2005). Scintigraphic image of metastases is one or more high uptake foci in 98% of the cases, and the usual pattern consists of increased radiotracer deposition in areas of osteoblastic reparative activity in response to tumor osteolysis. The presence of multiple, randomly, distributed areas of increased uptake of varying size, shape, and intensity is highly suggestive of bone metastases, specially at sternum, scapula and ribs. Although multiple foci of increased activity may be encountered in other pathologic conditions, it is often possible to distinguish metastatic disease from other entities by analyzing the pattern of distribution of the abnormalities. Traumatic injury, in contrast to metastatic disease, generally manifests as discrete focal abnormalities of similar intensity. Multifocal rib trauma has a characteristic linear distribution. In patients with osteoporosis, the presence of kyphosis and/or an H-shaped sacral fracture suggests the correct diagnosis. In older patients, osteoarthritis and degenerative changes may manifest as areas of intense activity on radionuclide bone images. These changes can be distinguished from metastatic disease by virtue of their characteristic location (eg, knees, hands, wrists). Involvement of both sides of the joint is common in arthritis but unusual in malignant conditions. The remaining 2% is mild uptake foci owing to preponderance of osteolytic activity. The possibility of an artifact should be ruled out in cases of well-defined cold spot. In cases of wide-spread metastases, the radiopharmaceutical can be almost completely captured and it may lead to a superscan image, where kidney or bladder silhouettes are not initially seen by the delay in urinary excretion of radiotracer. A superscan may also be associated with metabolic bone disease but, in this case, the uptake is more uniform in appearance and extends into the distal appendicular skeleton. Intense calvarial uptake that is disproportionate to that in the remainder of the skeleton is another feature of a metabolic superscan. SPECT is reported to detect 20 to 50% more lesions in the spine compared with planar scintigraphy, and it increases both the sensitivity and specificity. The new hybrid system, SPECT with multislice CT, improves diagnostic accuracy (Dasgeb et al., 2007). The most common radiotracer is Tc-99m-MDP but in patients with follicular thyroid carcinoma or in cases of neuroblastoma, iodine-131 (131I) and 123I-Metaiodobenzylguanidine (123I-MIBG) are more sensitive. Increased uptake of these radiotracers reflects the osteoblastic reaction of bone to the destruction of bone by the tumor cells, whereas increased 18F-FDG activity at the sites of bone

lesions on PET study represents active tumor itself. Bone scintigraphy is more sensitive than FDG-PET for detection of blastic/sclerotic lesion, whereas FDG-PET is more sensitive for lytic lesions and bone marrow disease. The latter has the additional ability to assess extraskeletal metastatic disease. Hybrid PET/CT imaging improves the specificity of FDG-PET for skeletal metastases (Dasgeb et al., 2007; as cited in Even-Sapir, 2005). An additional finding from scanning the peripheries, particularly in patients with bronchogenic carcinoma, may be the observation of hypertrophic osteoarthropathy secondary to cortical periostitis, that typically appears as symmetrical, nonuniform, irregular cortical uptake involving the long bones, most often seen in the femora, tibiae and wrists, and giving rise to the "tramline sign" (Gnanasegaran et al., 2009; Love et al., 2003; as cited in Ernstoff & Meehan, 2000). In patients with bone metastases who have received chemotherapy, reparative osteoblastic reaction that occurs after this treatment may lead to the appearance of bone areas with intense uptake during the first 3 months (flare phenomenon). As healing progresses, uptake in the lesion disminishes and by 6 months it should generally be possible to differentiate response from progression (Love et al., 2003).

18F-FDG-PET has become a routine imaging modality for staging and monitoring the response to therapy in patients with lymphoma. There are accumulating data indicating that 18F-FDG-PET may detect early marrow infiltration and may add clinically relevant information when performed in patients with primary or secondary lymphomatous bone involvement. FDG-PET can detect early marrow infiltration and therefore is more sensitive than planar scintigraphy or CT for assessment of early skeletal involvement in lymphoma (Dasgeb et al., 2007). A pattern of heterogeneous patchy marrow activity should raise the suspicion of marrow involvement in an 18F-FDG-PET study prior to therapy, while a pattern of diffuse uptake, mainly in Hodgkin's Lynphoma, is more commonly associated with reactive hematopoietic changes or myeloid hyperplasia (Even-Sapir, 2007).

Metastatic disease occasionally manifests as a solitary abnormality, usually in the spine, although other causes such as fractures, avascular osteonecrosis, primary bone tumors and infections must be previously ruled out. The location and/or characteristics of the lesion may guide the diagnostic suspicion but, especially if it is a solitary lesion, it must be studied with other imaging techniques such as CT or/and MRI (Schneider, 2006). Approximately 50% of cases in which scintigraphy detect a solitary focal uptake in a patient with a history of cancer, it is a metastasis. In patients with breast cancer, the sternum is a relatively common site to be affected often as a solitary lesion and probably results from local spread from the involved internal mammary lymph nodes. If a sternal lesion is situated distant from the manubriosternal junction, is irregular, asymmetric, or eccentric, then malignant involvement should be suspected. In a retrospective study of patients with breast cancer, 3.1% presented with an isolated sternal lesion and 76% of these were found to represent metastatic disease (Gnanasegaran et al., 2009; as cited in Kwai et al., 1988). Vertebral body fractures have a characteristic appearance on bone scintigraphy, showing a horizontal linear pattern of increased tracer accumulation. However, it is usually not possible to differentiate fractures due to benign diseases, such as osteoporosis from malignant collapse. In such cases, further evaluation with MRI is often the most informative. However, multiple linear abnormalities of varying intensity favour a benign etiology with presumed osteoporotic fracture occurring at different time points. Also, a follow-up bone scan after a few months that shows reducing activity at a vertebral fracture site, suggests a benign cause and a healing fracture. SPECT technique improves the localization and characterization of the vertebral lesions, due to its ability to delineate the body, pedicles, and spinous process:

Lesions that extend from the vertebral body into the posterior vertebral elements or involve the pedicle are more likely to represent metastases than lesions confined to the facet joints, anterior vertebral body, or either side of a disc (Gnanasegaran et al., 2009).

10. Osteoarthritis

Osteoarthritis (OA) is the most prevalent chronic joint disease and it has the greatest health economic impact. Conventional radiography is still the first and most commonly used imaging technique for evaluation of a patient with a known or suspected diagnosis of OA (Guermazi, 2009). MRI is an appropriate tool for describing changes in cartilage volume and concomitant soft-tissue alterations. But for qualitative cartilage imaging, MRI has, to date, not been fully validated. Bone scan allows the differentiation of inflammatory from degenerative joint affections and may add information on the activity of the subchondral bone, which may develop to a prognostic marker of OA (Zacher et al., 2007). Another pronostic marker of slower progression that can help us deciding the most appropriate management is the imaging of the joints that show up as "cold" (Colamussi et al., 2004). Radionuclide joint imaging is more sensitive than clinical or radiographic techniques in detecting early joint involvement but usually it must be supplemented by other techniques to establish a specific diagnosis (Hoffer & Genant, 1976).

Usefulness of molecular imaging for early diagnosis of OA is still a challenge. Cartilage damage in OA is being recharacterized as having an earlier dynamic phase, where cartilage damage is potentially reversible, followed by an irreversible pathologic phase that ultimately leads to joint pain and immobility (Hu & Du, 2009). The point at which cartilage damage is deemed irreversible has not been defined but probably depends on the size of the lesion, age of the patient, underlying cause, comorbid factors, activity level, use of joint stabilizers, genetic predisposition, and other factors. To detect early cartilage damage, molecular imaging research has focused on the identification of better ways to either visualize extracellular matrix depletion or measure events that are associated with cartilage damage, such as chondrocyte death and the elaboration of matrix-degrading enzymes. In OA, there is general acceptance that abnormal chondrocyte apoptosis is a pivotal event in the eventual destruction of articular cartilage (Biswal et al., 2007). A method for the study of cell death in living subjets is based on an endogenous protein, annexin V, whose function is not clearly understood but which is thought to play a role in coagulation (Biswald et al., 2007; as cited in Reutelinsperger & Van Heerde, 1997). This protein has an extremely strong affinity for the cell membrane phospholipid phosphotidylserine, which is expressed to the outer surface of the cell membrane during the apoptotic cascade. The use of annexin V, labelled with either a radioisotope or a fluorescent marker, provides an excellent opportunity to image programmed cell death. To date, annexin V has been labelled with 99mTc, iodine (125I, 124I, 123I), 111In, 11C, gallium (Ga-67, Ga-68), and 18F, making it appropriate for either SPECT or PET imaging (Biswald et al., 2007; as cited in Blankenberg, 1998; Glaser, 2003; Lahorte, 2004; Russell, 2002; Zijlstra, 2003). However Annexin V imaging has yet to be applied to the assessment of human OA. Another event associated with cartilage damage is the elaboration of matrix-degrading enzymes. In OA damaged cartilage appears to activate hibernating proteases such as matrix metalloproteinases and cathepsins. Using a cathepsin B–sensitive near-infrared fluorescent probe, researchers have found significant amounts of signal arising from an arthritic knee compared with normal knees in an animal model of OA (Biswald et al., 2007; as cited in Lai, 2004).

11. Heterotopic ossification

Heterotopic ossification (HO) is defined by the presence of bone in soft tissue where bone tissue normally does not exist, and it usually takes place around large joints (Medina et al., 2008). Its etiology is unknown, but is frequently precipitated by trauma, spinal cord injury or central nervous system injury (Shebab et al., 2002). The incidence of HO varies widely between populations. The incidence after hip replacement ranges from 16% to 53%; among patients with spinal cord injury HO develops in 20-25% and in brain injury patients the incidence of HO ranges from 10 to 20% (Medina et al., 2008; as cited in Vanden & Vanderstraeten, 2005). Around 20% of the patients who have an HO will develop functional limitation and it will be severe in 8% to 10% (Medina et al., 2008; as cited in Buschbacher, 1992; Subbarao, 1999). HO may closely mimic the presentation of cellulitis, osteomyelitis, or thrombophlebitis. HO can even be confused with some bone tumors such as osteosarcoma or osteochondroma. To resolve such diagnostic uncertainty and to prevent functional limitations, clinicians often request bone scanning and other imaging studies for patients at risk (Shebab et al., 2002). Radiography, MRI and CT have low sensibility in early stages of HO and three-phase bone scintigraphy (**Fig. 7**) is the most sensitive imaging modality during this period. It is also useful for its monitoring (Vanden & Vanderstraeten, 2005).

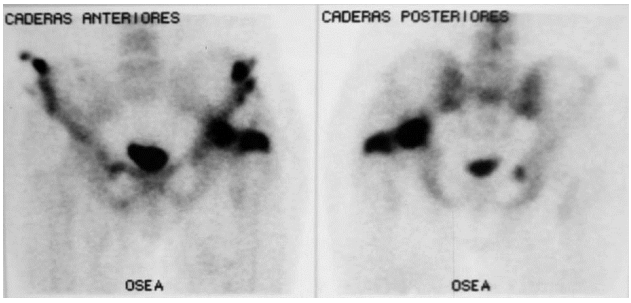


Fig. 7. Bone Scanning: increased uptake around the left hip consistent with Heterotopic Ossification.

First and second phases of three-phase bone scintigraphy are especially sensitive to detect incipient HO, which may be diagnosed 2.5 weeks after injury. Findings on the third phase may become positive approximately 1 week later. Radiographic studies do not show any change for at least 5- 8 weeks after initial injury (Shebab et al., 2002; as cited in Freed et al., 1982; Orzel & Rudd, 1985). Activity on the delayed bone scans usually peaks in a few months and after that the intensity of HO activity progressively lessens and thus the uptake of the radiotracer on the scans, which return toward normal within 12 months. However, in some cases activity remains slightly elevated even though the underlying HO has become mature (Shebab et al., 2002; as cited in Tibone et al., 1978). During the course of HO, bone scans made on follow-up may show radiotracer uptake on third phase even after flow and blood-pool images have returned to normal. Serial bone scans have been used successfully to monitor the metabolic activity of HO and determine the appropriate time for surgical resection, if needed, and to predict postoperative recurrence (Shebab et al., 2002; as cited in Freed et al., 1982; Muheim et al., 1973; Rossier et al., 1973; Tanaka et al., 1977). For the differential diagnosis of osteomyelitis complementary imaging with gallium-67 citrate (for spinal infection) or indium-111-labeled autologous leukocytes (for the appendicular

skeleton) may be necessary, as commented in that section. Gallium-67 citrate uptake in HO is proportional to the uptake of 99m Tc-diphosphonates, in contrast to the relatively greater gallium-67 citrate uptake characteristic of osteomyelitis (Shebab et al., 2002).
A diagnostic-treatment algorithm of heterotopic ossification has been proposed, and three-phase bone scintigraphy has been recommended, after clinical signs and laboratory test, for its diagnosis in patients without HO but with high risk factor. If clinical signs and symptoms are present but initial radiographic studies are normal, bone scan should be repeated after 4-6 weeks, and when scintigraphic studies have displayed the HO, it should be made every three months during the first year. Bone scan has also been proposed during the follow-up after HO removal to monitor possible recurrences (Medina et al., 2008).

12. Fractures

Following known injury, fractures are commonly demostrated by conventional radiography of most sites of trauma. In such circumstances bone scintigraphy has no major role, although unsuspected lesions may be identified. Acute fractures show increased perfusion on the radionuclide angiogram; intense, poorly marginated increased tracer accumulation representing relatively increased vascularity on the blood pool images; and intense poorly defined increased tracer accumulation on delayed images (Holder, 1993).

12.1 Occult fractures

Scintigraphy may be valuable in the diagnosis of occult fractures, which are true fractures not immediately obvious on clinical examination or plain radiography, and it is particularly useful to detect certain type of fractures that require urgent orthopedic treatment, such as femoral neck and intertrochanteric fractures, scaphoid fracture, and Lisfranc fracture. Occult femoral neck and intertrochanteric fractures are frequents in older females with continued hip pain following a fall. Shortly following the time of injury, there is an increase in perfusion to the fracture site which can be demonstrated during the rapid sequence flow study and blood pool phases of the so called three-phase bone scan. The time for first appearance of increased uptake on delayed 99mTc-diphosphonate images remains controversial, fluctuating between 24 hours and 2 weeks (Collier et al., 1993; as cited in Holder et al., 1990; Matin, 1979; Spitz, 1991). These problems are not encountered in the identification of scaphoid fracture which is readily visualized within 3 days of trauma. Bone scan demonstrates a focus of intense uptake usually centered in the scaphoid (Collier et al., 1993; as cited in Patel et al., 1992; Tiel-van-Buul et al., 1992). High-resolution bone scan images obtained with the wrist first in a neutral position and then in ulnar deviation are used to localize the scintigraphic abnormality to the scaphoid. With ulnar deviation there is movement and rotation of the scaphoid relative to adjacent bony landmarks such as the radial styloid (Collier et al., 1993). Premature imaging withing 48 hours must be avoided, particularly as the osseous scintigraphic changes may be obscured by the diffuse uptake resulting from superficial hyperemia or traumatic sinovitis. Prolonged delay of this study may also result in increased uptake associated with disuse and thus, masking the fracture (Murray, 1998). Scintigraphy is therefore of considerable value in identifying this lesion before X-ray change appears, especially as difficulty may be encountered in radiological diagnosis even after 2-3 weeks (Murray, 1998). Difficulties in identifying the exact anatomic localization of a focus of uptake can be overcome by the technique of a combined display of the scan and the X-ray (Murray, 1998; as cited in Hawkes, 1991). Other occult fracture that

can require urgent treatment is Lisfranc fracture. This fracture presents a characteristic appearance on bone scan with a band of increased uptake extending across multiple tarsometatarsal joints, typically involving the first through fifth or the second through fifth tarsometatarsal joints (Collier et al., 1993; as cited in Fogelman & Collier, 1989).

12.2 Stress fractures

Stress fracture occurs when a bone breaks after being subjected to repeated tensile or compressive stresses, none of which would be large enough to cause individually the bone to fail, in a person who is not known to have an underlying disease that would be expected to cause abnormal bone fragility (De Weber, 2011). The incidence of stress fractures is less than 1 % in the general population. The reported incidence in athletic populations varies with the type of athlete. Among military recruits the incidence ranges from 1 to 31 %, among runners 13 to 52 %, and among participants in collegiate team sports 1 to 8 % (De Weber, 2011; as cited in Bennel, 1997). In most instances, the individuals who suffer stress fractures have been engaging in vigorous activity to which they have not yet become conditioned. The failure to recognize the characteristic clinical and imaging findings of a stress fracture and the continued excessive exercise by the athlete will occasionally lead to a complete fracture (Collier et al, 1993). Imaging is needed when high risk stress fractures are suspected or a definitive diagnosis is necessary. The sites at high risk complications are the pars interarticularis of the lumbar spine, femoral head, superior side of the femoral neck, patella, anterior cortex of the tibia, medial malleolus, talus, tarsal navicular, proximal fifth metatarsal, great toe sesamoids, and the base of the second metatarsal bone (De Weber, 2011).

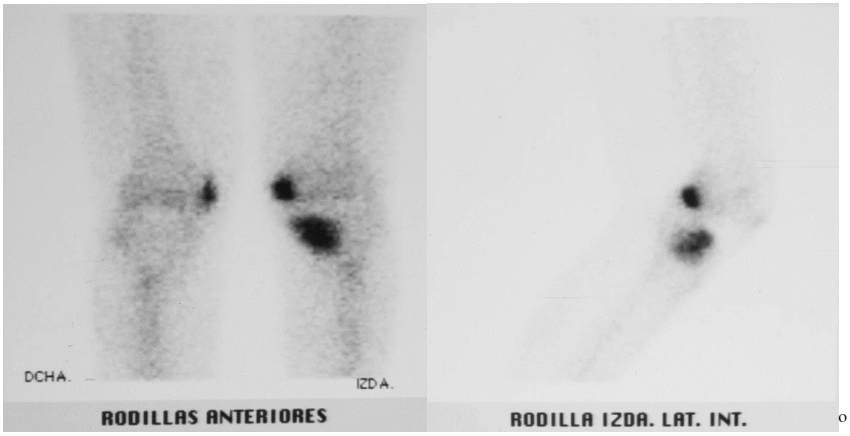


Fig. 8. Scintigraphy: localized uptake in tibial metaphysis and both internal femoral condyles.

Three-phase bone scan has traditionally been used for diagnosis of stress fractures because it can show evidence of stress fracture within 2 to 3 days of injury and has high sensitivity. Acute stress fractures appear as discrete, localized, sometimes linear areas of increased uptake on all three phases (angiographic, soft tissue, and delayed phases) of a Tc-99m-MDP bone scan (**Fig. 8**). However, the specificity of bone scan is low. Approximately 40 % of positive findings occur at asymptomatic sites (De Weber, 2011; as cited in Bennell et al., 1999). Bone scan can

also be falsely positive with shin splints, despite shin splints are typically positive only during the delayed phase of the scan (De Weber, 2011; as cited in Deutsch, 1997). Areas of increased uptake may represent subclinical sites of bone remodeling or stress reactions. Increased uptake can also appear in the setting of bone tumors, osteomyelitis, or avascular necrosis. Although rare, there are reports of false-negative bone scans (De Weber, 2011; as cited in Gaeta et al., 2005; Spitz & Newberg, 2002). Because of these limitations, MRI is supplanting bone scan as the diagnostic tool of choice when plain radiographs are negative and confirmation of suspected stress fracture is needed.

12.3 Insufficiency fractures

Insufficiency fracture occurs when the mechanical strength of a bone is reduced to the point that a stress which would not fracture a healthy bone breaks the weak one (De Weber, 2011). Most commonly postmenopausal osteoporosis is the cause for insufficiency fractures. Additional conditions affecting bone turnover include osteomalacia, chronic renal failure, and high-dose corticosteroid therapy (Krestan et al., 2011). Insufficiency fractures occur most commonly in the pelvis, including the sacrum, followed by the proximal femur and the vertebral bodies, in particular in the lower thoracic and the lumbar spine. Other sites frequently affected by insufficiency fractures are the tibia, fibula, and calcaneus (Krestan & Hojreh, 2009; as cited in Soubrier, 2003). Radiographs are the basic modality used for screening of insufficiency fractures, but depending on the location of the fractures, sensitivity is limited. Thus, MRI and CT are both standard techniques when insufficiency fracture is suspected and initial radiological studies are negative. MRI is a very sensitive tool to visualize bone marrow abnormalities associated with insufficiency fractures and allows differentiation of benign versus malignant fractures. Multidetector CT depicts subtle fracture lines allowing direct visualization of cortical and trabecular bone (Krestan et al., 2011). Bone scintigraphy is also highly sensitive and specific when typical pattern of abnormality is present. One of those typical patterns of uptake is the classical H ('Honda' sign) or butterfly-shaped appearance in sacral insufficiency fracture in the elderly osteoporotic patient without definite trauma history. The vertical limbs of the H lie within the sacral ala, parallel to the sacroiliac joints, while the transverse limb of the H extends across the sacral body. Other sacral variant uptake patterns occur frequently and include the unilateral ala, incomplete H and horizontal linear dot patterns. Iliac fractures are seen as linear areas of increased radionuclide uptake. Pubic and supra-acetabular fractures produce areas of linear or focal uptake. Concomitant findings of two or more areas of increased uptake in the sacrum and at another pelvic site are considered diagnostic of insufficiency fractures of the pelvis. If a typical pattern of abnormality is not present, the radionuclide bone scan is much less specific. If abnormal or incomplete patterns of uptake are observed, findings may be mistaken for malignancy and other etiologies. PET–CT with hybrid-scanners has been the upcoming modality for the differentiation of benign from malignant fractures (Krestan et al., 2011).

12.4 Pathologic fractures

This type of fractures is due to a localized loss of strength secondary to an underlying disease process. Examples of pathologic fractures include those that occur at sites of bone tumors (primary or metastatic), bone cysts, and infections (De Weber, 2011). About 10% of patients with known bone metastases will sustain a fracture. Most patients with high-risk conditions for bone metastasis are followed serially with bone scan to detect occult

metastasis. In general, lytic lesions are considered more prone to fracture than blastic ones. In the spine, CT or MRI are both indicated to quantify the extent of tumor infiltration, including any extension into the spinal cord and are useful in distinguishing osteoporotic vertebral collapse from pathologic fracture.

12.5 Non-union fractures

In the setting of impaired fracture healing we can distinguish three complications: the delayed union, non-union and pseudoartrhosis. Delayed union describes the situation where there are distinct clinical and radiological signs of prolonged fracture healing time (Panagiotis, 2005). Scintigrams demonstrate intense tracer concentration at the fracture site, as does a fracture undergoing normal or non-union. Therefore, differentiation of a normal or delayed union from nonunited fracture may not be possible by scintigram alone. Clinical findings along with roentgenograms are usually adequate to distinguish delayed healing from nonhealing (Desai et al., 1980). Non-union fracture is defined as the cessation of all reparative processes of healing without bone union 6 to 8 months following the fracture or by the absence of progressive repair that has not been observed radiographically between the third to sixth months following a fracture (Panagiotis, 2005). Two main types of non-union fractures are differentiated according to the viability of the ends of the fragments (Frölke& Patka, 2007; as cited in Weber & Cech, 1976): Avascular non-union and hypervascular non-union. In the first type the ends of the fragments are avascular or atrophic, inert and incapable of biologic reaction, and therefore bone scintigraphies indicate a poor blood supply at the edges of the fragments (Frölke& Patka, 2007). On delayed images atrophic non-union rim is seen as a photon deficient band between fracture ends (Holder, 1993). The main problem in this type is the poor quality of the bone ends and the significantly diminished potential for repair (Gelalis et al., 2011). In the second type the rims of the fragment are hypervascular or hypertrophic and are capable of biological reaction. Bone scintigraphy in the latter indicates a rich blood supply in the ends of the fragments (Frölke& Patka, 2007). The main problem in this type is inadequate fracture stability or reduction. The third complication, pseudoarthrosis, is a non-union fracture which may take years to develop and may occur without clinical symptoms. It is characterised by the formation of a false joint where a fibrocartilaginous cavity is lined with synovium producing synovial fluid (Panagiotis, 2005; as cited in McKee, 2000). Scans using Tc-99m-MDP show the presence of a synovial pseudoarthrosis (Csongradi & Maloney, 1989; as cited in Esterhai et al., 1984). Two types can be distinguished as in the non-union fractures: atrophic and hypertrophic pseudoarthrosis. The first one is characterized in the scintigraphy by the absence of peripheral accumulation in contrast with the intense uptake surrounding a hypertrophic pseudoarthrosis. Those finding in the bone scan are highly suspect for pseudoartrhosis after 12 months. The use of SPECT with bone scanning enhances the sensitivity and specificity, especially in the pseudoarthrosis of the spine after a lumbar spinal fusion (Collier et al., 1993; Lee & Worsley, 2006). SPECT identifies a more focal area of intense activity within the area of increased accumulation at the fusion site (Murray, 1998). Some authors have used radionuclide scans to determine whether the fracture has the biologic ability to respond to a specific therapy such as electrical stimulation. With mature nonunions, radionuclide scans can identify large hypovascular areas that have no potential for healing. In such cases, operative intervention is needed. In a case of nonunion, the possibility of infection must be considered. An increase in activity at the fracture site on the radionuclide scan is consistent with both bony healing and infection. Infection at the

fracture site can also be a cause of persistent pain and contribute to the non-union (Csongradi & Maloney, 1989). Gallium scan is indicative of infection if 67Ga uptake exceeds 99mTc uptake on the bone scan. The most specific tracers for infection however are leukocytes labelled with indium-111 or 99mTc (Schelstraete et al., 1992).

13. Technical aspects and applications of bone scintigraphy in pediatric populations

13.1 Technical aspects of bone scintigraphy in pediatric populations

Technical considerations concerning care of the child, immobilization, dosing of radiopharmaceuticals, and instrumentation are of major importance in pediatric nuclear medicine. It is routine in many dedicated pediatric nuclear medicine departments to allow parents or siblings to remain in the imaging room to provide a sense of security and safety for the child. Similarly, the patient is allowed to hold a favorite toy or a prized possession and parents are instructed to bring such items with them for the test. Children are often most worried about the needle required for the injection. Many nuclear medicine departments now routinely use the application of topical anesthetic creams as part of the preparation for the examination (Nadel & Stilwell, 2001). Immobilization techniques to gain patient support in pediatric studies can vary from wrapping the patient to the use of sedation and general anesthesia. For neonates to age 2, it may suffice to hold the patient in place, deprive sleep, and feed the child while on the imaging table. Papoose techniques for bundling and entertainment including television, movies, music, or stories can be used to immobilize children older than 4 to 5 years of age. The cooperation of an older child can often be obtained if the procedure is carefully explained to them and their parents. Children between the ages of 2 and 5, or who are mentally retarded, or have severe attention deficit problems, are more likely to require sedation (Nadel & Stilwell, 2001). Guidelines from the American College of Radiology and the American Academy of Pediatrics can help in developing an appropriate institutional sedation protocol (Shammas, 2009; as cited in Gilday, 2003).

The correct dosing for administration of radiopharmaceuticals to children is available in standard pediatric nuclear medicine texts and can be based on either body surface area or the weight of the child relative to adult dosage (Nadel & Stilwell, 2001; as cited in Miller & Gelfand, 1994; Treves, 1995). 99mTc- MDP is the most commonly used radiopharmaceutical for bone scintigraphy. Scanning is usually performed as a three-phase bone scan with immediate blood flow and blood pool imaging of the site of symptoms obtained after injection, followed by delayed imaging 1.5 to 2 hours later. It is important that the children are well hydrated to have optimum visualization. Other radiopharmaceuticals are also useful in the evaluation of musculoskeletal disease, such as 67Ga citrate or labelled leukocytes using indium-111 or 99mTc for musculoskeletal infection or a bone marrow scan using a 99mTc-sulfur colloid for bone marrow infarction, particularly in sickle cell disease (Shammas, 2009; as cited in Connolly et al., 2007; Gilday, 2003; Nadel & Stilwell, 2001). 18F-FDG is the most common radiopharmaceutical used for PET or PET/CT. 18F-FDG accumulation occurs in inflammation and infection (Shammas, 2009; as cited in Love et al., 2005; Zhuang & Alavi, 2002). Imaging of inflammation with 18F-FDG PET relies on the fact that infiltrated granulocytes and tissue macrophages use glucose as an energy source. When they are activated in inflammation, metabolism and thus FDG uptake increases (Shammas, 2009; as cited in Kubota et al., 1992).

Proper positioning is important in pediatrics particularly in young infants, and although children are smaller, it does not imply that more of a child can be imaged on a single scintigraphic view. In fact, examinations take longer in children and infants because of the requirement of joint-to-joint images for detailed assessment. Although the new gamma camera systems often allow whole-body passes it is often necessary to supplement these images with magnified spot views or even pinhole imaging. Image magnification either with camera zoom, computer magnification, or collimation is essential when performing scintigraphic examinations in children. Magnification is either optical with collimation or electronic. Optical magnification uses either a pinhole or converging collimator, enlarges the image, and improves overall system resolution. Electronic magnification makes the image bigger without altering overall system resolution. The capability for SPECT imaging is essential in pediatric scintigraphy. SPECT allows for improved image contrast and hence improved diagnostic accuracy. It is helpful in localizing and further defining most musculoskeletal abnormalities to include the extremities and is essential when assessing a child with the clinical problem of back pain. Multiple head detector gamma camera systems are becoming more available in pediatric centers. The advantages of these systems include increased resolution and sensitivity and decreased time of examination in a child. Correlative imaging is essential to state of the art practice of pediatric nuclear medicine. Computer multimodality image fusion programs are becoming available and more sophisticated. They allow comparison of different isotope scintigraphic studies or serial studies in the same patient or comparison of scintigraphy with other imaging modalities, such as CT, MR imaging, and PET for better correlation of anatomy and function. New combined gamma camera and CT devices allowing direct anatomic and physiologic correlation are also being manufactured and will have further impact on the care of the pediatric patient.

The normal distribution in a pediatric bone scan may differ from adults (Shammas, 2009; as cited in Nadel, 2007). In children there is high physeal and apophyseal uptake due to their rich blood supply and active enchondral ossification. Absence of uptake in nonossified cartilaginous structures should not be mis- taken for avascular necrosis. Regions where this may be of concern in younger children include the femoral capital epiphysis, patella, and navicular bone. Before ossification, the ischiopubic synchondrosis appears as a discontinuity of the inferior pubic ramus. During ossification, increased uptake in ischiopubic synchondroses is a common normal variant and should not be misinterpreted as a pathological lesion (Shammas, 2009).

13.2 Applications of bone scintigraphy in pediatric populations

13.2.1 Infections

Acute osteomyelitis is a common pediatric disease that mostly affects children under 5 years old. It usually is the result of hematogenous spread of infection due to the rich vascular supply of the growing skeleton. Typically, bone scan become positive 24 to 72 hours after the onset of infection, while plain films do not manifest evidence of infection until 3 to 4 weeks after. Therefore, three-phase bone scintigraphy is the most sensitive imaging modality for early diagnosis. The sensitivity of a three-phase bone scan has been estimated as 94% with a specificity of 95% (Shammas, 2009; as cited in Schauwecker, 1992). Ideally, scintigraphic imaging should be obtained before joint aspiration, and a delayed whole-body scan on skeletal phase should be obtained because osteomyelitis in childhood can be multifocal or present with referred pain. In addition, malignant disease such as leukemia

and sarcoma may mimic acute osteomyelitis (Shammas, 2009; as cited in Connolly et al., 2007; Ma et al., 2007). All three phases of the bone scan show focally high uptake in the affected bone. Occasionally, the affected bone in children shows low uptake or a photopenic defect (cold osteomyelitis) (Shammas, 2009; as cited in Pennington, 1999). This is most likely due to reduced tracer delivery by increased intraosseous pressure from inflammation, oedema, and joint effusion (Shammas, 2009). Cellulitis may be differentiated from osteomyelitis because the former typically demonstrates diffuse increased activity in the soft tissues on the first two phases, without focal osseous abnormality on the third phase (Shammas, 2009; as cited in Wegener & Alavi, 1991). Although chronic recurrent multifocal osteomyelitis (CRMO) and acute osteomyelitis share a common histopathologic feature, namely chronic inflammation, they are different in important ways (Nadel & Stilwell, 2001). CRMO occurs most frequently in the latter half of the first decade and the first half of the second decade of life, and it is more common in girls, differently from acute osteomyelitis that occurs in children under 5 years old (Shammas, 2009). A predisposing cause is not found for CRMO in contrast to conventional osteomyelitis (Nadel & Stilwell, 2001). Bone scintigraphy is helpful in identifying the multifocal bone lesions and characteristically displays high uptake in both symptomatic and asymptomatic lesions (Shammas, 2009, as cited in Connolly, 2007). Other infection typical of children under 3 years of age is septic arthritis. Monoarticular involvement is the most common pattern. The more affected joints are the knees and the hips. As in the osteomyelitis, there is an increased uptake on all three phases of three-phase bone scan, but in septic arthritis there is a symmetric uptake in both sides of the joint (Diaz& De Haro, 2005). Transient synovitis is the most common condition that mimics septic arthritis. In this case, three-phase bone scan may be normal or may show diffuse increased activity on the first two phases. Delayed images may displa periarticular increased activity in the affected joint (Shammas, 2009).

13.2.2 Legg-Calve Perthe disease

Legg-Calve Perthes disease is an idiopathic ischemic necrosis of the femoral head that occurs characteristically in children between 5 to 8 years. Bone scintigraphy is more sensitive than radiography for early diagnosis, and comparable to MRI (Shammas, 2009; as cited in Ma et al., 2007). Studies performed early after the onset of clinical symptoms show absence of activity in the capital femoral epiphysis and it may precede radiographic changes (Shammas, 2009; as cited Connolly & Treves, 1998). Later scans may demonstrate increased activity due to revascularization and remodeling. Bone scintigraphy has also a pronostic value and can be used in routine management to identify patients at high risk for a poor outcome (Shammas, 2009; as cited in Comte et al., 2003): Persistent absence of bone uptake in the proximal femoral epiphysis after 5 months or metaphyseal hyperactivity is highly correlated with more severe disease and a poorer prognosis. The early formation of a lateral column of tracer uptake in the capital femoral epiphysis, even before radiography, is associated with a good prognosis due to early revascularization (Shammas, 2009; as cited in Conway, 1993 and Tsao et al., 1997).

13.2.3 Slipped capital femoral epiphysis

Slipped capital femoral epiphysis is characterized by a displacement of the capital femoral epiphysis from the femoral neck through the physeal plate with medial and posterior rotation of the epiphysismost commonly in the adolescence. Bone scintigraphy is useful for

assessing the vascularity of the femoral head. In the absence of avascular necrosis, the bone scan findings in slipped capital femoral epiphysis are nonspecific and consist of mildly increased activity with widening and blurring of the growth plate activity (Shammas, 2009; as cited in Connolly et al., 2006, 2007).

13.2.4 Sickle cell disease

Sickle cell disease is the most common hereditary blood disorders. It occurs almost exclusively among black americans and black africans, related with the presence of a mutated form of hemoglobin, hemoglobin S. Bone and joint problems are the most common manifestations. Distinguishing sickle cell crisis with possible bone marrow infartion from osteomyelitis is a challenge (Shammas, 2009; as cited in Connolly et al., 2007). Bone marrow scan with 99mTc-sulfur colloid plus conventional bone scan may be used in the evaluation of sickle cell disease, but it should be done within the first 7 days after the pain onset to be helpful in the differential diagnosis (Shammas, 2009). If the bone marrow scan is abnormal at the site of pain, followed by normal or decreased uptake on conventional bone scan, infarction is the likely diagnosis. Increased uptake in blood pool and delayed images on conventional bone scan is more suggestive of osteomyelitis (Shammas, 2009; as cited in Gilday, 2003).

13.2.5 Reflex sympathetic dystrophy

Reflex sympathetic dystrophy has also been described elsewhere in this chapter. The typical findings on three-phase bone scan are hyperemia on the first two phases with intense periarticular activity in the affected extremity. In children, a cold variant has been reported, which is characterized by decreased activity in the three phases of the scintigraphy in the affected limb, compared with the nonaffected limb (Shammas, 2009; as cited in Nadel, 2007).

13.2.6 Fractures

The occult fracture more common in children is the Toddler's fracture, which is a spiral or oblique fracture that can occur from pelvis to feet but mostly involves the tibia (Shammas, 2009). Radiographic findings are often subtle and fractures may not be apparent, for that reason bone scan is a valuable tool for detecting this injury. Scintigraphy shows diffuse increased uptake in the tibial diaphysis or the bone affected. A linear or spiral pattern of high uptake may be seen in some children (Shammas, 2009; as cited in Connolly et al., 2006; Gilday 2003).

Among stress fractures, spondylolysis is the more important in children with back pain, which represent a stress fracture of the pars interarticularis of the vertebra, commonly in the lower lumbar spine secondary to repetitive minor trauma such as hyperextension (Shammas, 2009). Clinical signs and symptons and radiographies are normally used for the diagnosis. A bone scan or a MRI may be necessary to determine if the spondylolysis is active or inactive. Bone scintigraphy shows little or no abnormality on blood pool images, but it typically demonstrates focally high uptake in the region of the pars interarticularis on delayed images. SPECT imaging is more sensitive than planar studies and detects abnormalities in about a third of individuals with normal planar examinations and so, it is recommended in the evaluation of low back pain in young athletes (Shammas, 2009; as cited in Sty, 1993).

Scintigraphy has also an important role to provide a quick assessment for defining and characterizing the extent and severity of trauma in the setting of child abuse, complementary

to other radiologic investigations. Its major advantage is the increased sensitivity in detecting evidence of soft-tissue and bone trauma (25%to 50%), and in the documentation of specific and characteristic sites of abuse, such as in the ribs or the diaphyses of the extremities (Nadel & Stilwell, 2001; as cited in Conway et al., 1993, Sty & Wells, 1994).

13.2.7 Primary bone tumors in childhood

Benign bone tumors are by far the most common type of tumors that grow within the skeleton. Nonossifying fibromas, osteochondromas and simple bone cysts are the types most often found in children and teenagers. Children between the ages of 6 and 12 are the most likely to develop benign bone tumors, although the tumors sometimes show up in children as young as age 2. Exostosis tumors are slightly more common in boys than girls. Nonossifying fibroma usually is in the actively growing sections of long bones such as the thighbone (femur). Exostosis (osteochondroma) contains both bone and cartilage and usually grows in the thighbone, the shinbone (tibia) or the bone in the upper arm (humerus). Unicameral (simple) bone cysts are holes in the bone that fill with fluid and tissue. They usually occur in the bone in the upper arm or in the upper part of the thighbone. In some cases, a benign bone tumor can cause problems while it grows. It can weaken the child's bone and make it more likely that the bone will break. Tumors also can press on nerves and cause pain. In cases like these, surgery may be necessary. Malignant primary bone tumors make up 5% of childhood malignancies, and osteosarcoma is the most commonly isolated malignant bone tumor in children, followed by Ewing's sarcoma. These bone neoplasms usually begin during childhood and adolescence, when bones are growing quickly and they often are taking part in sports and other physical activities. Langerhans cell histiocytosis is also more common in the pediatric population. A smaller number of patients have other diagnosis such as malignant fibrous histiocytoma, angiosarcoma and chondrosarcoma, but these conditions are very rare in paediatric population. The use of nuclear medicine techniques in the diagnosis, staging and monitoring of the different bone tumors has been detailed in a previous section of this chapter. FDG-PET has become to be one of the best tools for the baseline evaluation and follow-up, although some benign bone lesions may show high 18F-FDG accumulation, equivalent to osteosarcomas. Despite this, 18F-FDG-PET has a high specificity for excluding malignant bone tumors (Cook et al., 2010). FDG- PET has been shown to help determine the presence and extent of sarcomas and even may allow the noninvasive estimation of the histologic grade of some tumors, although the biopsy remains necessary. This technique allows targeted biopsies, which can reduce the likelihood of underestimation of tumor grade and inadequate therapy. Furthermore, 18F-FDG-PET is useful in the pediatric population for detection of skip metastases in cases of equivocal MRI findings (Even-Sapir, 2007).

14. Therapeutic alternatives with radionuclides: Radiosynoviorthesis

In the treatment of inflammatory rheumatic diseases with chronic course, operative and respectively arthroscopic synovectomy on the one hand and synoviorthesis on the other hand come into question. Synoviorthesis by corticosteroids has a very large indication if the corresponding measures of precaution are heeded. Chemical synoviorthesis, mainly by osmium tetroxide, is applied above all in exudative inflammatory diseases, whereas radiosynoviorthesis with the nuclides used at present is mainly applied in proliferative diseases. The cytotoxic effects intrinsic to the beta radiation emission from some

radionuclides have been exploited by nuclear medicine and, as well as treating several forms of neoplasia, this method can also be used to treat a number of benign articular pathologies in the field of rheumatology. Carry out a 'radiosynovectomy' procedure is possible after intra-articular administration of suitable radiopharmaceuticals. The direct irradiation of the synovial membrane can produce a therapeutic effect on persistent synovitis that is resistant to traditional drug treatment. The radiopharmaceuticals that have been used to date for radiosynovectomy are made up of small colloidal particles labelled to β-emitting isotopes (yttrium-90, rhenium-186, erbium-169, samarium-153). These compounds release their radiation energy within a radius of a few millimetres from the uptake sites. These substances are phagocytized by synoviocytes localised in relation to the synovia and it creates a radiation source that can act locally and reduce inflammatory and proliferative elements (Colamussi et al., 2004; as cited in Gumpel et al., 1975). The availability of new radiopharmaceuticals, created by replacing the colloid vector with hydroxyapatite crystals, has allowed the main undesired effect of these substances (radiation to other organs such as drainage lymph nodes, liver, spleen and bone marrow, due to the passage of the radio compound from the articular cavity to the lymphatic and then to the blood flow systems) to be avoided (Clunie et al., 1996). In the absence of side effect, this technique of low cost may be useful, not only in the treatment of advanced stage and drug-resistant arthropathies, but also to manage pain and improve articular function in the first stages of rheumatoid arthritis (Colamussi et al., 2004; as cited in Uyeo et al., 1978). A fundamental element to the success of radiosynovectomy therapy is that treatment is started early in the disease's history. This is because while radiation therapy can successfully control proliferation of the inflamed synovial membrane, it is not effective in joints that have suffered advanced osteo-cartilage damage and where the synovitic component is virtually non-existent (Franssen et al., 1989). Cases reported would further suggest its use in a wider spectrum of rheumatic disorders ranging from spondylitis to Paget's disease and from hæmophiliac synovitis to pigmented villonodular synovitis. Nevertheless, despite abundant anecdotal evidence of its efficacy, there is a paucity of controlled trials and those that have been done have produced conflicting results (Dos Santos et al., 2009, 2011) and/or have been of insufficient sample size. Two meta-analyses have been published. The first one (Jones, 1993) was made in order to assess the evidence on yttrium-90 therapy for chronic synovitis of the knee. It found out that Yttrium was superior to placebo (OR 2.42, 95% CI 1.02-5.73), although possible publication bias limited the interpretation of this result. Yttrium was not superior to triamcinolone (OR 1.89, 95% CI 0.81-10.55) or other active modalities (OR 1.04, 95% CI 0.72-1.52). The second one and most recent (Van der Zant et al., 2009) has been published with the objective to perform a systemic review and meta-analysis on the effectiveness of radiosynoviorthesis. It has shown high success rates of radiosynoviorthesis, but differences in effect with glucocorticoid injection are less evident, although there is marked heterogeneity in study design of a small number of comparative studies. Therefore the efficacy of radiosynovectomy alone or in combination with steroid therapy must be assessed by other sufficiently powered randomised controlled studies.

15. Conclusion

Nuclear medicine techniques supply physiological information that is complementary to that provided by radiological techniques and can play a fundamental role not only for the examination and treatment of articular disorders but also in overall patient evaluation.

Though scintigraphical examination is ideal in the early stages of diseases, it also plays a complementary role to radiographical investigations in more advanced disease stages. An assessment as complete as possible which includes different complementary studies must be performed to achieve the best diagnostic and prognostic accuracy. In this context, conventional scintigraphy is still a major test in a limited number of rheumatological diseases such as Paget, reflex sympathetic dystrophy and osteonecrosis, and can be a useful complementary study in other diseases. New molecular imaging tools for the evaluation of musculoskeletal diseases are now available and these particular tools will advance the understanding and management of several chronic musculoskeletal diseases. In the next decade, PET/CT and SPECT/CT will be the major workhorses for molecular imaging, with the advantage that PET-based technologies have high sensitivity and the ability to use biologic molecules that can be radiolabelled.

Despite the important role of the anatomic imaging techniques in the evaluation of primary bone tumors and metastases, radionuclide imaging techniques have all been used in the assessment of these disorders. PET and hybrid PET/CT imaging are becoming the most important modalities in this field.

B-radiation emission from some radionuclides has been exploited by nuclear medicine and has been used to treat benign joint pathologies, as well as treating several forms of neoplasia. It is of interest in the field of rheumatology, since it is as a safe procedure and, after intra-articular administration of suitable radiopharmaceuticals, is able to control proliferation of the inflamed synovial membrane in the treatment of chronic arthropathies, particularly in the initial stages of the disease.

16. References

Aoki J, Watanabe H, Shinozaki T, Takagishi K, Ishijima H, Oya N, Sato N, Inoue T & Endo K. (2001). FDG PET of primary benign and malignant bone tumors: Standardized uptake value in 52 lesions. *Radiology*; 219: 774-777.

Bálint G & Szebenyi B. (1996). Diagnosis of osteoarthritis. Guidelines and current pitfalls. *Drugs*; 96; 52 Suppl 3:1-13.

Beheshti M, Langsteger W & Fogelman I. (2009). Prostate cancer: Role of SPECT and PET in imaging bone metastasis. *Semin Nucl Med*; 39 (6): 396-407.

Benning R & Steinert H. (1988). Diagnostic criteria of Sudeck's syndrome. *Rontgenblatter*; 41 (6): 239-45.

Biswal S, Resnick DL, Hoffman JM & Gambhir SS. (2007). Molecular imaging: integration of molecular imaging into the musculoskeletal imaging practice. *Radiology*; 244 (3): 651-71.

Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L & Bobbaers H. (2006). Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. *Arthritis Rheum*; 55: 131–137.

Brenner W, Bohuslavizki KH & Eary JF. (2003). PET Imaging of Osteosarcoma. *J Nucl Med*; 44: 930–942.

Brown ML, Collier BD, Fogelman Jr & Fogelman I. (1993). Bone Scintigraphy: Part 1. Oncology and Infection. *J Nuci Med*; 34: 2236-2240.

Buckland-Wright C. (1997). Current status of imaging procedures in the diagnosis, prognosis and monitoring of osteoarthritis. *Baillieres Clin Rheumatol*; 11 (4): 727-48.

Chew FS & Hudson TM. (1982). Radionuclide bone scanning of osteosarcoma: Falsely extended uptake patterns. *AJR Am J Roentgenol*; 139: 49-54.

Clunie G, Lui D, Cullum I, Ell PJ & Edwards JC. (1996). Clinical outcome after one year following samarium-153 particulate hydroxyapatite radiation synovectomy. *Scand J Rheumatol*; 25: 360–366.

Colamussi P, Prandini N, Cittanti C, Feggi L & Giganti M. (2004). Scintigraphy in rheumatic diseases. *Best Pract Res Clin Rheumatol*; 18 (6): 909–926.

Collier D, Fogelman I & Brown ML. (1993). Bone Scintigraphy: Part 2. Orthopedic Bone Scanning. *J Nuci Med*; 34: 2241-2246.

Cook GJ, Blake GM, Marsden PK, Cronin B & Fogelman I. (2002). Quantification of skeletal kinetic indices in Paget's disease using Dynamic 18F-fluoride positron emission tomography. *J Bone Miner Res*; 17: 854-859.

Cook GJR, Gnanasegaran G & Chua S. (2010). Miscellaneous Indications in Bone Scintigraphy: Metabolic Bone Diseases and Malignant Bone Tumors. *Semin Nucl Med*; 40: 52-61.

Csongradi JJ & Maloney WJ. (1989). Ununited lower limb fractures. *West*; 150 (6): 675-80.

Dasgeb B, Mulligan MH, Kim CK. (2007). The current status of bone scintigraphy in malignant diseases. *Semin Musculoskelet Radiol*; 11 (4): 301-11.

De Gersem R & Jamar F. (2010). Nonspecific human immunoglobulin G for imaging infection and inflammation: what did we learn? *Q J Nucl Med Mol Imaging*; 54 (6): 617-28.

De Leonardis F, Orzincolo C, Prandini N & Trotta F. (2008). The role of conventional radiography and scintigraphy in the third millennium. *Best Pract Res Clin Rheumatol*; 22: 961- 979.

De Weber K. (2011). Overview of stress fractures, In: *Uptodate*. Eiff P & Grayzel J.

Desai A, Alavi A, Dalinka M, Brighton C & Esterhai J. (1980). Role of bone scintigraphy in the evaluation and treatment of nonunited fractures: Concise communication. *J NuclMed*; 21: 931-934.

Devogelaer JP & de Deuxchaisnes CN. (2003). Paget´s disease of bone. In: *Rheumatology* Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME & Weishman MH (ed SV Mosby). 3rd edn. pp. 2139-2147. Toronto.

Diaz C & De Haro FJ. (2005). Estudios isotópicos del sistema musculoesquelético y densitometría ósea, In: *Técnicas de exploración en Medicina Nuclear*. (Ed) Masson, pp 131 – 148. ISBN 84-458-1420-6, Barcelona, Spain.

Dos Santos MF, Furtado RN, Konai MS, Castiglioni ML, Marchetti RR, Silva CP & Natour J. (2011). Effectiveness of radiation synovectomy with Yttrium-90 and Samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled, randomized, double-blinded trial. *Clin Rheumatol*; 30 (1): 77-85.

Dos Santos MF, Furtado RN, Konai MS, Castiglioni ML, Marchetti RR & Natour J. (2009). Effectiveness of radiation synovectomy with samarium-153 particulate hydroxyapatite in rheumatoid arthritis patients with knee synovitis: a controlled randomized double-blind trial. *Clinics (Sao Paulo)*; 64 (12): 1187-93.

Driessens M, Dijs H, Verheyen G & Blockx P. (1999). What is reflex sympathetic dystrophy? *Acta Orthop Belg*; 65 (2): 202-17.

Durie BG, Waxman AD, D'Agnolo A & Williams CM. (2002). Whole-body 18F-FDG PET identifies high-risk myeloma. *J Nucl Med*; 43: 1457-1463.

El-Maghraby TA, Moustafa HM & Pauwels EK. (2006). Nuclear medicine methods for evaluation of skeletal infection among other diagnostic modalities. *Q J Nucl Med*; 50 (3): 167-92.

Elzinga EH, van der Laken CJ, Comans EF, Boellaard R, Hoekstra OS, Dijkmans BA, Lammertsma AA & Voskuyl AE. (2011). 18F-FDG PET as a tool to predict the clinical outcome of infliximab treatment of rheumatoid arthritis: an explorative study. *J Nucl Med*; 52 (1):77-80.

Even-Sapir E. (2005). Imaging of Malignant Bone Involvement by Morphologic, Scintigraphic, and Hybrid Modalities. *J Nucl Med*; 46:1356-1367.

Even-Sapir E. (2007). PET/CT in Malignant Bone Disease. *Semin Musculoskelet Radiol*; 11 (4): 312 – 321.

Fogelman I & Carr D. (1980). A comparison of bone scanning and radiology in the assessment of patients with symptomatic Paget's disease. *Eur J Nucl Med*; 5: 417-421.

Fogelman I & Cook GJR. (2003). Scintigraphy in Metabolic Bone disease. In: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* Murray J. Favus (5th ed.) pp. 189 – 195. ISBN 0-9744782-0-2.

Frölke JP & Peter P. (2007). Definition and classification of fracture non-unions. *Injury*; 38 (2): 19-22.

Fournier RS & Holder LE. (1998). Reflex sympathetic dystrophy: diagnostic controversies. *Semin Nucl Med*; 28 (1): 116-23.

Fransen P, Mestdagh C & Dardenne G. (1998). Pagetic sarcoma of the calvarium: report of two cases. *Acta Neurol Belg*; 98: 352–355.

Franzius C, Daldrup-Link HE, Sciuk J, Rummeny EJ, Bielack S, Jürgens H & Schober O. (2001). FDG-PET for detection of pulmonary metastases from malignant primary bone tumors: comparison with spiral CT. *Ann Oncol*; 12: 479–486.

Franssen MJ, Boerbooms AM, Karthaus RP, Buijs WC & van de Putte LB. (1989). Boerbooms AM, Karthaus RP et al. Treatment of pigmented villonodular synovitis of the knee with yttrium-90 silicate: prospective evaluations by arthroscopy, histology, and 99mTc pertechnetate uptake measurements. *Ann Rheum Dis;* 48: 1007–1013.

Gelalis ID, Politis AN, Arnaoutoglou CM, Korompilias AV, Pakos EE, Vekris MD, Karageorgos A & Xenakis TA. (2011). Diagnostic and treatment modalities in nonunions of the femoral shaft. *Injury*, doi: 10.1016/j.injury.2011.06.030.

Gemmel F, Dumarey N & Palestro CJ. (2006). Radionuclide imaging of spinal infections. *Eur J Nucl Med Mol Imaging*; 33 (10): 1226-37.

Glaudemans AW, Dierckx RA, Kallenberg CG & Fuentes KL. (2010). The role of radiolabelled anti-TNFα monoclonal antibodies for diagnostic purposes and therapy evaluation. *Q J Nucl Med Mol Imaging*; 54(6): 639-53.

Gnanasegaran G, Cook G, Adamson K & Fogelman I. (2009). Patterns, Variants, Artifacts, and Pitfalls in Conventional Radionuclide Bone Imaging and SPECT/CT. *Semin Nucl Med*; 39: 380-395.

Gotthardt M, Bleeker-Rovers CP, Boerman OC & Oyen WJG. (2010). Imaging of Inflammation by PET, Conventional Scintigraphy, and Other Imaging Techniques. *J Nucl Med*; 51: 1937–1949.

Green RAR. Nuclear Medicine. (2009). In: *Imaging of Bone Tumors and tumor-like lesions: Techniques and Applications*. Davies AM, Sundaram M & James SLJ (Ed) pp. 53- 93. ISBN 978-3-540-77982-7, Berlin, Germany.

Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H & Roemer FW. (2008). Imaging in osteoarthritis. *Rheum Dis Clin North Am*; 34 (3): 645-87.

Guermazi A, Eckstein F. Hellio Le Graverand-Gastineau MP, Conaghan PG, Burstein D, Keen H, Roemer FW. (2009). Osteoarthritis: current role of imaging. *Med Clin North Am;* 93 (1): 101-26, xi.

Hang LW, Hsu WH, Tsai JJ, Jim YF, Lin CC & Kao A. (2004). A pilot trial of quantitative Tc-99m HMPAO and Ga-67 citrate lung scans to detect pulmonary vascular endothelial damage and lung inflammation in patients of collagen vascular diseases with active diffuse infiltrative lung disease. *Rheumatol Int*; 24 (3): 153-6.

Haugeberg G. (2008). Imaging of metabolic bone diseases. *Best Pract Res Clin Rheumatol*; 22 (6): 1127–1139.

Hautzel H, Sander O, Heinzel A, Schneider M & Müller HW. (2008). Assessment of large-vessel involvement in giant cell arteritis with 18F-FDG PET: introducing an ROC-analysis-based cutoff ratio. *J Nucl Med*; 49: 1107–1113.

Herranz R, Pons F & Del Río L. (1990). Exploraciones isotópicas del sistema musculoesquelético, In: Imágenes en medicina nuclear. Diagnóstico morfológico y funcional, Idepsa, pp.126-153, ISBN: 8485600754, Madrid, Spain.

Hoffer PB & Genant HK. (1976). Radionuclide joint imaging. *Semin Nucl Med*; 6 (1): 121-37.

Holder LE. (1993). Bone scintigraphy in skeletal trauma. *Radiol Clin North Am*; 31(4):739-81.

Horwich P. (2011). Approach to imaging modalities in the setting of suspected osteomyelitis, In: *UpToDate,* Sexton DJ, Hochman M &Baron EL.

Howman-Giles R, Hicks RJ, McCowage G & Chung DK. (2006). Primary bone tumors. In: *Practical Pediatric PET imaging*. Martin Charron (Ed), pp: 267 – 301. ISBN-10: 0-387-28836-8. Toronto, Japan.

Hu J & Du N. (2009). Early evaluation of osteoarthritis using objective diagnostic methods. *Zhongguo Gu Shang*; 22 (5): 402-4.

Jones G. (1993). Yttrium synovectomy: a meta-analysis of the literature. *Aust N Z J Med*; 23 (3): 272-5.

Jones LC. (2011). Osteonecrosis. In: *UpToDate*, Goldenberg DL.

Kim EE, Haynie TP, Podoloff DA, Lowry PA & Harle TS. (1989). Radionuclide imaging in the evaluation of osteomyelitis and septic arthritis.*Crit Rev Diagn Imaging,* 29(3):257-305.

Krestan CR, Nemec U & Nemec S. (2011). Imaging of insufficiency fractures. *Semin Musculoskelet Radiol*; 15 (3): 98-207.

Krestan C & Hojreh A. (2009). Imaging of insufficiency fracture. *Eur J Radiol*; 71 (3): 398-405.

Lalani T. (2011). Overview of osteomyelitis in adults. In: *UpToDate,* Sexton, DJ & Baron EL.

Lee E & Worsley DF. (2006). Role of radionuclide imaging in the orthopedic patient. *Orthop Clin North Am;* 37 (3): 485-501.

Lee GW & Weeks PM. (1995). The role of bone scintigraphy in diagnosing reflex sympathetic dystrophy. *J Hand Surg Am*; 20 (3): 458-63.

Lodge MA, Lucas JD, Marsden PK, Cronin BF, O'Doherty MJ, Smith MA. (1999). A PET study of 18FDG uptake in soft tissue masses. *Eur J Nucl Med*; 26: 22-30.

Love C, Din AS, Tomas MB, Kalapparambath TP & Palestro CJ. (2003). Radionuclide bone imaging: an illustrative review. *Radiographics*; 23 (2): 341-58.

Love C, Marwin SE & Palestro CJ. (2009). Nuclear medicine and the infected joint replacement. *Semin Nucl Med*; 39 (1): 66-78.

Love C, Tomas MB, Marwin SE, Pugliese PV & Palestro CJ. (2001). Role of nuclear medicine in diagnosis of the infected joint replacement.*Radiographics*; 21 (5): 1229-38.

Malizos KN, Karantanas AH, Varitimidis SE, Dailiana ZH, Bargiotas K & Maris T. (2007). Osteonecrosis of the femoral head: etiology, imaging and treatment. *Eur J Radiol*; 63 (1): 16-28.

Malviya G, Conti F, Chianelli M, Scopinaro F, Dierckx RA & Signore A. (2010). Molecular imaging of rheumatoid arthritis by radiolabelled monoclonal antibodies: new imaging strategies to guide molecular therapies. *Eur J Nucl Med Mol Imaging*; 37: 386–398.

McQueen FM & Ostergaard M (2007). Established rheumatoid arthritis: new imaging modalities. *Best Pract Res Clin Rheumatol*; 21: 841–856.

Meller J, Sahlmann CO, Gürocak O, Liersch T & Meller B. (2009). FDG-PET in patients with fever of unknown origin: the importance of diagnosing large vessel vasculitis. *Q J Nucl Med Mol Imaging*; 53: 51–63.

Moog F, Kotzerke J, Reske SN. (1999). FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. J Nucl Med; 40: 1407–1413.

Murray IPC (1998). Bone scintigraphy: the procedure and interpretation. In: Nuclear Medicine in clinical diagnosis and treatment, Livingstone, pp 1125 – 1152, ISBN 044305861X, Edinburgh, Scotland.

Murray IPC. (1998). Bone scintigraphy in trauma, In: Nuclear Medicine in clinical diagnosis and treatment, Livingstone C; 1241-1267, 044305861X, Edinburgh.

Murray IPC. (1998). Vascular manifestations, In: Nuclear Medicine in clinical diagnosis and treatment, Livingstone C; 1223-1239, 044305861X, Edinburgh.

Naddaf SY, Collier BD, Elgazzar AH & Khalil MM. (*2004).* Technical Errors in Planar Bone Scanning. *J Nucl Med Technol;* 32: 148-153.

Nadel HR & Stilwell ME. (2001). Nuclear medicine topics in pediatric musculoskeletal disease: techniques and applications. *Radiol Clin North Am*; 39 (4): 619-51.

Nanni C, Zamagni E, Farsad M, Castellucci P, Tosi P, Cangini D, Salizzoni E, Canini R, Cavo M & Fanti S. (2006). Role of 18F-FDG PET/CT in the assessment of bone involvement in newly diagnosed multiple myeloma: preliminary results. *Eur J Nucl Med Mol Imaging*; 33: 525–531

Ornetti P & Maillefert JF. (2004). Reflex sympathetic dystrophy: still a poorly defined entity. *Rev Prat*; 31; 54 (2): 123-30.

Ostendorf B, Mattes-György K, Reichelt DC, Blondin D, Wirrwar A, Lanzman R, Müller HW, Schneider M, Mödder U & Scherer A. (2010). Early detection of bony alterations in rheumatoid and erosive arthritis of finger joints with high-resolution single photon emission computed tomography, and differentiation between them. *Skeletal Radiol*; 39:55–61.

Ozcan Z, Burak Z, Kumanlioglu K, Sabah D, Başdemir G, Bilkay B, Cetingül N & Ozkiliç H. (1999). Assessment of chemotherapy induced changes in bone sarcomas: Clinical experience with 99mTc-MDP three-phase dynamic bone scintigraphy. *Nucl Med Commun*; 20: 41-48.

Palestro CJ. (1998). Radionuclide diagnosis of the painful joint replacement, In: Nuclear Medicine in clinical diagnosis and treatment, Livingstone C; 1209-1221, 044305861X, Edinburgh.

Palestro CJ & Torres MA. (1997). Radionuclide imaging in orthopedic infections. *Semin Nucl Med*; 27 (4): 334-45.

Palestro, CJ & Torres, MA. (1997). Radionuclide imaging in orthopedic infections. Semin Nucl Med; 27 (4): 334-45.

Panagiotis M. (2005). Classification of non-union.Injury, 36 (4): 30-7.

Pape D, Seil R, Kohn D & Schneider G. (2004). Imaging of early stages of osteonecrosis of the knee. *Orthop Clin North Am*; 35 (3): 293-303.

Reinartz P. (2009). FDG-PET in patients with painful hip and knee arthroplasty: technical breakthrough or just more of the same. *Q J Nucl Med Mol Imaging*; 53 (1): 41-50.

Schelstraete K, Daneels F& Obrie E. (1992). Technetium-99m-diphosphonate, gallium-67 and labeled leukocyte scanning techniques in tibial nonunion. *Acta Orthop Belg*; 58 (1): 168-72.

Schneider R. (2006). Radionuclide techniques. In: *Bone and joint imaging*. Resnick & Kransdorf, pp 88 – 119. ISBN 84-8174-883-8. Spain.

Shammas A. (2009). Nuclear medicine imaging of the pediatric musculoskeletal system. *Semin Musculoskelet Radiol*; 13(3): 159-80.

Song IH, Carrasco-Fernández J, Rudwaleit M & Sieper J. (2008). The diagnostic value of scintigraphy in assessing sacroiliitis in ankylosing spondylitis: a systematic literature research. *Ann Rheum Dis*; 67 (11): 1535-40.

Strobel K, Exner UE, Stumpe KD, Hany TF, Bode B, Mende K, Veit-Haibach P, von Schulthess GK & Hodler J. (2008). The additional value of CT images interpretation in the differential diagnosis of benign vs. Malignant primary bone lesions with 18F-FDG-PET/CT. *Eur J Nucl Med Mol Imaging*; 35: 2000-2008.

Strobel K & Stumpe KD. (2007). PET/CT in musculoskeletal infection. Semin Musculoskelet Radiol; 11 (4): 353-64.

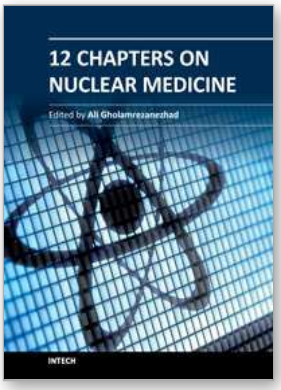
Termaat MF, Raijmakers PG, Scholten HJ, Bakker FC, Patka P & Haarman HJ. (2005). The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. *J Bone Joint Surg Am*; 87 (11): 2464-71.

Tian R, Su M, Tian Y, Li F, Li L, Kuang A & Zeng J. (2009). Dual-time point PET/CT with F-18FDG for the differentiation of malignant and benign bone lesions. *Skeletal Radiol*; 38: 451-458.

Van der Laan L & Goris RJ. (1997). Reflex sympathetic dystrophy.An exaggerated regional inflammatory response? *Hand Clin*; 13 (3): 373-85.

Van der Zant FM, Boer RO, Moolenburgh JD, Jahangier ZN, Bijlsma JW & Jacobs JW. (2009). Radiation synovectomy with (90)Yttrium, (186)Rhenium and (169)Erbium: a systematic literature review with meta-analyses. *Clin Exp Rheumatol*; 27(1): 130-9.

Zacher J, Carl HD, Swoboda B & Backhaus M. (2007). Imaging of osteoarthritis of the peripheral joints. *Z Rheumatol*; 66 (3): 257-8, 260-4, 266.



12 Chapters on Nuclear Medicine

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The development of nuclear medicine as a medical specialty has resulted in the large-scale application of its effective imaging methods in everyday practice as a primary method of diagnosis. The introduction of positron-emitting tracers (PET) has represented another fundamental leap forward in the ability of nuclear medicine to exert a profound impact on patient management, while the ability to produce radioisotopes of different elements initiated a variety of tracer studies in biology and medicine, facilitating enhanced interactions of nuclear medicine specialists and specialists in other disciplines. At present, nuclear medicine is an essential part of diagnosis of many diseases, particularly in cardiologic, nephrologic and oncologic applications and it is well-established in its therapeutic approaches, notably in the treatment of thyroid cancers. Data from official sources of different countries confirm that more than 10-15 percent of expenditures on clinical imaging studies are spent on nuclear medicine procedures.

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