FDG-PET Imaging Can Diagnose Periprosthetic Infection of the Hip

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Abstract A battery of diagnostic tests is often required to differentiate aseptic loosening from periprosthetic infection since the gold standard remains elusive. We designed a prospective study to determine the accuracy of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging in diagnosing periprosthetic infection in a large multicenter setting. One hundred and thirteen patients with 127 painful hip prostheses were evaluated by FDG-PET. Images were considered positive for infection if PET demonstrated increased FDG activity at the bone-prosthesis interface of the femoral component. A combination of preoperative tests, intraoperative findings, histopathology, and clinical followup constituted the gold standard for diagnosing infection. Among the 35 positive PET scans, 28 hips were confirmed infected according to our criteria for diagnosing periprosthetic infection. Of the 92 hip prostheses with negative FDG-PET findings, 87 were considered aseptic. The sensitivity, specificity, positive and negative predictive values for FDG-PET were 0.85 (28 of 33), 0.93 (87 of 94), 0.80 (28 of 35), and 0.95 (87 of 92), respectively. The overall accuracy of this novel

noninvasive imaging modality reached 0.91 (115 of 127). Based on our results, FDG-PET appears a promising and accurate diagnostic tool for distinguishing septic from aseptic painful hip prostheses.

Level of Evidence: Level II, diagnostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

Total hip arthroplasty (THA) is an effective procedure that alleviates the debilitating effects of osteoarthritis and affords the patient adequate functional capacity to perform activities of daily living pain free [14]. Complications after THA are not unheard of; two of the most common etiologies for revision arthroplasty are aseptic loosening of components and periprosthetic infection [4]. The treatment and surgical intervention as well as outcome of the two modes of failure are quite different [9, 15]. Therefore, identifying the underlying process preoperatively is essential for optimal patient care. Although numerous diagnostic algorithms exist for workup of a painful THA, they are not absolute and the diagnosis can be baffling [2]. A diagnostic dilemma will undoubtedly emerge, especially during the next decade with the increasing prevalence of infection and a predicted surge in THA procedures and their concomitant mechanical failures [7].

An initial workup for periprosthetic infection (PPI) entails taking a detailed patient history and performing a thorough physical examination. Serologic testing for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels as well as needle aspiration is often pursued in cases of high suspicion for infection [18]. One problem that arises is that inflammatory markers are

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Fig. 1 In this patient with a painful left hip prosthesis, the dramatically increased FDG uptake at the bone-prosthesis interface surrounding the femoral stem provides clear evidence of infection (red arrows). The blue arrows indicate the absence of isolated uptake around the prosthesis neck and cup commonly seen in aseptic loosening.

nonspecific and are frequently elevated in both cases of aseptic loosening and infection, particularly in the setting of inflammatory arthritis, autoimmune diseases, and malignancy [19]. Although the specificity of joint aspiration has been reported to approach 100%, the sensitivity has varied considerably from 0% to 100% in the literature [1]. Aspiration carries a risk of contaminating a noninfected joint, whereas false-positive cultures can lure a surgeon away from the correct path of treatment. Recently, the search for a more accurate, cost-effective, and noninvasive diagnostic test has been the focus of intense investigation.

Radionuclide imaging represents an attractive alternative in diagnosing PPI. Conventional technetium-99 m sulfur colloid bone marrow scintigraphy is an excellent screening tool to rule out infection [9]. Combining colloid marrow imaging with indium-111 labeled white blood cells (TcSC-Ind WBC) improves both the sensitivity and specificity [17]. Many consider this combined modality the imaging gold standard in diagnosing infection in total joint replacements. However, this test does include a laborious process of extracting WBCs from the patient and labeling them with radioactive markers followed by transfusing them back into the patient [10]. Expense, time, and the risk

of handling blood products are just some of the drawbacks to this imaging technique [17].

Fluorodeoxyglucose-positron emission tomography (FDG-PET) is a tomographic imaging technique that provides images with superior-resolution compared to other functional imaging techniques [3, 12]. The imaging process is less time-consuming and does not entail any invasive procedures that may expose the patient or healthcare providers to unnecessary risk. In a previous multicenter study performed at our institutions, we established the normal uptake pattern of FDG after uncomplicated THA and elucidated the optimal diagnostic criteria for differentiating septic from aseptic painful hip prostheses by FDG-PET [16]. PET findings were suggestive of sepsis if increased uptake was observed at the stem-prosthesis interface, while uptake limited to the soft tissues or only adjacent to the neck of the prosthesis was consistent with aseptic loosening (Fig. 1). The objective of our current ongoing investigation is to determine the reliability of FDG-PET imaging in a large scale clinical setting with extension of our previously published work [16] and to compare its results with frequently used serology and aspiration.

Materials and Methods

We prospectively enrolled 113 patients with 127 painful hips scheduled to undergo clinical and diagnostic evaluation for revision of a total hip prosthesis between 2003 and 2006. A total of 128 patients were initially invited to participate in our study which constitutes a capture rate of 88%. Only 53 patients enrolled in our previous study were included in our current investigation. Institutional review board approval was obtained prior to initiating the study. A data management system was developed to track laboratory results, PET results, and all patients' followup data throughout the course of the study. Exclusion criteria included (1) any etiology (e.g. abductor weakness, periprosthetic fracture, low back pain) for hip pain other than aseptic loosening or infection; (2) considerable comorbid medical, surgical, or psychiatric conditions that were currently uncontrolled or that may have interfered with completion of the trial; (3) inability to tolerate being in a PET scanner; and (4) systemic sepsis.

Postoperative FDG-PET scans were performed in an individual at three specific time points after surgery (12, 18, and 24 months) and the patients were followed by their treating surgeon. Each subject with a painful total hip prosthesis was evaluated by an orthopaedic surgeon from one of the collaborating institutions. A routine evaluation for each subject was performed, including a history, physical examination, laboratory studies (complete blood count, ESR, and CRP), and radiographic and scintigraphy

imaging. An initial diagnosis was established based on the collective results from these studies.

FDG was administered intravenously in a weight-based dose of 140 $\mu\text{Ci/kg}$ with a maximum dose of 10 mCi. This dose was based on optimal count rates for the scanning instruments. We performed FDG-PET studies on an Allegro GSO crystal PET scanner (ADAC Laboratories, Milpitas, CA). An emission transmission scan was performed in single acquisition mode using a 20 mCi ^{137}Cs point source. Image segmentation was applied to the transmission image, which was then incorporated into a system-modeled attenuation correction during image reconstruction. Sixty minutes after the intravenous injection of FDG (140 $\mu\text{Ci/kg}$), we acquired emission data over the area of interest with successive overlapping axial frames. The area of interest included the pelvis and the upper four-fifths of the femora. Total acquisition time was less than 30 minutes.

Three experienced observers (AA, AN, HZ) who were blinded to the clinical and radiographic information independently evaluated each study. Each study was read once, and the outcome was regarded as the clinical conclusion. Any area of increased uptake was identified and its location, size, and shape were recorded. PET findings were suggestive of sepsis if physicians noted abnormally increased FDG uptake at the prosthesis-bone interface and were not suggestive of infection if the uptake was limited to the soft tissues or only adjacent to the neck of the prosthesis [16]. If the readers held consensus, the reading was considered final. If the readers disagreed, a consensus reading determined the final interpretation.

The findings of FDG-PET imaging were compared to the patients' postoperative diagnosis based on the diagnostic criteria for periprosthetic infection listed below. Intraoperative histology and cultures were performed for all patients to determine the diagnosis and grading of infection. To ensure thorough and consistent tissue sampling, we harvested at least three routine specimens for frozen and permanent histology from the pseudocapsule, areas considered suspicious for infection, and tissues identified at the various host-implant interfaces. To avoid additional inconsistencies in tissue sampling, culture swabs were acquired on the same tissue sampled for histologic analysis.

All pathologic sections were investigated using standard hematoxylin and eosin staining techniques. Sections were analyzed according to the criteria as described by Feldman et al. [6]: (1) presence of granulation tissue; (2) utilization of the five most cellular fields for final diagnosis as determined on the basis of the number of polymorphonuclear (PMN) leukocytes; (3) cell count determination under $\times 40$ magnification; (4) utilization of at least two samples of tissue; and (5) inclusion of only PMN leukocytes, identified

within tissue rather than fibrin, with well-defined cytoplasmic borders. Frozen specimens with fewer than five PMN leukocytes per high-power field were considered aseptic, whereas specimens with at least 10 PMN cells indicated infection. Specimens with five to nine PMN leukocytes raised suspicion for infection, leaving culture reports in this equivocal group to determine the final diagnosis. A permanent specimen was considered positive if five or more PMN leukocytes per high-power field were noted.

A final diagnosis was given to each patient postoperatively based on the interpretation of the clinical presentation and/or the preoperative and intraoperative findings. Sepsis was confirmed if the patient met at least one of the following three criteria: (1) an open wound or sinus in communication with the joint; (2) a systemic infection with pain in the hip and purulent fluid within the joint; or (3) a positive result on at least three tests (ESR, CRP, joint aspiration, intraoperative frozen section, and intraoperative culture). We considered the normal range for ESR and CRP levels to be 0 to 25 mm/h and 0.1 to 0.9 mg/dL, respectively. As for aspiration results, any growth that was observed when the extracted fluid was cultured indicated a positive signal for infection.

One hundred and thirteen surgical candidates for revision of painful hip prosthesis were prospectively enrolled in the study. Fourteen patients had bilateral painful hip prostheses for a total of 127 hips. The incidence of periprosthetic infection in this study is 25.9% (33 of 127 cases). Our cohort included 54 males and 59 females with an average age of 59 years (range, 31–87 years). The average time to diagnosis of infection from date of primary surgery was 158 months (range, 5–914 months).

Results

Patients with an infected prosthesis had higher average ESR (48 versus 26, $p = 0.029$) and CRP (3.1 versus 1.2, $p = 0.016$) than in the noninfected group. Although both ESR and CRP were commonly elevated in the infected cohort, 9% (three of 33) had normal ESR levels, whereas 6% (two of 33) had false-negative CRP levels. False-positives were also commonly encountered; ESR and CRP were abnormally elevated in 16% and 10% of the aseptic revisions performed, respectively. A total of 25 hip aspirations were performed during the preoperative workup of 16 noninfected and nine proven infected patients. Fluid cultures were negative in all of the 16 aseptic revisions, whereas an organism was obtained in only two of the nine infected revisions.

FDG-PET correctly diagnosed 28 of the 33 infected cases (sensitivity, 84.8%), while it ruled out infection in 87

of the 94 aseptic hips (specificity, 92.6%). It was associated with a positive predictive value of 80% (28 of 35) and a negative predictive value of 95% (87 of 92). Although ESR and CRP were more sensitive than PET imaging, they had a greater percentage of false positives and hence a lower specificity. FDG-PET was able to diagnose infection in all nine of the patients with infected revisions who underwent aspiration of the hip joint.

Discussion

The diagnosis of septic joint arthroplasty remains challenging even with the advent of new diagnostic techniques. The hierarchy of the diagnostic algorithm begins with simple serologic blood tests and radiographic studies [13]. ESR and CRP are some of the most frequently requested serologic tests; however, they lack the adequate specificity to confirm infection [19]. Although culture of aspirated joint fluid has high specificity [13], aspiration of the hip joint is invasive, technically demanding, and requires fluoroscopic guidance. Therefore, renewed interest in imaging diagnostics surfaced and novel advances were achieved during the past decade. We hypothesize that FDG-PET imaging is a potentially formidable preoperative diagnostic tool that can compensate for some of the pitfalls encountered with serology and joint fluid culture during the preoperative diagnostic workup.

We note several limitations. Although our investigation is a prospective multicenter study that involves a large cohort of patients, some caveats must be kept in mind. Not all patients approached consented to the study and hence this may have biased our results. Only a fraction of the cohort underwent joint aspiration which limits the comparison of FDG-PET to aspirate culture. Given that the gold standard for diagnosing periprosthetic infection remains vague, the criteria we implemented to diagnose our patients with septic hips may have missed some patients and skewed our results.

Bone scans were introduced as a potential adjunct in the preoperative workup for infection; the specificity remained too low for proper confirmation of PPI [9]. Technologic advancement permitted the radiolabeling of the patient's WBCs *in vitro*, reintroduction of the labeled cells into the patient, and scintigraphic evaluation for WBC congregation, which is indicative of ongoing infection [8]. Although TcSC-Ind BM/WBC is currently the preferred imaging modality in evaluating painful hip prostheses, the sensitivity, specificity, and accuracy ranges from 60% to 100%, 58% to 100%, and 70% to 94%, respectively. In a preliminary trial conducted at our institution, TcSC-Ind BM/WBC was prospectively compared with FDG-PET in a

cohort of 89 patients [16]. We found a sensitivity of 85% and a specificity of 93% for FDG-PET imaging in diagnosing PPI. The results showed FDG-PET is a promising tool for distinguishing aseptic prosthetic loosening from PPI irrespective of the postsurgical inflammation observed after THA.

The concept of FDG-PET revolves around a basic notion that at the sites of infection, activated leukocytes, and macrophages have an increased energy requirement, which is reflected by an increased uptake of FDG [11]. The patient's cells, including those residing or traveling to areas of inflammation, are labeled in an *in vivo* fashion soon after administration of the radiolabeled glucose within 2 hours after the intravenous injection of FDG. Another important feature is treatment with antibiotics is not likely to affect the sensitivity of PET in delineating sites of infection because FDG uptake does not rely on leukocyte migration. De Winter et al. [5] reported that FDG-PET is considerably more accurate than the combination of bone scan and white blood cell scan for diagnosing chronic infections in the central skeleton ($p < 0.05$) with a sensitivity, specificity, and accuracy of 100%, 90%, and 94%, respectively.

On the other hand, the usefulness of FDG-PET for differentiating PPI and aseptic loosening has varied. Mumme et al. [11] reported a sensitivity of 91% and a specificity of 92% (accuracy 91%) for FDG-PET compared with a sensitivity of 78% and specificity of 70% (accuracy 74%) for conventional triple-phase bone scintigraphy. Stumpe et al. [20] reported that although PET was more specific in the diagnosis of hip infection, the sensitivity of conventional radiography compared favorably with that of both FDG-PET and bone scintigraphy. Recently, a meta-analysis of seven articles, including a total of 273 cases of suspected musculoskeletal infection, concluded FDG-PET was an accurate technique for evaluating periprosthetic infection, even within 12 months of surgery. This discrepancy in results may stem from the smaller sample size of previous studies and weaker diagnostic criteria for defining PPI.

FDG-PET is a promising, unique tool for diagnosing prosthetic loosening and infection. Early inflammatory reactions result from implant wear long before clinical or radiographic signs of loosening appear. This may enable them to offer more limited interventions such as the removal of granulomatous tissue or early replacement of individual components before end-stage loosening occurs. By establishing appropriate diagnostic criteria, FDG-PET may prove highly accurate and become the only imaging technique necessary to differentiate PPI from aseptic loosening in patients with THA.

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