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To evaluate use of positron emission tomography with 2-(fluorine-18) fluoro-2-deoxy-D-glucose in detection of chronic osteomyelitis

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Abstract

Nuclear medicine plays an important role in the evaluation of infection and inflammation. Fluorine 18 fluorodeoxyglucose is a readily available radiotracer that offers rapid, exquisitely sensitive high-resolution tomography. In the musculoskeletal system, fluorodeoxyglucose PET accurately helps diagnose spinal osteomyelitis, it appears to be useful for defining the extent of disease and monitoring response to treatment. Baseline fluorodeoxyglucose uptake by normal cortical bone is quite low. Bone marrow uptake is variable and can be slightly to moderately more intense than that of bone.

Keywords: Fluorodeoxyglucose, osteomyelitis, PET

1. Introduction

FDG is transported into cells by glucose trans-porters and is phosphorylated by hexokinase enzyme to F-2-FDG-6 phosphate but is not metabolized. The degree of cellular FDG uptake is related to the cellular metabolic rate and the number of glucose transporters. Increased FDG uptake is presumably due to an increased number of glucose transporters as in tumour cells. A similar situation exists in inflammation and infection: Activated inflammatory cells also demonstrate increased expression of glucose transporters. In addition, in inflammatory conditions, the affinity of glucose transporters for deoxyglucose is apparently increased by various cytokines and growth factors, a phenomenon that has not been observed in tumors.

Nuclear medicine plays an important role in the evaluation of infection and inflammation. Fluorine 18 fluorodeoxyglucose (FDG) is a readily available radiotracer that offers rapid, exquisitely sensitive high-resolution tomography. In the musculoskeletal system, FDG PET accurately helps diagnose spinal osteomyelitis, it appears to be useful for defining the extent of disease and monitoring response to treatment.

1.1 Osteomyelitis

Osteomyelitis is a bone infection and is usually caused by bacterial, fungal, or mycobacterial microorganisms. Osteomyelitis can be subdivided into the acute, subacute, or chronic type based on the time course of disease. Acute osteomyelitis usually does not pose a diagnostic challenge to clinicians, as systemic symptoms such as fever, fatigue, and malaise along with localized signs including reduced motion, pain, and tenderness of the involved bone usually aid in making the correct diagnosis. However, the accurate diagnosis of subacute or chronic osteomyelitis is often difficult by physical examination and existing radiological or nuclear medicine techniques, particularly when there are preexisting alterations in osseous structures due to previous trauma or surgery. Radionuclide imaging techniques play an important role in the diagnosis of osteomyelitis. In the absence of underlying bone abnormalities, three- phase bone scintigraphy is both sensitive and specific for osteomyelitis^[4]. However, in the setting of previous trauma, orthopedic hardware, or a neuropathic joint, bone scintigraphy is less useful. In these situations, dual radiotracer studies are often used: sequential bone-gallium, combined leukocyte-bone or, in most situations, combined leukocyte bone marrow imaging. However, these dual radiotracer studies have important limitations.

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The need for additional imaging adds to the complexity and cost of the study and is an inconvenience to patients, many of whom are elderly and debilitated. In labeled leukocyte imaging, the *in vitro* labeling process is labor intensive, not always available, and requires direct contact with blood products. Thus, investigators continue to search for suitable alternatives. One agent that has generated considerable interest is FDG. Baseline FDG uptake by normal cortical bone is quite low. Bone marrow uptake is variable and can be slightly to moderately more intense than that of bone. In osteomyelitis, the presence of inflammatory cells (eg, neutrophils, lymphocytes, macrophages) with heightened metabolic activity results in increased FDG uptake. FDG-PET has been shown to be highly sensitive for detecting chronic osteomyelitis, even in patients who have been treated with antibiotics prior to imaging. This is in contrast to WBC imaging, where the sensitivity of the test is significantly affected by prior use of antibiotics. Several publications in the literature reported the superiority of FDG-PET over imaging with radiolabeled WBCs, with an accuracy exceeding 90% in this clinical setting.

1.2 Review of Literature

Several studies have shown that FDG is useful in diagnosing osteomyelitis. However, increased osseous FDG activity has also been observed in inflammatory arthritis, in acute fractures, and in normally healing bone up to 4 months after surgery. These observations are not surprising. The healing process is associated with many of the same cellular components that are present in inflammation. Because FDG accumulates in the bone marrow, it is likely that some of this increased uptake, in the absence of infection, may also be related to localized hypercellular marrow. This phenomenon has in fact been observed in patients with failed lower extremity joint prostheses [1].

It is important to recall that not all radiotracers perform equally well in all situations. For example, although labeled leukocyte imaging is the radionuclide study of choice for diagnosing prosthetic joint infection and identifying pedal osteomyelitis in diabetic patients, it is of little use in spinal osteomyelitis. Thus, although initial reports about the value of FDG in diagnosing osteomyelitis have generally been encouraging, extensive investigations focusing on specific indications are needed to accurately define the role of FDG in the evaluation of musculoskeletal infection. Guhlmann *et al.* reported a higher accuracy for FDG-PET than antigranulocyte antibody scintigraphy for the evaluation of infection involving the central skeleton in patients with suspected chronic osteomyelitis [2].

De Winter *et al.* Prospectively evaluated the role of FDG-PET in the diagnosis of chronic musculoskeletal infections in 60 patients with recent surgery and reported a sensitivity, specificity, and overall accuracy of 100%, 86%, and 93%, respectively [3].

In another prospective study, Meller *et al.* Studied 30 patients with suspected chronic osteomyelitis and concluded that FDG-PET is superior to Inlabeled WBC imaging in establishing a diagnosis of chronic osteomyelitis in the central skeleton. In a study which utilized FDG-PET to detect chronic osteomyelitis, the authors concluded that FDG-PET holds great promise in the diagnosis of chronic osteomyelitis and that a negative FDG-PET study essentially excludes the presence of this disorder. In a study designed to evaluate the utility of FDG-PET to diagnose infections [4].

Several groups also investigated FDG-PET imaging for

assessments of both acute and chronic osteomyelitis. In a retrospective study, Kalicke *et al.* evaluated the role of FDG-PET in acute osteomyelitis, chronic osteomyelitis, and inflammatory spondylitis. They examined 15 patients who underwent surgery because of suspected bone infection and therefore histopathological confirmation of the underlying diagnosis. Of these 15 patients, 7 had acute and 8 had chronic osteomyelitis or inflammatory spondylitis. FDG-PET yielded true-positive results for all 15 patients, while bone scintigraphy performed in 11 patients yielded 10 true-positive results and 1 false-negative result. Those authors concluded that FDG-PET is an optimal technique for the diagnosis of bone infection. Moreover, follow-up FDG-PET scans performed on two patients showed a normalization of FDG uptake, which correlated well with clinical improvement in these patients [5].

A recent meta-analysis showed that FDG-PET not only is the most sensitive imaging modality for detecting chronic osteomyelitis but also has a greater specificity than radiolabeled WBC scintigraphy, bone scintigraphy, or MRI for this purpose. In that meta-analysis, the pooled data demonstrated that FDG-PET has a sensitivity of 96% (95% confidence interval, 88% to 99%), compared with 82% (95% confidence interval, 70% to 89%) for bone scintigraphy, 61% (95% confidence interval, 43% to 76%) for radiolabeled WBC scintigraphy, 78% (95% confidence interval, 72% to 83%) for combined bone and radiolabeled WBC scintigraphy, and 84% (95% confidence interval, 69% to 92%) for MRI. The pooled data demonstrated that bone scintigraphy had the lowest specificity, with a value of 25% (95% confidence interval, 16% to 36%), compared with 60% (95% confidence interval, 38% to 78%) for MRI, 77% (95% confidence interval, 63% to 87%) for radiolabeled WBC scintigraphy, 84% (95% confidence interval, 75% to 90%) for combined bone and radiolabeled WBC scintigraphy, and 91% (95% confidence interval, 81% to 95%) for FDG-PET [6].

1.3 Spinal Osteomyelitis

Spinal osteomyelitis accounts for less than 10% of all cases of osteomyelitis and has a predilection for the elderly. It may result from bacteremia or from direct inoculation of bacteria into the spine. Although spinal osteomyelitis is usually confined to the vertebral body and intervertebral disk, the posterior elements may be involved in up to 20% of cases. The majority of patients have prolonged symptomatology prior to diagnosis, and laboratory tests are of limited value. MR imaging, with an accuracy of 90%, is the diagnostic imaging procedure of choice for spinal osteomyelitis. MR imaging permits early diagnosis of infection and provides direct visualization of the spinal cord, subarachnoid space, extradural soft tissues, and spinal column without the use of intrathecal contrast material. On the other hand, MR imaging is sensitive to motion degradation, so that patients with movement disorders may not be suitable candidates, and certain metallic implants are contraindications for this modality. MR imaging cannot always help distinguish osteomyelitis from severe degenerative arthritis; in such cases, scintigraphy provides important information. The current radionuclide imaging method of choice for diagnosing spinal osteomyelitis is combined bone-gallium imaging, with results comparable to those of MR imaging having been reported. In addition to enhancing the specificity of the bone scan, gallium is useful for detecting the abscesses that often accompany spinal osteomyelitis. There are data that indicate that gallium single photon emission CT (SPECT) is

comparable to combined bone-gallium imaging for diagnosing this entity. Regardless of whether gallium imaging is performed alone or in combination with bone scintigraphy, the study is time consuming and requires that the patient make multiple visits to the nuclear medicine department. Although most of the series reported to date are small, FDG PET appears to be useful in diagnosing spinal osteomyelitis, with high sensitivities and specificities and an accuracy comparable to that of gallium imaging having been reported. FDG-PET appears to be the study of choice when chronic osteomyelitis is suspected. This is particularly true when this type of infection is suspected in the axial skeleton or anywhere else where there is a significant concentration of red marrow. In contrast to bone scintigraphy, which remains positive for an extended period of time following fracture, FDG uptake generally normalizes in less than 2 to 3 months following such incidents. As a result, this reduces the incidence of false-positive results as in the case of bone scanning when osteomyelitis is suspected in the setting of complex fractures. Therefore, FDG-PET is particularly suitable for the evaluation of suspected chronic osteomyelitis in patients with prior trauma [7, 8].

In an experimental study by Koort *et al.* who evaluated whether FDG-PET can differentiate between normal healing bones and those with osteomyelitis, localized osteomyelitis and fracture models of the rabbit tibia were created. In the aseptic fracture group, uncomplicated bone healing was associated with an initial increase in FDG uptake at 3 weeks, which subsequently returned to normal by 6 weeks. However, in the osteomyelitis group, localized infection resulted in an intense continuous uptake of FDG. Therefore, FDG-PET has the potential for the diagnosis of osteomyelitis in the setting of prior trauma or surgery. An additional advantage of FDG-PET over conventional nuclear medicine scintigraphy is that the tomographic images provided by PET can be coregistered and compared with anatomical images provided by both CT and MRI for a more precise localization of sites of infection [9, 10].

2. Study purpose and methods

Thirteen patients suspected to have chronic osteomyelitis in the peripheral or central skeleton were evaluated prospectively with FDG PET.

The final diagnosis was made by means of bacteriologic culture of surgical specimens and histopathologic analysis.

3. Conclusion

FDG PET enables noninvasive detection and demonstration of the extent of chronic osteomyelitis with a high degree of accuracy. Especially in the central skeleton within active bone marrow, FDG PET is highly accurate and shows great promise in diagnosis of chronic osteomyelitis.

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