Review
Nuclear Medicine Review 2012, 15, 2: 124–131
10.5603/NMR.2011.00022

ISSN 1506–9680

VIA MEDICA

Bone scan in metabolic bone diseases. Review

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[Received 16 I 2012; Accepted 31 I 2012]

Abstract

Metabolic bone disease encompasses a number of disorders that tend to present a generalized involvement of the whole skeleton. The disorders are mostly related to increased bone turnover and increased uptake of radiolabelled diphosphonate. Skeletal uptake of ^{99m}Tc-labelled diphosphonate depends primarily upon osteoblastic activity, and to a lesser extent, skeletal vascularity. A bone scan image therefore presents a functional display of total skeletal metabolism and has valuable role to play in the assessment of patients with metabolic bone disorders. However, the bone scan appearances in metabolic bone disease are often non-specific, and their recognition depends on increased tracer uptake throughout the whole skeleton. It is the presence of local lesions, as in metastatic disease, that makes a bone scan appearance obviously abnormal. In the early stages, there will be difficulty in evaluating the bone scans from many patients with metabolic bone disease. However, in the more severe cases scan appearances can be quite striking and virtually diagnostic.

KEY words: metabolic bone disease, superscan, focal uptake, ^{99m}Tc diphosphonate

Nuclear Med Rev 2012; 15, 2: 124–131

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Introduction

Metabolic bone disease encompasses a number of disorders that tend to present a generalized involvement of the whole skeleton. The disorders are mostly related to increased bone turnover and increased uptake of radiolabelled diphosphonate. Skeletal uptake of ^{99m}Tc-labelled diphosphonate depends primarily upon osteoblastic activity, and to a lesser extent, skeletal vascularity [1]. A bone scan image therefore presents a functional display of total skeletal metabolism and has valuable role to play in the assessment of patients with metabolic bone disorders (Figure 1). However, the bone scan appearances in metabolic bone disease are often non-specific, and their recognition depends on increased tracer uptake throughout the whole skeleton [2]. It is the presence of local lesions, as in metastatic disease, that makes a bone scan appearance obviously abnormal. In the early stages there will be difficulty in evaluating the bone scans from many patients with metabolic bone disease. However, in the more severe cases scan appearances can be quite striking and virtually diagnostic.

Many of the metabolic bone diseases, with the exception of osteoporosis, are characterized by high bone turnover and are often associated with elevated levels of serum parathyroid hormone, which causes increased bone resorption. It is recognized that bone-seeking radiopharmaceuticals adsorb onto bone at sites of new bone formation, with particular affinity for areas where active mineralization is occurring.

The most important features of bone scintigraphy in metabolic diseases are its high sensitivity and its capacity to easily image the whole body. Currently, the main clinical value of bone scan in metabolic bone disease is the detection of focal conditions or focal complications of such generalized disease, its most common use being the detection of fractures in osteoporosis, pseudofractures in osteomalacia and evaluation of Paget's disease.

^{99m}Tc diphosphonate bone scanning agents

Phosphate analogues can be labelled with technetium (^{99m}Tc) and are used for bone imaging because of their good localization in the skeleton and rapid clearance from soft tissues, and their uptake in bone is thought to reflect osteoblastic activity and to a lesser extent skeletal vascularity [1] (Figure 1). Skeletal uptake of tracer therefore reflects skeletal metabolism. Bone scintigraphy

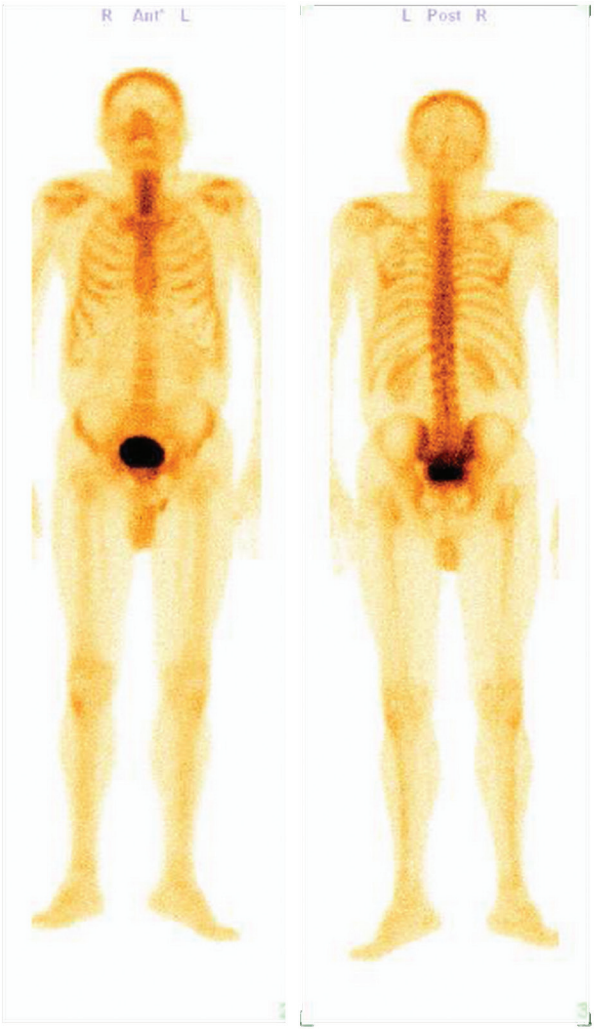

Figure 1. Patient A.C. 77 years old with normal bone scan

is an highly sensitive method for demonstrating disease in bone, often providing earlier diagnosis or demonstrating more lesions than are found by conventional radiological methods. In the metabolic bone disorders recognition of generalized high uptake of the tracer depends upon a subjective evaluation of the scan, and it is also likely that lesions will be more difficult to recognize against high background uptake of tracer by the skeleton.

The development of skeletal imaging agents has been focused around structural modification of methylene diphosphonate (MDP) molecule. The addition of hydroxyl group to the central carbon atom of MDP to produce hydroxymethylene diphosphonate (HMDP), or an additional methyl group to the hydroxylated central carbon atom to produce 1-hydroxyethylidene diphosphonate (HEDP), produce significant differences in both the pharmacokinetics and osseous specificity of the agents.

^{99m}Tc HEDP was the first diphosphonate to be introduced into clinical practice. ^{99m}Tc MDP is currently the most widely used bone scanning agent. It has higher bone uptake, higher whole body retention and faster blood clearance than ^{99m}Tc-HEDP. ^{99m}Tc-HMDP, has faster blood clearance and higher skeletal uptake than MDP. ^{99m}Tc DPD, is the newest of the available diphosphonate, it has significantly higher skeletal uptake than MDP.

Accurate quantitation of tracer uptake by bone is required for a positive identification of increased skeletal metabolic activity. Measurement of 24-hours whole body retention (WBR) of Tc-HEDP, using a shadow shield, whole body monitor is a sensitive measure of skeletal metabolism and of value in the diagnosis of metabolic disease.

The 24-hr value for WBR of Tc-99m-HEDP is a more convenient measurement than 8-hr value, in fact, almost 70% of an i.v. dose of ^{99m}Tc-HEDP is normally excreted through the urinary tract within 6 hr after injection. Therefore, by 24 hr the body burden of ^{99m}Tc HEDP represents almost entirely skeletal uptake. The use of a whole body monitor to calculate the 24-hr WBR of ^{99m}Tc-HEDP provides an overall measurement of skeletal retention of radiopharmaceutical. Very high values for WBR of ^{99m}Tc-HEDP can be expected in any patient unable to excrete the tracer due to severe renal impairment, in patients with renal osteodystrophy the high retentions were largely due to increased skeletal uptake of the tracer. A high WBR of ^{99m}Tc-HEDP cannot differentiate between uremic patients with significant renal osteodystrophy and those with other form of severe renal impairment, but the bone scintigram clearly shows the high uptake and low soft-tissue back-ground typical of renal osteodystrophy. Elevated value for 24-hr whole body retention of 99mTc-HEDP correlate with condition known to cause increased bone turnover.

WBR of diphosphonate is a simple non-invasive test that provides simple and sensitive measure of skeletal metabolism and can be used as a screening test for various metabolic disorders, and the patients with primary hyperparathyroidism, osteomalacia, renal osteodystrophy, and Paget's disease can be clearly differentiated from a healthy population [3–5].

Pentavalent Technetium 99m (V) dimercaptosuccinic acid (^{99m}Tc- (V) DMSA) uptake has been reported in bone metastases [6], and in metabolic bone disease such as renal osteodystrophy [7] and Paget's disease [8]. A striking similarity has been observed between ^{99m}Tc- (V) DMSA and ^{99m}Tc-MDP uptake for osseous and nonosseous lesions after a bone scan [6–9]. Higuchi et al. [7] described a patient with renal osteodystrophy with increased bone uptake on bone scintigraphy and ^{99m}Tc-(V) DMSA scans. They also concluded that ^{99m}Tc- (V) DMSA is a sensitive method for assessing patient response to therapy. ^{99m}Tc- (V) DMSA has early kidney uptake, and have a lower uptake in normal bone than in phosphate-based radiopharmaceuticals [10]. With those properties ^{99m}Tc- (V) DMSA can provide some complementary information in patients with renal disease who show evidence of a superscan. ^{99m}Tc- (V) DMSA scintigraphy could have a role in the evaluation of patients of equivocal bone scan findings who are thought to have superscan due to metastatic or metabolic disease.

In a recent study with PET and Fluorine-18-Fluoride, local bone blood flow and fluoride index rate were quantified in patients *in vivo.* Metabolically active zones showed an increased flow, which allows for classification and monitoring of therapy in metabolic bone diseases [11].

Bone scan appearances

In more severe cases of metabolic bone disease characteristic patterns of bone scan abnormality are commonly seen [12]. It is including some of the following characteristics:

1. "tie sternum";
2. beading of the costochondral junction;
3. reduced renal activity, faint or absent kidney images;
4. increased tracer uptake in long bones;
5. increased tracer uptake in axial skeleton;
6. increased tracer uptake in periarticular areas;
7. prominence of calvaria and mandible;

These features are non- specific and, with the exception of absent kidney images, can all be seen in normal subjects. These features are frequently seen in adolescents, in whom the growing skeleton is metabolically active.

The "classic" bone scan appearance in metabolic bone disease is an image of excellent quality because of the high contrast between bone and soft tissue, in some cases the scan seems almost too good to be true (Figure 2). There is extremely high contrast between bone and adjacent soft tissue, and individual metabolic features reflect increased tracer uptake at various sites throughout the skeleton. Increased tracer uptake in the calvaria and mandible may on occasion be particularly prominent and produce striking images which are recognizable as abnormal. Increased uptake in calvaria and mandible may be virtually pathognomonic of hyperparathyroidism. When there is increased skeletal avidity for tracer, renal images may appear faint or even be absent as a result of less tracer being available for excretion, with resulting heightened contrast between bone and kidneys. The costochondral junctions may be prominent, and this appearances known as" beading" or the "rosary bead" appearance. In the sternum, characteristic appearances may often be seen, with a general increase of tracer uptake by the manubrium and, in the lateral borders of the body. Sometimes instead of uniformly increased uptake of tracer by sternum, only horizontal stripes were seen "Striped- tie" sign [13].

A hot patella on the bone scan is defined as uptake of tracer in the patella greater than that by the distal femur and proximal tibia of the ipsilateral leg. This also can be found in a wide variety of other conditions, including degenerative and metastatic disease. In hypertrophic pulmonary osteoarthropathy, involvement of the patella was noted in 50% of cases. When increased tracer uptake is seen in both patellae, this may well be a pathological feature, but it has no differential diagnostic value. However, skeletal uptake of tracer can be quantitated much more accurately by measurement of 24-hr whole-body retention of ^{99m}Tc- diphosphonate, which has been shown to provide a sensitive means of identifying patients with increased bone turnover.

The features of bone scan in some of the metabolic diseases:

Renal osteodystrophy

Renal osteodystrophy encompasses the changes in bone metabolism due to prolonged chronic renal disease. Osteomalacia in renal dialysis is the result of aluminium toxicity. Some studies suggest that the bone disease can be observed in the absence of excess aluminium deposition, and that it could be due to the increased age of the patients receiving dialysis [14]. In patients with severe renal osteodystrophy, there is markedly increased tracer uptake throughout the skeleton, the kidney appear faint and are frequently not visualized. There is extremely high contrast between bone and soft tissues, and the overall effect is to produce a superscan image [15–17].

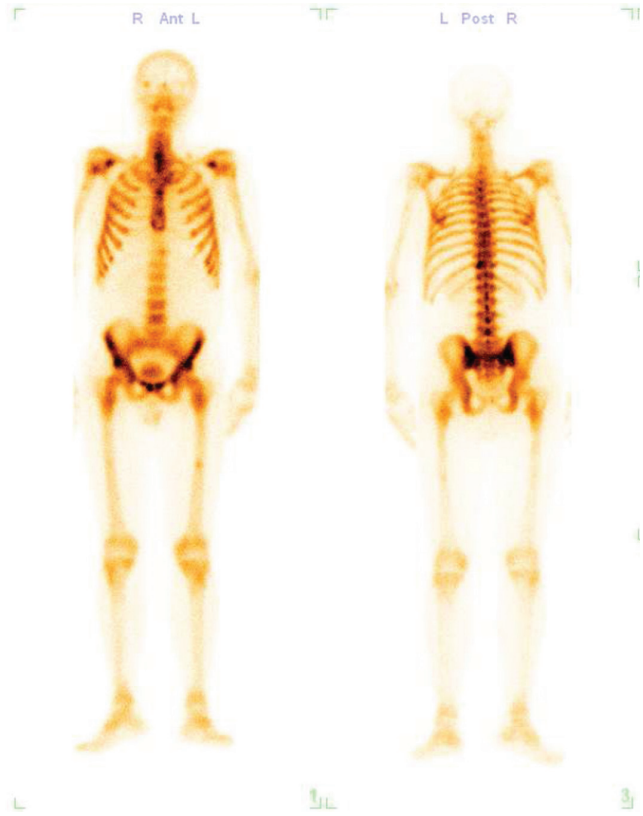

Figure 2. Patient Z.W. 49 years old with typical superscan

The skull appearances may be virtually pathognomonic of severe hyperparathyroidism, with markedly increased uptake throughout the calvaria and mandible. Beading of the costrochondral junctions and a "tie sternum" are also commonly seen. It is probable that the most of the scan findings are due to increased bone turnover resulting from secondary hyperparathyroidism [18], but coexistent osteomalacia may contribute in some cases. The bladder may not be visualized because of failure to excrete tracer. Absence of the bladder helps to differentiate the bone scan in renal osteodystrophy from that in other metabolic disorders. The increased uptake in the long bones can be detected with quantitative imaging even when bone image seems to be visually normal [18]. False-negative results of superscan can arise in the presence of obstructive uropathy, and poor renal function can give rise to false-positive result. When aluminium toxicity occurs, bone scan shows poor uptake images with heightened background activity due to inhibition of tracer uptake by bone caused by the paucity of ostoeoblasts and newly formed osteoid [19].

In renal osteodystrophy bone scan uptake is usually diffuse and symmetric as opposed to advanced primary hyperparathyroidism where uptakes are often asymmetric because of cystic lesions and brown tumours [20]. Some studies comparing bone scan and conventional radiography have been performed. In one study by Fogelman and Carr, ^{99m}Tc-HEDP scan showed changes suggestive of a metabolic bone disorder in all 24 patients studied, whereas only 14 showed radiographic abnormalities [5]. Another study of 30 patients with renal osteodystrophy showed a sensitivity of 83% using ^{99m}Tc-HEDP scan compared with

a 46% for radiography [18]. Therefore, it seems clear that in chronic renal failure the bone scan is more sensitive than radiography for detecting skeletal disease.

Osteosclerosis may occasionally be seen on radiographs of the spine in patients with renal osteodystrophy; the bone scan equivalent is linear areas of increased tracer uptake corresponding to the cortical borders of vertebrae, against a background of generalized high uptake in the spine [2]. Sites of ectopic calcification may be recognized, and the bone scan is more sensitive than routine radiography in identifying pulmonary calcification [21].

Osteomalacia

Osteomalacia results from vitamin D deficiency, which produces a profound mineralization defect. A common aetiology is a lack of vitamin D caused by different factors. In severe cases there is massive excess of osteoid present with markedly reduced mineralization. The bone scan appearances in osteomalacia are usually abnormal. The scan findings, however, are non-specific and will demonstrate the classical characteristics of metabolic bone disease [22]. Generalized increased uptake, most visible at the periarticular zones, costochondral junctions, vertebral column, calvaria, mandible, and sternum; although bone scan in the early stages can be normal. It is not well known why bone scan shows an increased uptake in osteomalacia if a defect in mineralization occurs. It has been suggested that there may be so much osteoid that even if mineralization were slower than normal at any given site, the total area of mineralization would be increased [23]. It may be an effect of secondary hyperparathyroidism. Bone uptake of tracer reflects skeletal metabolism and that is likely to be primarily due to parathyroid hormone effect [12].

Pseudofractures (Looser's zone or milkman's fractures) are often detected early in the disease, and are usually symmetric and perpendicular to the bone surface. They are commonly found in the scapula, medial aspect of the femoral neck, pubic rami, ulna (proximal third), radius (distal third), ribs, clavicle, metacarpals, metatarsals, and phalanges. Pulsating vessels on the softened bone cortex have been suggested to be the origin of pseudofractures [24]. Pseudofractures are most often seen in the ribs. It is uncommon to see pseudofractures in isolation at other sites such as femoral neck or pelvis. The bone scan provides a sensitive means of identifying pseudofractures, particularly in the ribs, where conventional radiology cannot detect the lesions [25]. However, lesions in the pelvis can on occasion be missed on the bone scan because of their symmetrical nature, or if they are obscured by bladder activity.

In a comparative study with conventional radiography, all 15 patients presenting with the disease were diagnosed by bone scan, whereas only 9 by radiography. Additionally, more pseudofractures were appreciated by the bone scan [26]. In another study, 5 patients suffering from osteomalacia had positive bone scans, follow up studies showed a reverse of bone scan images after appropriate treatment with calcium and vitamin D [27]. Other studies have also confirmed the better sensitivity of radiophosphate imaging over conventional radiography in the differential diagnosis between pseudofractures and metastatic disease when the lesions occur proximal to the knees and the elbows [28]. Pseudofracture detection is probably the most useful application of the bone scan in osteomalacia.

Primary hyperparathyroidism

Primary hyperparathyroidism is a common disorder involving an increased secretion of parathyroid hormone that causes hypophosphataemia and hypercalcaemia. Most cases are mild and asymptomatic, but in advanced cases, peptic ulcer, pseudogout, nephrolithiasis and less frequently, excessive bone resorption can be present. Radiographic changes are not usually present because the disease is diagnosed with increasing frequency and at an earlier stage. Bone scan usually shows slight generalized increased uptake with high bone to soft tissue ratios. The degree of bone scan abnormality generally reflects the amount of skeletal involvement, and there is thus a wide range of scan appearances from normal to those mimicking severe renal osteodystrophy [29]. However, the bone scan usually appears normal and thus has no clear diagnostic role in the routine evaluation of patients with suspected primary hyperparathyroidism [29]. The most sensitive radionuclide method seems to be the 24-hour total body retention measurement [5]. Radiographic skeletal surveys are also normal in most cases, but specific changes such as subperiosteal erosions can occasionally be seen. The bone scan is the more sensitive of the two investigations and if scan appearances are not suggestive of metabolic bone disease then radiographs will invariably be normal [26]. A comparison between visually graded ^{99m} Tc-HEDP images for metabolic characteristics and radiography showed that the first one detected 7 of 14 studied patients with primary hyperparathyroidism, whereas the latter detect 3 of them [26]. Despite apparently normal diphosphonate uptake on the bone scan by visual assessment, quantitative measurements (e.g. 24-hr WBR of diphosphonate) are frequently elevated as a result of mild diffuse increase in skeletal metabolism [1].

Ectopic calcification of the lungs and stomach can occur in advanced hyperparathyroidism, and can be detected with radiophosphate imaging [30]. Ectopic calcification is not a diagnostic feature; it can be present after the use of cytotoxic drugs, malignancy and in other conditions producing hypercalcaemia. The presences of focal abnormalities on the bone scan in primary hyperparathyroidism are uncommon but may be seen when Brown tumours are present, with chondrocalcinosis, or following vertebral collapse. In rare instances when a patient presents with aggressive, rapidly advancing primary hyperparathyroidism, multiple sites of ectopic calcification may be seen on the bone scan.

Paget's disease

Paget's disease of bone is a common disorder in the elderly in which excessive production of structurally abnormal bone occurs. Paget's disease is usually polyostotic, but may be monostotic; it is characterized in its initial phase by excess resorption of bone, which is followed by an intense osteoblastic response, with deposition of collagen in a mosaic pattern rather than the lamella arrangement seen in normal bone. Pagetic bone is extremely vascular, and it has been suggested that this contributes to the bone pain. It is usually asymptomatic and normally is discovered incidentally after the detection of an elevated serum alkaline phosphatase, or a finding on X-ray or bone scan. The most common sites are the pelvis, spine, femur, tibia, and the skull, but any bone in the skeleton may be affected. The weight-bearing bones were most often symptomatic, lesions which appear normal radiographically but abnormal on the bone scan are generally asymptomatic [26].

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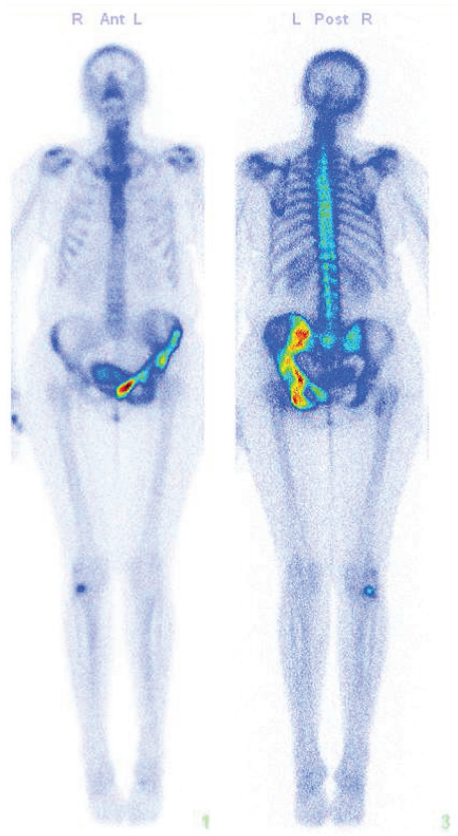

Figure 3. Patient E.J. 56 years old with Paget's disease

The bone scan appearances in Paget's disease are often characteristic, with predominant feature being markedly increased uptake of tracer throughout most or all of the affected bone [31], except in osteoporosis circumscripta (lytic skull disease), in which, tracer uptake may only be increased in the margins of the lesion or after therapy where patchy focal uptake may be observed [32]. Lesions in Paget's disease may be clearly identified because of the clear delineation between normal and abnormal bones [33]. Nowadays, bone scan is recognized to be more sensitive than radiography in detecting sites of Paget's disease in the skeleton, with the additional advantage of visualization of the whole skeleton in one exploration (Figure 3). Paget's disease usually affects transverse spinous processes of the vertebrae. The affected vertebra has then a typical appearance that has been described as a "Mickey Mouse'' sign because of the inverted triangular uptake distribution [34]. Other typical signs that have been described are the "black beard" sign (monostotic mandible disease) and the "short pants" sign (spine, pelvis and upper femoral disease) [35, 36].

The bone scan is generally of value in detecting complications of Paget's disease such as fracture or sarcoma [33]. In Paget's sarcoma, there is usually no evidence of increased uptake at the site of developing malignancy, unlike in uncomplicated Pagetic bone. Occasionally, a cold area within high uptake is present [37, 38]; in this situation, conventional radiography together with computed tomography and biopsy should be obtained to confirm the diagnosis of malignant transformation [39]. Similarly, if osteosarcoma develops at a site of pagetic involvement it may be difficult to recognize on the diphosphonate scan. ^{67}Ga scan is useful in confirming a diagnosis of sarcoma, because ^{67}Ga uptake at the site of sarcoma is always greater than the relative Tc-diphosphonate uptake. Distinction between Paget's disease and metastases is usually easy on bone scan when a typical Paget's disease pattern is present [40]. Rarely, when bone scan appearances are atypical and radiography is unhelpful, a CT scan or biopsy will be required to establish a diagnosis. A single lesion on the bone scan is generally more difficult to interpret, but even in this situation the typical scan features are likely to differentiate monostotic Paget's disease from other pathological conditions such as a sclerotic spinal metastasis from prostatic carcinoma. Bone scan is non-specific, where any doubt exists, radiographs should be obtained.

After calcitonin [31] or bisphosphonate [41] therapy, bone scan shows alteration in uptake distribution, the uniform uptake distribution on the bone scan may change to patchy focal uptake. It usually corresponds to biochemical findings, although the scan changes occur more slowly [42]. Bone scan may be a better diagnostic indicator of long-term response than biochemical measurements.

Bone scan is the most sensitive technique for Paget's disease detection and staging, and should be used in primary evaluation [12]. Because of its high sensitivity and the possibility to check the whole skeleton in the same study, bone scan should be the imaging technique of choice [33], with radiography used to obtain supplementary information whenever required. In clinical practice, bone scintigraphy is the ideal screening test in cases of suspected Paget's disease and in elderly patients with unexplained bone pain, bone deformity, or in patients with an elevated serum alkaline phosphatase.

Osteoporosis

Osteoporosis is characterized by a decrease in bone mass with thinning of the cortex and trabeculae and a reduction in the number of trabeculae. Bone densitometry is the most diagnostic procedure for the detection of reduced bone mass. The bone scan has not been found to have an important role to play in the diagnosis of osteoporosis. This is a disorder where gradual change in bone mass may occur over many years, the bone scan appearances are usually normal and shows very low radiophosphate uptake in the skeleton, poor vertebral definition and low bone to soft tissue ratio [43]. However, the scan images may on occasion appear poor in quality because of relatively low bone uptake of tracer with a "washed-out" pattern activity in the axial and appendicular bones. It has been suggested that this occurs in severe or "end--stage" osteoporosis caused by markedly reduced or even absent osteoblastic activity. Loss of vertebral height and closeness of the rib cage to pelvis in patients with multiple vertebral fractures may be observed in bone scan (Figure 4) [12]. These features are not diagnostic, but their presence may alert on the presence of osteoporosis. In practice the bone scan provides a less reliable means of diagnosing osteoporosis than radiography [26].

Osteoporotic bones are abnormally brittle and are at high risk of fractures from mild trauma. These are easily recognizable on the bone scan and are seen as focal areas of increased tracer uptake. If vertebral collapse is present, the classical appearance of a fracture in bone scan is a focal horizontal linear uptake on

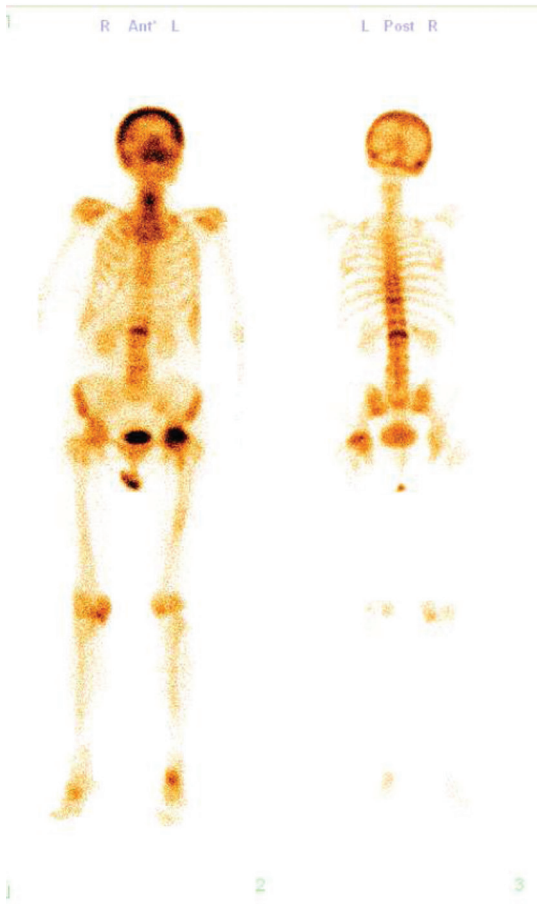

Figure 4. Patient P.W. 60 years old with osteoporosis complicated with vertebral fractures

blood pool and static images at the site of the fracture. This intense uptake usually decreases over a period of 6 to 18 months, and thus the scan is of value in assessing the age of vertebral collapse [26]. Even when scan appearances are quite typical of benign vertebral collapse, tumour cannot definitely be excluded and radiographs should be obtained. In the diagnosis of a patient with acute back pain with evidence of vertebral collapse on X-ray, the bone scan can help in the evaluation of the cause of pain. A normal scan would exclude a recent vertebral fracture, and other causes for back pain should then be considered. Bone scan can also suggest other causes of vertebral collapse or back pain such as metastases, infection, or Paget's disease. In a study by Rico et al., bone to soft tissue uptake indices in recent osteoporotic vertebral collapse using bone scan were examined [44]. The study suggests that bone scan may be useful in monitoring response to therapy, but seems to have limited clinical yield. SPECT studies may help to increase image contrast in bone scan. It has the capacity to separate uptake above and below the areas of interest, which means that, in the spine, uptakes can be separately identified in the different sites of one vertebra. Bone scan plays a very important role in the early detection of clinical suspected fractures with a negative or uncertain X-ray image. It may also allow the detection of clinically unsuspected fractures of the neck of femur, humerus, scapula, radius and ribs. In a study of Kobb et al., the bone scan was the only technique able to find unrecognised fractures of pelvis that produced back pain similar to vertebral collapse

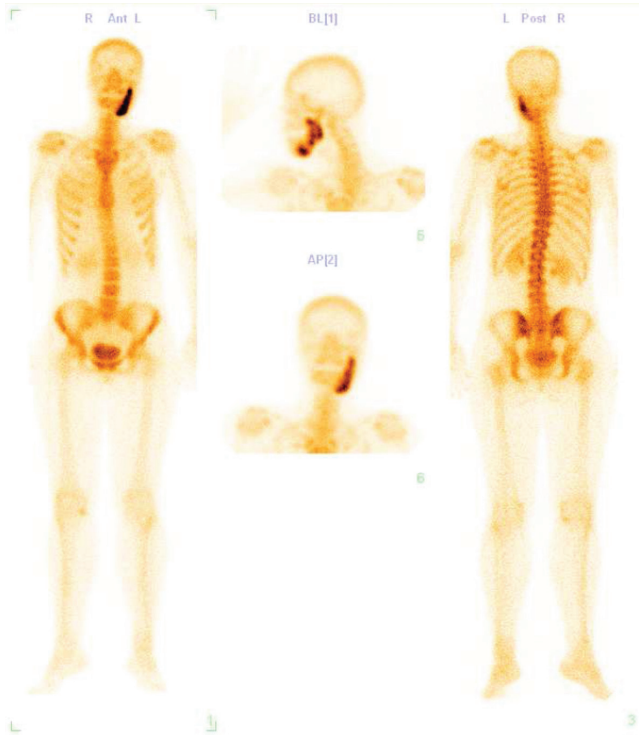

Figure 5. Patient A.M. 30 years old with fibrous dysplasia of the mandible

pain [45]. Bone scan is capable of finding not only fractures but also fracture complication such as osteomyelitis and non-union. It is usually able to detect and to exclude alternative diagnosis or coexistent diseases at the same time.

Miscellaneous conditions

There are many other conditions that can be considered under the heading of metabolic bone disease. In the majority of cases there is only limited experience with bone scanning. These conditions can cause generalized or focal alteration in skeletal metabolism:

— generalized skeletal involvement: seen in thyrotoxicosis, acromegaly, hypervitaminosis D, systemic mastocytosis, adult hypophosphatasia, and osteopetrosis;
— focal skeletal involvement: seen in Engelmann's disease (progressive diaphyseal dysplasia), fibrous dysplasia (Figures 4–5), osteopoikilosis, osteopathia striata, melorheostosis (benign sclerotic dysplasias), tumoural calcinosis, myositis ossificans, and scurvy.

Conclusions

Bone scintigraphy plays an important role in the management of metabolic bone disease. It's most important features are the high sensitivity, the capacity to image the whole body and the capacity to show typical diagnostic patterns of abnormality.

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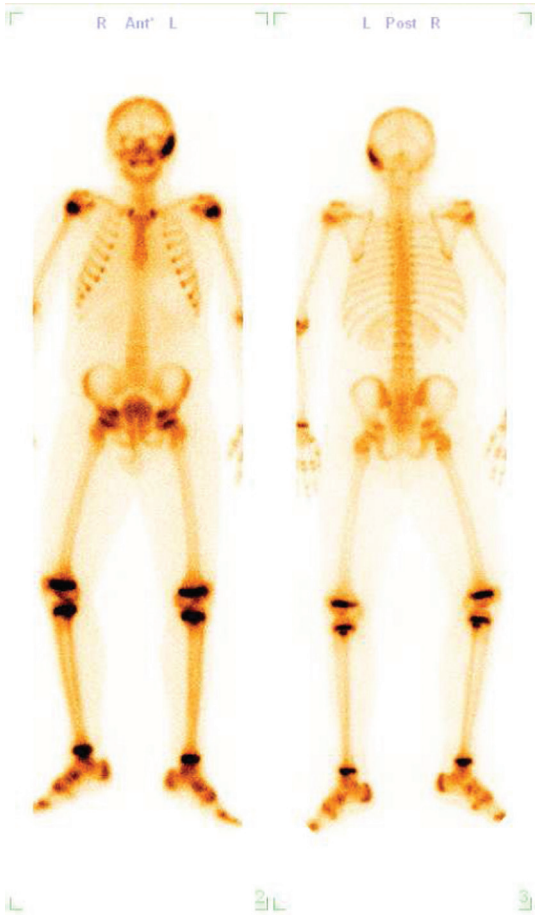

Figure 6. Patient R.P. 12 years old with fibrous dysplasia of left temporal bone

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