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Nuclear Medicine Imaging for Evaluation of Low Back Pain

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Published Date: August 15, 2016

INTRODUCTION

Low back pain is a common health problem that can be triggered by many factors. Multiple imaging modalities, ranging from plain radiography to advanced nuclear medicine and magnetic resonance techniques, have been used to assess spinal injuries and back pain. Despite this variety of imaging modalities, recent reports indicate that only approximately 10% of back pain might be actually diagnosable with current diagnostic technologies [1]. One of the major difficulties is related to the fact that morphologic imaging findings are frequently nonspecific and may be also present in asymptomatic patients. Edema, inflammation, and hypervascularity are more specific for sites of pain generation, but are often overlooked by imagers if physiologic imaging techniques are not used [2]. Visualization of spinal structures during movement has become possible by such techniques as cineradiography and fluoroscopic video techniques, which use X-rays to

record a film during patient motion. However, the procedures do not provide an internal view of the vertebrae, intervertebral disks or ligaments, and are not widely used. The dose of ionizing radiation during fluoroscopic procedures is also a consideration for many patients. Provocative discography, another diagnostic technique aimed at the pathophysiology of back pain, involves injecting a contrast dye into the center of suspected discs and pressurizing them. Discography is an invasive procedure performed only by highly skilled specialists and can be considered in selected patients with debilitating back pain and/or sciatica when other methods proved unsuccessful.

Recent advances in nuclear medicine techniques have provided new non-invasive methods aimed at investigating the cause of back pain. Technetium-99m (^{99m}Tc) Methylene Diphosphonate **(MDP)** bone scintigraphy is an important imaging technique that can be used to detect bone abnormalities that are triggering the bone's attempts to heal. According to the Society of Nuclear Medicine procedure guidelines, bone scintigraphy is a diagnostic study used to evaluate the distribution of active bone formation in the body [3]. A small amount of radioactive material (technetium-99m-MDP) is usually injected intravenously and subsequent images are acquired 2 to 5 hours post injection to allow sufficient time for the radiotracer to distribute throughout the skeleton, especially in the areas of increased bone turnover. A three phase bone scintigraphy includes additional blood flow and blood pool images and can be used to detect different types of pathology in the bone. The flow phase is also known as a nuclear angiogram, showing the perfusion to a lesion (dynamic images of the area of greatest interest are obtained as the tracer is injected). The blood pool phase, also known as the soft tissue phase, includes one or more static planar images of the areas of interest obtained within 10 min after tracer injection and show the relative vascularity to the area. Areas of inflammation usually have dilated capillaries where the radioisotope can "pool". Delayed images (3rd phase) are usually obtained 3 hours post injection after most of the radiotracer has been metabolized. Since about half of the injected technetium-99m-MDP is localized by the bones, this allows evaluating the amount of bone turnover in various lesions. Bone scintigraphy can also depict degenerative changes, particularly those that demonstrate a high degree of remodeling [4].

Planar scintigraphy images may be enough, even though they represent a 2-dimensional (2-D) view. In order to display the findings in a 3-dimensional (3-D) view, Single Photon Emission Computed Tomography **(SPECT)** imaging technique may be employed. For this purpose multiple 2-D images are acquired from different angles. Subsequently, the images are processed and displayed as a 3-D dataset, similar to those obtained for CT or MRI. The first use of SPECT for spinal imaging date back to 1983 [5]. Apart from providing a 3-D display, SPECT improves the lesion-to-background contrast and sensitivity of bone scanning. It has been reported that SPECT detected additional 30% of solitary vertebral lesions that were obscured on planar bone scintigraphy and identified various etiologies including benign tumors (osteoid osteoma and osteoma), facet arthritis, discitis, transverse process fractures and spondylolysis [6]. Typical SPECT patterns were even reported useful in differentiating malignant and benign lesions in the

given clinical context [6,7]. Hardware-based fusion between skeletal SPECT and CT offers a nearly perfect data match in the lower spine [8]. New advances in image processing such as iterative reconstruction-Ordered Subset Expectation Maximization with Three-dimensional resolution recovery **(OSEM-3D)** further improved the image quality of skeletal SPECT with either a 50% reduction in radiation dose or a 50% reduction in acquisition time or combination of the two [9].

Additional nuclear medicine modalities such as indium-111 labeled white blood cell scintigraphy, Galium-67 imaging, F-18 FDG PET/CT and F-18 Sodium Fluoride PET/CT can be also used to differentiate local infection from metastatic lesions in selected patients or to assess the interval response to administered therapy.

SPONDYLOLYSIS AND SPONDYLOLISTHESIS

Spondylolysis is an osseous defect of the pars interarticularis of the vertebral arch. Most cases occur in the lowest lumbar vertebra **(L5)** and may represent a developmental or acquired stress fracture caused by repetitive trauma done to the lumbar spine. The condition may present as an asymptomatic incidental finding on radiographs [10] or be a cause of spine instability, back pain, and radiculopathy. Spondylolysis is frequently suspected in adolescents involved in strenuous sports presenting with low back pain. Studies investigating variables associated with spondylolysis showed that subjects with an active spondylolysis were nearly five times more likely to be males and aged less than 20 years [11]. The results also showed that adolescent males with suspected spondylolysis were three and a half times more likely to have a positive bone scan [11]. Bilateral spondylolysis can result in spondylolisthesis - anterior or posterior displacement of a vertebra or the vertebral column in relation to the vertebrae below. Spondylolysis should not be confused with spondylosis, which refers to degenerative osteoarthritis of the joints between the centre of the spinal vertebrae and/or neural foraminae or with spondilitis, which is an inflammation of the vertebra.

Bone scintigraphy can provide useful information about the bone metabolic activity in the pars interarticularis in response to repeated stress of sporting activity and many investigators studied the usefulness of planar bone scintigraphy and SPECT imaging for diagnosing spondylolysis [10-24]. SPECT proved highly sensitive in revealing pars injuries as well as in identifying other potential sites of pathology, and should be considered in the workup of persistent low back pain in young children [25]. For example, SPECT imaging of the spine can identify early pars stress prior to the development of osseous change detectable with CT [18]. In fact, recent studies show that up to 20% of the stress injuries in the pars interarticularis detected by SPECT proved CT-negative in pediatric patients with new-onset back pain [19]. It has been even suggested that changes in SPECT imaging of spine are the first sign of spondylolysis in suspected cases [15]. Combined SPECT and CT imaging **(SPECT/CT)** has several advantages over SPECT alone, including more precise localization of sites of abnormal uptake in bone, identification of causes of abnormal uptake, and identification of osseous abnormalities without associated abnormal radiotracer

uptake [26]. The modality has also been reported useful in differentiating acute lesions from healing or chronic processes, directly affecting management strategies [10,12]. Follow-up studies of patients undergoing conservative treatment of active spondylolysis showed that osseous healing is most likely to occur in unilateral active spondylolysis. Chances of bony healing diminish when the fracture is bilateral, and diminish even further when it is pseudo-bilateral [20]. Bone SPECT scintigraphy was also useful in evaluating brace immobilization for acute spondylolysis in children and adolescents [27]. Patients with a longer pain history or concomitant spina bifida occulta may need careful follow-up because they are at increased risk of having occasional low back pain [21].

Even though spondylolysis is relatively common in adolescent athletes, there is no common agreement in the literature concerning the best methods for diagnosing and treating the condition since there have been no controlled trials [28]. Furthermore, the abnormalities of the pars interarticularis cover a wider spectrum that includes stress without spondylolysis, spondylolysis, and nonunion [26]. Given currently available data, nuclear imaging with SPECT followed by computed tomography has been commonly suggested as the standard for diagnosing a symptomatic pars lesion [28].

Degenerative Spondylolysis

Spondylolysis has commonly been associated with young subjects engaging in sporting activity, the pathophysiology being frequently attributed to a stress injury or congenital abnormality of the vertebral pars interarticularis. Although much rarer, spondylolysis in later life has also been encountered, the dominant patterns of presentation being with degenerative disease of the intervertebral disc, vertebral body and facet joints [29]. Marked restriction in movement at the level of facet joints affected by severe degenerative disease may transfer the flexion-extension and rotational forces from the facet joints to the pars interarticularis, leading to increased stress and eventual secondary spondylolysis in such patients. Furthermore, degenerative spondylolisthesis without a pars interarticularis fracture has been described in a subgroup of older patients with sagitally oriented L4-L5 facet joints that fail to lock the vertebral bodies together [29,30]. Concurrence of severe facet joint disease and fracture of the pars interarticularis in older patients detected on bone scintigraphy has been reported by Van der Wall *et al.* [29]. The authors even describe distinct scintigraphic patterns of tracer uptake. Thus, in spondylolysis, the radiotracer uptake is apparent as a triangle on sagittal images and as an oblong on coronal images, while in facet joint disease the uptake pattern is more rounded and occurs at the level of the disc space or upper vertebral body. In facet joint disease the tracer uptake may also abut, but does not cross the line through the posterior aspect of the spinal canal [29].

In a significant number of patients with low back pain, skeletal scintigraphy can also show uptake abnormalities supportive of diagnoses other than spondylolysis, including stress at the articulation between a transitional vertebra and the sacrum, injuries to the vertebral body ring

apophysis, sacral fracture, unexpected metastatic malignancy, compression fractures, peridiscal uptake, spinous process injury, and sacroiliac joint stress [31,32]. Bone scintigraphy therefore can contribute significantly in the diagnosis of patients with low back pain and their management. Chronic lesions without scintigraphic activity, however, are better followed by MRI as the modality has the potential to diagnose pathology outside the posterior elements [16].

FACET SYNDROME

In the human spine, the vertebral bodies and adjacent intervertebral discs make up the anterior aspect of each vertebral segment. Posteriorly, each vertebral segment has two paired facet joints, also called zygapophyseal joints (abbreviated as Z-joints). In the lumbar spine, facet joints provide about 20 percent of the twisting stability in the lower back. As any synovial joints, facet joints have a rich supply of nerve fibers, being sensitive to painful stimuli. Similar to other joints, the facets can become worn or injured upon repetitive, constant motion or trauma. Pain originating from facet joints is termed "facet syndrome", which is one of the major causes of chronic low back pain. The condition is less common in the thoracic compared to lumbar and cervical spine, being likely related to the amount of motion in these regions. In the lumbar spine, the pain caused by facet syndrome is usually felt directly over the affected joints, but may also radiate to the buttocks, groins, hips and back of the thighs depending on the injured facets. The sensation of the facet joints is controlled by the medial branch nerves, which are carrying pain signals to the spinal cord. These nerves are not responsible for sensation in the muscles of the back or extremities and are frequently blocked by local injections (medial branch block injection) or neurotomy (radiofrequency medial branch neurotomy) to control the back pain in patients with facet syndrome when other conservative measures fail.

A major barrier to understanding facetogenic low back pain has been the lack of radiographic diagnostic criteria [33]. In this situation, nuclear medicine techniques have become the target of many studies investigating facet syndrome [4,34-45]. Most studies support the role of skeletal SPECT scintigraphy in identifying the involved facet joint and the injection site for nerve blocks [4,12,33,35,38-44]. In an attempt to further classify the findings in patients with facet syndrome, Kim *et al.* described four basic morphological patterns of facet arthropathy based of synovial appearance on MRI scans - light, mottled, narrowed, and obliterated [33]. The mottled type demonstrated synovial fluid increase suggestive of inflammation and a high specificity on SPECT. The authors showed that synovial abnormalities correlated best with SPECT findings in this group and proposed even defining it as a "subtype of SPECT(+) inflamed joint". Interestingly, facet hypertrophy was not predictive of bone scan positivity, perhaps suggesting the protective nature of a hypertrophied facet [33]. It should be remembered; however, that radiopharmaceutical uptake in bone scintigraphy can vary from subtle to pronounced, depending on the metabolic activity and degree of bone remodeling. For example, osteophytes that is in the process of growing exhibit a high uptake, whereas mature osteophytes tend to have a normal or slightly increased uptake [4]. In patients with suspected pseudarthrosis, bone SPECT showed a higher sensitivity

compared to CT for detecting facet joint degeneration, and a similar sensitivity for detecting screw loosening [43]. The modality also showed a high negative predictive value for diagnosing active facet syndrome, in separate studies reaching 100% [38]. Recent studies report that in patients with suspected facet joints arthropathy, SPECT/CT imaging identified potential pain generators in over 85% of lumbar spine and in over 90% of cervical spine scans [42].

In subjects considered for medial branch block injection, spinal SPECT scintigraphy proved helpful not only in determining the site of the block, but also in predicting the response to therapy [4,39,41]. Furthermore, it has been reported that intraarticular lumbar facet joint injections are more effective than medial branch nerve blocks in SPECT-positive patients [35]. Comparative studies also indicate that facet joint signal change on fat-suppressed MRI does not always correlate with increased radiotracer activity on ^{99m}Tc-MDP SPECT/CT and the two modalities should not be considered interchangeable for facet joint evaluation [46].

Recently emerged modalities such as positron emission tomography with (18)sodium-flouride, i.e. (18)F-PET/CT may bring new findings in patients with low back pain; however, most of them are still under development and require validation in patients with various types of spinal pathology. In a study evaluating the performance of (18)F-PET/CT for diagnosing facet arthropathy versus disc disease abnormalities in patients with back pain and suspected facet syndrome, Gamie *et al*. report an overall detection ability of 84% [45].

SPINAL AND PARASPINAL INFECTION

Spinal infections may be caused by open spinal trauma, infections in adjacent structures, hematogenous spread of bacteria, surgical procedure or invasive investigations. The most commonly affected region is the lumbar spine and early diagnosis is often difficult. The diagnosis of spinal infections in many cases is delayed, and this may result in permanent neurological damage or even death [47]. Anatomically, spinal infections can involve the vertebral column, intervertebral disc space, the spinal canal and adjacent soft tissues. Spread of infection to the vertebra commonly results in vertebral osteomyelitis, which frequently involves two adjacent vertebrae and the intervertebral disk between them, causing narrowing of the disc space. Intervertebral disc space infections involve the space between adjacent vertebrae and are commonly divided into childhood disk infections (diskitis), adult disk infections (spontaneous) and postoperative intervertebral disc infections. Spinal canal infections can be divided into epidural (i.e. involving the tissues surrounding the spinal cord and nerve roots), subdural (between the dura mater and pia mater/arachnoid) and subarachnoid/intramedullary (i.e. within the spinal cord parenchyma). Paraspinal soft-tissue infections commonly include abscesses, cellulitis and granulomas involving paraspinal soft tissues and psoas muscles.

Various nuclear medicine techniques have been applied for diagnosing spinal and paraspinal infections [47-67]. The standard three-phase bone scintigraphy with ^{99m}Tc MDP is highly sensitive for osteomyelitis, but commonly requires confirmation by other tests due to its relatively low

specificity. Labeled White Blood Cell **(WBC)** scintigraphy has become the procedure of choice to diagnose most cases of skeletal infections except for those of the spine, where its value is limited due to increased physiologic radiotracer distribution in this region [48,68]. For example, the reported sensitivity of labeled WBC scintigraphy in detecting chronic osteomyelitis in the peripheral skeleton ranged between 72-91% compared with only 11-38% in the axial skeleton [66]. In this situation, 67Ga citrate has been frequently used for diagnosing spinal infections, becoming also the focus of research studies [49-51]. Comparison studies of patients with suspected spinal osteomyelitis who underwent three-phase bone scintigraphy with SPECT, Ga-67 scintigraphy with SPECT, and MRI with and without contrast report that SPECT bone/Ga-67 was significantly more accurate (92%) than both planar bone/Ga-67 (75%) and bone SPECT [50]. Ga-67 SPECT proved as sensitive as MRI (91%) in these patients and slightly but not significantly more specific (92% *vs.* 77%) than MRI [50]. Of note is that tracer uptake in two contiguous vertebrae, as noted on SPECT, was the most accurate bone scan criterion for detecting spinal osteomyelitis (71%). The study results indicate that spinal osteomyelitis and accompanying soft tissue infection can be diagnosed accurately with SPECT Ga-67, which can be used as a reliable alternative when MRI cannot be performed and as an adjunct in patients in whom the diagnosis is uncertain [50]. In a separate study, Tzen, *et al*. suggest performing a 67Ga whole-body survey as early as possible in patients with fever of unknown origin, fever and back pain and/or the spinal syndrome, before MRI is performed [51]. If a spinal epidural abscess is strongly suspected, SPECT is needed for further confirmation of spinal versus non-spinal and contiguous versus non-contiguous lesions [51]. In patients with sickle cell disease, an early differential diagnosis between bone infarction and osteomyelitis is frequently impossible and nuclear medicine techniques have been explored. Radioisotope studies during vaso-occlusive crises showed a three stage process. The first stage is characterized by decreased radiotracer activity on Tc-99m **(MDP)** bone scintigraphy; however, in osteomyelitis, an increased uptake area is usually seen at this early stage, corresponding to increased uptake in Ga-67 citrate scanning [69]. Therefore Tc-99m MDP bone scanning is suggested in the early stages of a vaso-occlusive crisis if osteomyelitis is suspected. This can be followed by a Ga-67 citrate scintigraphy in doubtful cases. Later studies can be used for the assessment of the healing process [69].

Recent advances in FDG-PET/CT have demonstrated its utility in the assessment of many infectious and inflammatory conditions, including those involving spinal and paraspinal regions [53-59,66,67]. Thus, FDG-PET/CT was reported to be superior to MRI, 67Ga citrate and 99mTc-MDP in evaluating patients with suspected spondylitis, particularly in diagnosing low-grade spondylitis (as compared with MRI), adjacent soft tissue infections (as compared with 67Ga citrate) and advanced bone degeneration (as compared with 99mTc-MDP) [55]. The modality was recommended for distinguishing between common Modic changes and spinal infection [54,59], discriminating residual and nonresidual spinal infection following therapy [57], differentiating pyogenic and tuberculous spondylitis and reflecting the activity of infectious spondylitis [67]. In a

study aimed at the interim evaluation of response to therapy in patients affected by hematogenous infective spondylodiscitis (of the 38 patients, 7 had tubercular infection, 1 fungal infection and 30 pyogenic discitis), FDG PET/CT provided a higher sensitivity and specificity for the early identification of responders, which may have an important clinical impact in guiding antibiotic therapy [70]. FDG PET/CT may prove especially helpful when MRI cannot be performed or is non-diagnostic, and as an adjunct in patients in whom the diagnosis is inconclusive [56].

New radiotracers for diagnosing spinal infections are also under investigation, including Avidin/111In-labelled Biotin or radiolabelled streptavidin-biotin complex, (99m)Tc-labelled antimicrobial peptide Ubiquicidin 29-41 (UBI 29-41), as well as radiolabelled antibiotics, such as 99mTc-ciprofloxacin [47,60-63]. Thus, Streptavidin/111In-biotin scintigraphy was reported to be highly sensitive and specific for detecting vertebral osteomyelitis in the first 2 weeks after the onset of clinical symptoms [61]. In a cohort of 110 patients with suspected vertebral osteomyelitis, 111In Biotin scintigraphy showed a sensitivity of 84% and specificity of 98% in hematogenous vertebral infections and a sensitivity of 100% and specificity of 84% in postoperative spinal infections [62]. The Avidin/111In-labelled Biotin scan technique was described as much simpler than the common scintigraphic methods which employ labeling of blood components and its target-to-background ratio appeared greater [71]. In experiments with Tc-ubiquicidin-derived peptides, radioactivity at the site of infection also correlated well with the number of viable bacteria [47]. Finally, radiolabelled antifungal tracers could potentially distinguish fungal from bacterial infections [47]. However, most indicated tracers under investigation require further development and validation in new clinical trials.

SPINE TUMORS AND VERTEBRAL METASTASES

The spine is the third most common site for metastatic disease, after the lung and liver [72,73]. Common malignancies with a high rate of osseous metastases include tumors of the breast (72%), prostate (84%), thyroid (50%), lung (31%), kidney (37%), and pancreas (33%). Approximately 60-70% of patients with systemic cancer develop spinal metastases, which can involve the bone, epidural space, leptomeninges, and spinal cord [73]. Early diagnosis is important for treatment planning and preventing neurological damage.

Radionuclide bone scanning with (99m)technetium-labeled diphosphonates has long been widely used as a diagnostic test in searching for bone metastases due to its availability, high sensitivity, and low cost [74]. However, it shows limited sensitivity and specificity. For example, the presence of vertebral non-neoplastic pathology in oncologic patients can cause several false positive results and these increases the difficulty in defining the etiology of a focal uptake [75]. The addition of SPECT and SPECT/CT improved the diagnostic accuracy of planar bone scanning, especially for the evaluation of the spine [75-85]. SPECT and SPECT/CT proved particularly helpful in determining the precise anatomic location of spinal abnormalities, providing useful information for differentiation between malignant and benign lesions [75-79,81-85]. Thus, it has

been established that lesions affecting the pedicle are a strong indicator for malignancy, whereas involvement of the facet joints is usually related to benign disease [77]. Lesions affecting the vertebral body or the spinous process did not show a clear tendency towards either malignancy or benignity [77]. Categorizing 125 spinal lesions in cancer patients and 127 lesions in patients with back pain according to their location in the vertebra on SPECT images, Even-Sapir et al indicate that lesions showing focal or diffuse uptake in the body were usually benign (96% and 87%, respectively). Lesions showing uptake in the body and pedicle were usually metastases (83%). When abnormal uptake was seen in both the body and posterior elements, but with an intervening normal pedicle, benign disease was the most common cause (93%). Lesions in the apophyseal joints were all benign. Lesions manifesting as abnormal uptake projecting beyond the vertebral body surface were osteophytes [52]. In a separate study, Delpass and *et al*. report that 24 of 25 lesions involving the vertebral body with extension into posterior elements were metastases, as well as 10 of 39 lesions found in the vertebral body and 1 of 4 found in the spinous process. All lesions limited to the anterior aspect of the vertebral body (13/13), facet joints (23/23), and intervertebral disk space (6/6) were benign [83]. A characteristic Facet Osteoarthritis Sign **(FOS)** is even described by Kim *et al*. [86]. FOS typically appears oval/elongated in shape, located along the lateral margin of the spine; its superior end is usually outside (lateral to) or just at the margin of the spine, and the inferior end is just at or inside (medial to) the margin, yielding a pattern of slightly oblique activity. The sign is most often seen at the fifth lumbar level and has an extremely high negative predictive value for metastasis (i.e. none of the 28 patients with facet osteoarthritis sign had metastases at the site of the FOS) [86]. Comparison studies with MRI showed that vertebral SPECT, using high-resolution SPECT equipment, produced excellent results that were comparable to and complementary with MRI in detecting vertebral metastases and superior to MRI in detecting extra-vertebral body metastases [87]. SPECT-guided CT was able to further clarify more than 90% of SPECT findings classified as indeterminate. Nevertheless, new studies addressing the cost efficiency of this approach are required for routine clinical applications [80].

With the advancement of PET imaging, FDG PET/CT is becoming one of the most commonly used procedures, being also widely supported for detection of spinal malignancies [73,74,88-93]. FDG PET/CT is highly sensitive and has the advantage of demonstrating the presence of disease in both bone and soft tissues. Because FDG PET/CT relies on the increased cellular metabolism of metastatic foci it may enable earlier detection than bone scintigraphy, which relies on detecting an osteoblastic response. In the spine, the modality can be used for detecting both lytic and sclerotic lesions, including in their early stage when the process is still confined to the bone marrow. For example, in patients with differentiated thyroid carcinoma, FDG PET/CT was superior to (99m)Tc-bone scintigraphy in detecting osseous metastases because of its lower incidence of false-positive results [93]. In patients with multiple myeloma, FDG PET/CT proved more sensitive than skeleton X-ray and is widely used for diagnosing, staging and therapeutical evaluation, including in myeloma subjects presenting with back pain [94]. FDG-PET/CT-guided

biopsies of vertebral metastases in patients with low back pain have also been reported [95]. Apart from initial diagnosis, FDG PET/CT can be reliably used to monitor the response to therapy and proved helpful for radiosurgery planning and response monitoring in patients with recurrent spinal metastases [90].

Other Radiotracers for Spinal Tumor Imaging

Osseous metastases from many neuroendocrine tumors can be detected with a high degree of specificity by PET using somatostatin analogs [92]. Other novel PET radiotracers are under evaluation, which will further enhance the diagnostic capability of PET/CT in specific types of tumors. For example, PET radiotracers that have been tested for use in the evaluation of prostate cancer patients, including metastases to the spine, target a variety of pathways such as increased glycolysis ((18)F-FDG), cell membrane proliferation by radiolabeled phospholipids ((11)C and (18)F choline), fatty acid synthesis ((11)C acetate), amino acid transport and protein synthesis ((11)C methionine), androgen receptor expression ((18)F-FDHT), and osteoblastic activity ((18)F-fluoride) [89]. (18)F-fluoride was reported particularly promising, with a higher sensitivity and accuracy than bone scintigraphy for detection of both lytic and sclerotic lesions [74]. Results of a recent pilot phase prospective trial also demonstrated superior image quality and evaluation of skeletal disease extent with 18F NaF PET/CT compared to 99mTc-MDP scintigraphy [96,97]. (18)F-fluoride PET can be also used for assessing osseous metastases in a variety of malignancies following chemotherapy, when evaluation by FDG PET is limited due to intense reactive bone marrow activity throughout the skeleton. Studies investigating whether Tc-99m MIBI could distinguish vertebral metastases from traumatic vertebral fractures showed no abnormal findings in traumatic vertebral fractures, although increased activity was seen in 73% of vertebral metastases [98]. The authors suggest that Tc-99m MIBI scans may play an important complementary role in differentiating vertebral metastases from traumatic vertebral fractures, given the high specificity of Tc-99m MIBI scans compared with Tc-99m MDP scintigraphy. Studies investigating the sensitivity and specificity of thallium-201 scintigraphy for the diagnosis of malignant vertebral fractures reported that sensitivity, specificity, positive and negative predictive values for a malignant fracture on early 201-TI vertebral scintigraphy images were 28.6, 92.9, 66.6, and 72.2%, respectively, and on delayed images were 28.6, 100, 100, and 73.7%, respectively [99]. The authors point out that the weak sensitivity does not support the wide use of 201-TI bone scintigraphy to distinguish a benign from a malignant vertebral fracture. However, the high specificity suggests that such evaluation might be proposed prior to vertebral biopsy in some difficult cases [99]. Other advanced nuclear medicine techniques such as targeting the alpha(v)beta(3) integrin on osteoclasts to image osteolytic bone metastases, or compartmental intrathecal radioimmunotherapy for selective therapy of central nervous system metastases are also under development [100,101]. Many of these promising techniques have shown great potential for detecting malignancies and differentiating benign from malignant lesions, including in patients with low back pain, although the studied cohorts remain generally small and further evaluations in larger trials are required.

PERSISTENT BACK PAIN AFTER LUMBAR SPINE SURGERY

Back pain in patients who have undergone spinal surgery may be secondary to a variety of postoperative complications, including infection, surgical trauma, unstable fusion sites, residual malignancy, altered spinal biomechanics or even be unrelated to surgery. The postoperative back pain can pose a substantial diagnostic challenge, especially in the presence of orthopaedic devices [48,102-107]. Nuclear medicine techniques have been commonly employed in patients with various spinal intervantions like percutaneous vertebroplasty, laminectomy, diskectomy, facetectomy and lumbar fusion procedures [104,105,108-110]. Basic knowledge about these techniques is required to interpret the scan and to correlate the findings with possible pathology or postsurgical complications.

Percutaneous vertebroplasty is a minimally invasive procedure in which a bone cement (like polymethyl methacrylate) is injected percutaneously into a fractured vertebra for relieving back pain caused by acute or subacute compression fractures. Possible associated risks are related to the leak of acrylic cement outside of the vertebral body, infection, bleeding, numbness, and neurological complications due to misplacement of the needle or cement. Studies performed in patients with vertebral fractures considered for percutaneous vertebroplasty showed that bone scintigraphy and SPECT/CT proved good predictors of postprocedural response, adding valuable information related to the cause of the back pain [104,108]. Positive SPECT-CT findings predicted clinical improvement in 91% of these patients [104], being also useful in reassessing the vertebroplasty indication [105]. FDG PET/CT is commonly used in the differential diagnosis of benign and malignant vertebral compression fractures and showed slightly higher sensitivity and lower specificity compared to MR imaging [109]. FDG PET/CT-guided biopsies of vertebral lesions have also been reported in equivocal cases [95].

Spinal decompression procedures are performed to relieve pressure on the spinal cord or nerves, which can be caused by a variety of conditions like herniated disks of bony overgrowths within the spinal canal (i.e. spinal stenosis). Depending on their extension, spinal decompression procedures can include laminectomy (removal of the entire lamina, i.e. posterior arch of the vertebral bone covering the spinal canal and lying between the spinous process), laminotomy (removal of a small portion of the lamina and adjacent ligaments), foraminotomy (removal of bone around the neural foramen, i.e. the space between vertebrae where the nerve root exits the spinal canal), facetectomy (partial or complete removal of the enlarged facet joints), discectomy (excision of an intervertebral disc), etc. In some cases, decompression procedures are supplemented by spinal fusion to stabilize the sections of the spine affected by the excised bone segment. Spinal fusion, also known as spondylodesis or spondylosyndesis, is the joining of two or more adjacent vertebrae with a bone graft and special hardware such as rods, plates, pedicle screws, or cages. There are two main types of lumbar spinal fusion - posterolateral and interbody fusion. In posterolateral spinal fusion, the bone graft is placed between transverse processes, the fused vertebrae being also fixed with screws through the pedicles and metallic rods on each side

of the spine. In interbody spinal fusion, the intervertebral disc is removed and the bone graft is placed between the vertebrae. This may be supplemented by a special device, which is also placed between the vertebrae to maintain spine alignment and disc height. Depending on the incision made to access the intervertebral disc, interbody spinal fusions in the lubmar region can be subdivided into Anterior Lumbar Interbody Fusion **(ALIF)**, Posterior Lumbar Interbody Fusion **(PLIF)**, Transforaminal Lumbar Interbody Fusion **(TLIF)** and Transpsoas Interbody Fusion **(DLIF or XLIF)**. Fusion rates are reported to be higher with interbody than with posterolateral fusion. Using both types of fusion is known as 360-degree fusion. Bone SPECT results in patients with lumbar fusion correlated with biomechanical studies that have shown posterior fusion to produce the largest amount and lateral fusion to produce the least amount of stress in the free segments adjacent to the fusion, suggestive lateral fusion to have a more stabilizing effect than posterior fusion [111].

Bone SPECT/CT is a highly sensitive and specific tool for the exclusion of screw loosening in patients who present with recurrent low back pain after having undergone lumbar arthrodesis [112]. Bone SPECT after lumbar surgery was reported useful to identify various conditions such as pseudarthrosis, abnormal facets, vertebral body or disc space lesions [102], being particularly valuable in conditions with a high likelihood of instability as the improved contrast and better three-dimensional information gained through lumbar spine SPECT allowed more accurate delineation of the level of maximum instability and stress on the vertebra [106]. SPECT/CT may be also useful to detect a lack of fixation of the metallic implants, and hence instability of the spondylodesis by evaluating the focal bone mineralization activity in relation to the pedicle screws [110]. In addition, SPECT proved of value in the assessment of painful pseudoarthrosis and painful late effects of lumbar fusion [111]. Caution, however, should be exercised with interpretation of radiotracer activity in sacroiliac joints as previous studies showed that in patients with history of lumbar spinal fusion and/or laminectomy, increased unilateral or bilateral sacroiliac joint uptake was usually caused by altered spinal mechanics rather than malignancy or infection [103]. More specific radiotracers for imaging infection, like 99mTc-ciprofloxacin, proved also effective for diagnosing spinal and paraspinal postoperative infections [48,107]. The reported sensitivity, specificity and accuracy for diagnosing postoperative spinal infections using 99mTc-ciprofloxacin were respectively 54%, 71% and 67% (1 h), 62%, 77% and 73% (3 h), 42%, 91% and 77% (24 h) for planar imaging and 100%, 74% and 81% for SPECT. When recently operated patients (< 6 months) were excluded, the specificity of SPECT imaging rose to 81% [48]. Given its relatively lower specificity in the immediate postoperative period, the author's advice planar and SPECT imaging at 3 h post injection and an interval of at least 6 months after surgery to minimize the likelihood of false positives [48,107]. Additional radiotracers targeting infection that are still under development are described under the heading "Spinal and paraspinal infection".

Positron-emission tomography imaging also showed potential utility for identifying causes of persistent back pain following vertebral surgical interventions [45,113,114]. Thus, in subjects

with recurrent symptoms after spinal fusion surgery, 18 F-fluoride PET/CT proved useful in identifying those patients and vertebral sites requiring surgical revision [113]. In particular, the ratio between SUVmax in Screw Regions of Interest **(ROIs)** and the values in reference regions was reported as the most significant parameter for distinguishing screws positive and screws negative for loosening [115]. The modality was also helpful for assessment of bone graft incorporation in patients with persisting symptoms after posterior lumbar interbody fusion. In particular, intervertebral cage subsidence highly correlated with the degree of PET hyperactivity at the vertebral endplates and pedicle screw entry points, suggesting nonunion with instability as the source of pain in patients with persisting symptoms [114]. The authors point out that PET/CT may offer valuable insights in device design by demonstrating patterns of bone stress during incorporation and conclude that new prospective studies using 18 F-fluoride PET/CT are required to specifically assess the role of intervertebral cage subsidence as a cause of persisting pain in patients with spinal fusion [114].

MISCELLANEOUS CONDITIONS INVOLVING LUMBAR SPINE

Lumbosacral Transitional Vertebrae **(LSTVs)** are defined as either sacralization of the lowest lumbar segment or lumbarization of the superior sacrum. LSTVs are common in the general population, with a reported prevalence of 4%–30% and demonstrate varying morphology, ranging from broadened transverse processes to complete fusion [116]. Low back pain associated with an LSTV is also known as Bertolotti syndrome and may arise from the level above the transition, the contralateral facet when unilateral, and/or the anomalous articulation when present [116]. In a cohort of 28 patients with LSTVs, Pekindil et al report that focal, markedly increased, radiotracer uptake on bone SPECT may show the metabolically active degenerative changes of LSTV articulation [117]. The authors point out that bone scintigraphy may be considered for the evaluation of patients with low back pain thought to arise from LSTV articulation. Nuclear medicine techniques proved also useful in revealing or differential diagnosis of a variety of other conditions involving lumbar spine, including spinal tuberculosis [118], fibrous dysplasia [119], osteitis condensans ilii [120], vertebral body hemangiomas [121-124], osteoid osteomas [125-127], avascular necrosis of the femoral head [128], ankylosing spondylitis [128], early stage spine infarct [129], neurolymphomatosis [130,131], primary spinal Hodgkin lymphoma [131], metastatic deposits in vertebral Paget's disease [132], multiple myeloma and plasmacytoma [128,133], etc.

Quantitative radionuclide imaging using either Tc-99m MDP scintigraphy or fluorine-18 sodium fluoride PET/CT provides a novel tool for studying bone metabolism that complements conventional methods [134-137]. The techniques can be used to measure either bone uptake or bone plasma clearance and have been employed for quantification of bone loss in patients with osteoporosis and for evaluation of osteoporosis treatments. Unlike bone turnover markers, which measure the integrated response to treatment across the whole skeleton, radionuclide imaging can distinguish the changes occurring at sites of particular clinical interest, including lumbar spine

[134]. For example, in patients with glucocorticoid-induced osteoporosis, fluorine-18 sodium fluoride PET/CT revealed that Alendronate treatment resulted in significant decreases in bone metabolism and turnover in the lumbar spine, the results correlating with a gradual increase in bone mineral density of the lumbar spine [136]. In symptomatic patients with osteoporosis, nuclear medicine techniques such as Tc-99m MDP scintigraphy may be also helpful in elucidating the etiology of back pain [135]. For example, studies performed in patients with osteoporosis and chronic back pain showed that bone scintigraphy may identify a subgroup of osteoporotic patients who would benefit from treatment to the facet joints [137]. Associating regional changes in bone metabolism of the lumbar vertebrae obtained by quantitative radionuclide imaging techniques with detected structural abnormalities may help shed new light on the underlying pathology in many patients with low back pain.

CONCLUSION

Advances in nuclear medicine techniques have provided new non-invasive methods for investigating the cause of back pain. The addition of SPECT to planar skeletal scintigraphy increases sensitivity and improves disease localization without exposing the patient to additional radiation. SPECT and SPECT/CT proved particularly helpful in determining the precise anatomic location of spinal abnormalities, frequently providing useful information for differentiation between malignant and benign lesions. With the advancement of PET imaging, FDG PET/CT is becoming one of the most commonly used procedures for detection of spinal malignancies and has the advantage of demonstrating the presence of disease in both bone and soft tissues. In the spine, the modality can be used for detecting both lytic and sclerotic lesions, including in their early stage when the process is still confined to the bone marrow. Recently emerged modalities such as positron emission tomography with (18)sodium-flouride may bring new findings in patients with low back pain; however, most of them are still under development and require validation in patients with various types of spinal pathology.

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