Detection of Musculoskeletal Infection with ^{18}F-FDG PET: Review of the Current Literature

William B. Crymes, Jr., MD[1]; Harry Demos, MD[2]; and Leonie Gordon, MD[1]

[1]*Department of Radiology, Medical University of South Carolina, Charleston, South Carolina; and* [2]*Department of Orthopedics, Medical University of South Carolina, Charleston, South Carolina*

There are several studies on ^{18}F-FDG PET in the evaluation of musculoskeletal infection; however, a search of the literature failed to identify any large-scale studies. The 7 articles reviewed included 273 cases of suspected musculoskeletal infection evaluated by ^{18}F-FDG PET. This method was found to be sensitive and specific in the evaluation of chronic and acute osteomyelitis and prosthetic infection. Furthermore, ^{18}F-FDG PET was accurate in the evaluation of infection at previous surgical sites even within 12 mo of surgery. The current literature suggests that ^{18}F-FDG PET is a highly accurate method to detect musculoskeletal infection.

Key Words: bone; infectious disease; ^{18}F-FDG PET; arthroplasty; musculoskeletal infection; osteomyelitis

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There are numerous noninvasive techniques presently in use to evaluate cases of suspected musculoskeletal infection. Although white blood cell count, C-reactive protein, and erythrocyte sedimentation rate are still widely used, they are rudimentary parameters of inflammation and lack both sensitivity and specificity (*1–4*). As such, physicians have turned to functional imaging for the evaluation of infection. These imaging techniques include 3-phase bone scintigraphy (*5,6*), ^{67}Ga scanning (*5,7,8*), imaging with ^{111}In-oxyquinoline–labeled (*5,7,9*) or ^{99m}Tc-hexamethylpropyleneamine oxime–labeled (^{99m}Tc-HMPAO) (*5,7,10*) leukocytes, and ^{99m}Tc-labeled antigranulocyte antibody imaging (*5,11,12*). The use of ^{18}F-FDG PET has been recently added to this expansive repertoire of imaging modalities.

^{18}F-FDG PET is a functional imaging technique that can exploit the differences in the glycolytic rate between normal and diseased tissue. The tracer that makes this possible is the glucose analog FDG, which is transported into cells and phosphorylated under kinetics similar to those of glucose. However, the chemistry of the FDG prevents the metabolism or catabolism of the phosphorylated FDG, effectively trapping the molecule in the cell. The hyperglycolytic state of tumor cells has been known for >70 y (*13*). Not surprisingly, ^{18}F-FDG PET imaging has been used extensively in oncology for tumor staging and grading in several cancers (*14–17*). Similarly, the hyperglycolytic state of inflammatory cells during infection has also been well established (*18*). Tahara et al. first demonstrated the use of ^{18}F-FDG PET in the evaluation of infection in patients in 1989 (*19*). The design of the FDG molecule and the increased glucose utilization by activated inflammatory cells makes ^{18}F-FDG PET a useful tool for the evaluation of musculoskeletal infection.

The ability of ^{18}F-FDG PET to detect infection or the inflammatory response has been established in numerous disease processes, including pneumonia (*20*), tuberculosis (*21,22*), mastitis (*23*), myositis (*24*), sinusitis (*25*), abscesses (*19*), and sarcoidosis (*26*). These promising results prompted the following literature search and analysis for the effectiveness of ^{18}F-FDG PET in the evaluation of musculoskeletal infection.

MATERIALS AND METHODS

Using the Medline database from 1966 to present, approximately 50 articles were retrieved using Medical Subject Headings (Osteomyelitis/; Musculoskeletal diseases/; Infection/; Tomography, Emission-Computed/; and Arthroplasty/) and keywords (^{18}F-FDG PET; FDG PET; and musculoskeletal infection). Inclusion criteria were as follows: (1) the study must include suspected infections of the musculoskeletal system, including osteomyelitis (chronic and acute), spondylodiscitis, discitis, synovitis, soft-tissue infection with or without osteomyelitis, periprosthetic infection, and septic arthritis; (2) image interpretation of the PET scans must be performed by at least 2 independent radiologists, certified in nuclear medicine; (3) the radiologists must be unaware of the results of other diagnostic studies; and (4) the final diagnosis of musculoskeletal infection must be made on a histologic or microbiologic basis or clinical finding after a minimum of 6 mo follow-up. The Materials and Methods section of each study was used as confirmation. Although not stated in the study by Zhuang et al. (*27*), criterion 2 was confirmed by electronic written communi-

For correspondence contact: Leonie Gordon, MD, Department of Radiology, Medical University of South Carolina, 169 Ashley Ave., P.O. Box 250322, Charleston, SC 29425.
E-mail: gordonl@musc.edu

cation from Zhuang (2003). The 7 publications reporting a total of 273 cases of suspected musculoskeletal infection evaluated by PET imaging and satisfying the above criteria are outlined in Table 1.

A total of 7 patients from 2 studies were omitted from the analysis for the following reasons. In the study evaluating ^{18}F-FDG PET and ^{99m}Tc-labeled antigranulocyte antibody in chronic osteomyelitis by Guhlmann et al. (*28*), 1 patient was omitted because both interpreters read the PET scan and immunoscintigraphic scan as "indeterminate," although a final diagnosis of chronic osteomyelitis was eventually ruled out. In the study of Kälicke et al. (*29*), 6 patients were omitted secondary to lack of histologic or follow-up confirmation. To avoid confusion, the study by Zhuang et al. (*27*) included 74 separate cases of suspected infection in a total of 62 patients; the patients scanned more than once had more than one site of suspected infection.

RESULTS

The overall sensitivity and specificity for the detection of musculoskeletal infection by PET were 97.5% and 86.3%, respectively. Of the 21 false-positive results, 10 cases came from 1 study on infected lower limb prosthesis implants. Furthermore, 7 of these were false-positive results from suspected infection of knee prosthesis implants (*27*). In 103 cases of chronic osteomyelitis, the sensitivity and specificity of PET were 98.1% and 94.1%, respectively. In 47 cases of suspected infection of the central skeleton, PET was 100% sensitive and 92.3% specific. In 63 cases of suspected infection of the peripheral skeleton, PET was 97.0% sensitive and 93.3% specific. A total of 109 cases of suspected periprosthetic infections were reported. PET was found to be 94.1% sensitive and 80.0% specific in detecting periprosthetic infections. The sensitivity and specificity for the evaluation of 45 hip prosthesis implants were 92.9% and 90.3%, respectively. By contrast, PET was 95.0% sensitive and 72.7% specific in the evaluation of 64 knee prosthesis implants.

DISCUSSION

This review has examined the use of ^{18}F-FDG PET in the evaluation of musculoskeletal infections. The compiled data suggest that PET is both sensitive and specific for this use. Furthermore, these findings suggest that PET is more accurate in detecting chronic osteomyelitis than other functional imaging techniques, including the 3-phase bone scan (*6*,*30*), ^{99m}Tc-labeled antigranulocyte antibody imaging (*28*), ^{99m}Tc-HMPAO–labeled leukocyte imaging (*31*), and the combined 3-phase bone scan and ^{99m}Tc-HMPAO–labeled leukocyte scan (*31*) in the detection of infection. The combined data presented confirm the previous findings that PET is useful in both the exclusion of (*32*) and the diagnosis of (*33*) chronic osteomyelitis.

The high number of false-positive results from the report of Zhuang et al. on infected lower limb prosthesis implants deserves further discussion (*27*). Zhuang et al. discuss the possibility that postsurgical changes could be interpreted as positive results for infection on PET; however, none of the 10 false-positive cases had had surgery within 12 mo of the PET scan. The study of De Winter et al. provides useful information regarding postsurgical changes (*34*). A close look at the data presented in this article reveals 52 patients who had had surgery at the site of suspected infection. Under these conditions, PET was 100% sensitive and 85.7% specific at detecting infection. Of these, 24 patients had surgery within 12 mo of the PET study. The sensitivity was unchanged, whereas the specificity increased to 86.7%. These data do not completely support the explanation that postsurgical changes decrease the specificity of PET. Furthermore, the 2 studies that included details of previous surgery presented herein report no false-positive or false-negative results in 12 cases (*28*) in which surgery occurred at least 2 y before PET scanning or in 6 cases (*33*) in which surgery occurred at least 1 y before PET scanning. As discussed below, false-positive interpretation appears to be a very important issue when evaluating knee prosthesis implants.

In the study of Zhuang et al., the overall specificity was 81.1%. If one examines only the 36 cases of suspected infected knee prosthesis implants, the specificity drops to 72.0%, compared with the specificity of 89.3% in the 38 cases of suspected hip prosthesis implants in the same study. Zhuang et al. previously reported similar findings when they compared the use of PET imaging in hip and knee prosthetic

TABLE 1
Articles Meeting Inclusion Criteria

Study focus	Infections evaluated	*n*	TP/TN/FP/FN
Chronic musculoskeletal infection (*34*)	Spondylodiscitis, osteomyelitis, arthrosis deformans, soft-tissue infection, superficial infection, bursitis, aseptic loosening	60	26/30/4/0
Chronic osteomyelitis (*28*)	Osteomyeltitis, soft-tissue infection	50	27/22/0/1
Chronic osteomyelitis (*33*)	Osteomyelitis, synovitis, soft-tissue infection	31	17/12/1/1
Infectious bone diseases (*29*)	Acute and chronic osteomyelitis, spondylitis	15	15/0/0/0
Total knee arthroplasty (*36*)	Knee prosthetic infection, aseptic loosening	21	6/11/4/0
Lower limb prostheses (*27*)	Hip and knee prosthetic infection	74	19/43/10/2
Chronic osteomyelitis (*32*)	Chronic osteomyelitis	22	6/14/2/0

TP = true-positive; TN = true-negative; FP = false-positive; FN = false-negative.
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infections (*35*). The low specificity for PET evaluation of knee prosthesis implants has been reported in other studies (*34*,*36*). A possible explanation for these results may be aseptic loosening of the prosthesis implant. There are studies documenting ^{18}F-FDG accumulation in prosthesis loosening (*36*–*39*). Van Acker et al. found that both PET and the 3-phase bone scan were equally able to detect aseptic loosening of knee prosthesis implants, and both methods were superior to the ^{99m}Tc-HMPAO–labeled leukocyte scan (*36*). In the same study, Van Acker et al. reported that 2 of the 3 false-positive PET results were due to aseptic loosening (*36*). Further study on the evaluation of aseptic loosening by ^{18}F-FDG PET should help to answer this question.

Suspected infection in knee prosthesis implants still remains a diagnostic challenge. In addition to clinical evaluation, plain film radiography, erythrocyte sedimentation rate, and leukocyte count, joint aspiration and culture is the most sensitive method for detecting implant infection that is widely used today. However, Levitsky et al. found the sensitivity of a positive culture from joint aspiration to be only 67% (*3*). By contrast, the data presented herein showed that PET was 95% sensitive in detection of infected knee prosthesis implants.

PET imaging offers several advantages over conventional functional imaging. PET scanning does not require multiple scans. The images are ready for interpretation within hours, not days. The uptake of ^{18}F-FDG in bone and bone marrow is relatively low. Furthermore, PET imaging provides resolution in the millimeter range. Although the cost is a limiting factor, the increasing use of PET for oncology may make PET financially feasible.

Given these advantages, future prospective studies designed to compare PET with other functional imaging will be needed to validate these initial findings. Furthermore, the evaluation of PET in a larger number of patients with suspected musculoskeletal infection will be necessary to help reduce the selection bias typically seen in the initial evaluation of new imaging modalities and to assess the utility of PET in a more varied range of clinical circumstances.

CONCLUSION

The current literature suggests that ^{18}F-FDG PET is a highly sensitive and specific method for the evaluation of musculoskeletal infection.

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