F-18 Fluoride Positron Emission Tomography of the Hip for Osteonecrosis

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Abstract Osteonecrosis (ON) of the femoral head continues to be a devastating disorder for young patients. We evaluated the F-18 fluoride positron emission tomography (PET) imaging modality for use in detection of the bone involved in ON of the hip. We retrospectively reviewed the records of 60 consecutive patients diagnosed with ON and interviewed all by phone. Eleven patients (17 hips) of those interviewed agreed to participate in the study. We classified the ON using the University of Pennsylvania classification system and compared each patient's plain AP bone scan, single photon emission 3-D computed tomography, and MRI. ON was associated with HIV, alcohol, steroid use, and polycythemia vera in this group. Nine of 17 hips (8 patients) had acetabular increased uptake when using the F-18 fluoride PET scans that were not seen on MRI, single photon emission computed tomography, or

bone scans. These data suggest earlier acetabular changes in osteonecrosis may exist that traditional imaging modalities do not reveal.

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

Introduction

Osteonecrosis (ON) of the hip can be a devastating problem, especially in young patients, and may result in irreversible changes of the hip [6, 8, 12]. Once collapse and substantial degenerative changes occur, the patient usually undergoes reconstruction of the hip with an arthroplasty [10, 15, 17, 18]. In young patients, this can lead to considerable future difficulties, including multiple revision arthroplasties and loss of income or considerable career changes, which can have a major socioeconomic impact throughout the patient's life [10, 15].

The pathogenesis and etiology of ON remain unclear. Known associated factors include traumatic dislocation or injury, steroid use, and alcohol abuse; some patients have no identifiable risk factors. Most data point to a microvascular insult or hyperlipidemia in nontraumatic cases [10, 13, 15, 18]. Even though there is evidence that distinguishes a specific cause-and-effect relationship between certain risk factors (steroid use, hyperlipidemia and sickle cell disease) and ON, standard diagnostic techniques (MRI or technetium bone scan) do not always provide prognostic information. Given the array of potential risk factors, from steroid use and alcohol abuse to HIV, an analysis which reflected the metabolic activity of the bone might be useful. In cases of osteonecrosis, an infarct region on the femoral head may have a proprioceptive impact on the joint that

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may start to overload the acetabular side of the joint. If this finding is discovered on an image modality then it aids in predicting which patients may go on to progression of disease.

Positron emission tomography (PET) scans provide a real-time image of physiology based on the type of radio-labeled marker used. Traditionally, PET scans, in addition to MRI and SPECT scans, have been utilized to determine vascularity and uptake changes in patients with tumor progression; however, PET scan may be more sensitive in detecting early changes compared to MRI and these changes might predict subsequent progression. PET imaging has been utilized extensively in orthopaedic skeletal disease assessment as well as in cases where interference from implants inhibits the use of other imaging modalities [2, 4]. F-18 FDG accumulates in cancer cells due an increased glucose metabolism. The process, however, is not specific to tumors. FDG-18 also accumulates in inflammatory cells, such as lymphocytes, neutrophils, and macrophages which have elevated glucose requirements, and therefore the process may be useful in ON [3, 5, 11, 14–17]. As suggested above, it is possible PET scans will detect ON earlier than MRI and single-photon emission computed tomography (SPECT) scans or that some early uptake or vascular changes might predict the lesions that are going to progress to changes on both sides of the joint and eventual arthroplasty. PET scan is a powerful tool in oncology and it may also play a role in diagnosing ON [17]. In a pilot study, Schiepers et al. [17] determined a flow ratio could be established and used to predict a successful outcome with a conservative regimen in patients with ON of the femoral head. The authors suggested this type of image modality could be used in clinical practice and would permit prediction of the outcome depending upon regional skeletal flow measurements [17].

We hypothesized F-18 fluoride PET scan imaging would match the traditional “gold standard” imaging studies of MRI and SPECT modalities but would also provide further information not seen with standard imaging modalities. If PET scan imaging can be determined to give further information concerning areas of activity in the hip itself, then it may potentially be utilized as a prognostic study in the future.

Materials and Methods

Utilizing the ICD-9 code for osteonecrosis of the femoral head and neck in a county-based hospital clinic in April 2003, a list of active patients with this diagnosis were identified and recruited until December 2003 for inclusion in this pilot study. Inclusion criterion was simply a diagnosis of ON of the femoral head without a history of

trauma and without surgical intervention in at least one hip if bilateral disease was present. Sixty patients were identified with the diagnosis of ON of the femoral head at this time.

The study was designed to identify hips with atraumatic etiologies of ON to determine if any differences between F-18 fluoride PET scan imaging and the traditional MRI and SPECT scan imaging were found. Sixty patients were identified with the diagnosis of ON of the femoral head. All of the patients were then contacted by phone for inclusion in the study. Out of the original 60 patients 11 (18%) with aseptic and atraumatic ON of one or both femoral heads agreed to participate. Each patient underwent staging by the University of Pennsylvania classification system (Table 1) [19]. In this study group two hips were excluded due to previous unilateral core decompression (these two hips were in patients with bilateral ON, leaving them in the study for the untreated side) and three hips in three patients

Table 1. Comparison of the University of Pennsylvania osteonecrosis classification system to Ficat

Stage	Ficat	University of Pennsylvania
I	No changes on radiograph	Normal radiograph
	Clinical symptoms suspicious	Abnormal MR or bone scan
		A = mild, < 15% of femoral head affected; B = moderate, 15–30% affected; C = severe, > 30% affected
II	Bone remodeling	Cystic and sclerotic change in femoral head
	No changes in the shape of the femoral head	A = mild, < 15% of femoral head affected;
	Subchondral sclerosis	B = moderate, 15–30% affected;
III	Cysts	C = severe, > 30% affected
	Crescent sign	Crescent sign without flattening
		A = mild, < 15% of femoral head affected; B = moderate, 15–30% affected C = severe, > 30% affected
IV	Joint space narrowing	Flattening of the femoral head
	Degenerative changes on both sides of the joint	A = mild, < 15% of femoral head affected and < 2 mm of depression;
	Femoral head deformation	B = moderate, 15–30% affected and 2–4 mm of depression; C = severe, > 30% affected)
V	—	Joint narrowing or acetabular changes (can be graded according to severity)
VI	—	Advanced degenerative changes

Table 2. Demographics of patients who met the inclusion criteria and agreed to participate in the study

Patient	Age	Gender	Etiology	U of Penn. Stage	
				Right	Left
1	58	M	steroids	IB	IB
2	36	F	steroids	IA	NA*
3	78	M	ETOH	VA	VI
4	31	F	HIV	NA [†]	IVB
5	58	M	ETOH	NA*	IIIB
6	51	F	polycythemia	IIB	IIA
7	34	F	steroids	IVA	IA
8	54	M	ETOH	IA	VB
9	48	M	steroids	IB	IVC
10	53	M	steroids	IA	NA [†]
11	41	M	ETOH	IIIA	NA*

* = not applicable due to a previous THA; † = not applicable due to a previous core decompression; ETOH = alcohol abuse.

for the presence of a total hip arthroplasty opposite an active case of ON of the femoral head (Table 2). This left 11 patients with 17 osteonecrotic hips for inclusion. Osteonecrosis was associated with steroid use (five patients, eight hips), alcohol abuse (four patients, six hips), and with HIV (one patient, two hips), polycythemia vera (one patient, one hip). All patients underwent PET scanning, SPECT and bone scans, and MRI imaging over 2 days. Patients received no financial incentive other than free transportation to the imaging center provided by the nuclear medicine department. This study was approved by the Investigational Review Board at our institution.

For MRI, we obtained both T1- and T2-weighted images without contrast during one of the imaging days. Images of each hip and pelvis were in the axial, coronal, and sagittal planes. No patients had contraindications to obtaining an MRI. Three-phase bone and SPECT scans were obtained on a dual head Vertex camera (ADAC Laboratories, Milpitas, CA). For three-phase bone and SPECT scans, approximately 20 to 25 mCi of Tc-99m MDP was injected intravenously while the subject was lying in the SPECT camera gantry. Twenty-five-second dynamic acquisition frames were acquired over the hip regions followed by a blood pool image. Approximately 2 hours later, anterior and posterior planar views of the hips were obtained in a static mode (256 × 256 matrix) with high-resolution collimators. Next, SPECT of the pelvic region was acquired and the images reconstructed in 3-D mode.

For F-18 fluoride PET scans, on a separate day, a transmission scan of the pelvis overlapping the full axial field of view covered by the dynamic emission data was acquired. Next, 2.5 to 3.5 mCi of F-18 fluoride was

injected intravenously. For the dynamic study, 12 frames, each for 5 seconds, were acquired during the first minute using the Minimize Wait Program (ADAC C-PET PLUS 250, Philips Medical Systems, Netherlands), with NaI scintillation crystal transmission imaging of Cs-137 transmission scan 45 sec/rotation (2 rotations = 1.5 min) and small sinograms (2-mm slice thickness). Then, a 1-minute frame was acquired for the next 4 minutes followed by 2-minute frames 10 times. Static images, 5 minutes per frame, were acquired over the next 15 minutes. Total acquisition time, including transmission, was approximately 55 minutes.

One board-certified nuclear medicine physician (HN) evaluated PET scans and bone scans and provided descriptive results. The scan area of the bone in the ilium was utilized as a baseline normal for each PET scan and the difference in the femoral head and surrounding bone of the hip was then determined to have more uptake in each PET scan image window. This provided an objective means of determining differences in each of the image windows analyzed for the PET scans. Two attending physicians (WM, MA) and one resident (VD) in the orthopaedic department reviewed all MRI images and staged all hips using the University of Pennsylvania classification system [10].

The data were organized by presence of changes on each imaging modality and compared utilizing a Kappa score to determine agreement between the PET scan findings and each of the traditional imaging modalities. Any differences where PET scan images revealed changes not recorded on the traditional imaging modalities were recorded as well for analysis. Confidence intervals were also calculated and reported to reveal the effects of the small sample size. All data were calculated using SPSS software (Chicago, IL).

Results

In general, all patients had MRI findings of the femoral head consistent with ON. The patient with HIV (Stage IV) showed consistent findings between the PET scan and bone scans. Both showed increased uptake of the acetabulum; however, the left femoral head showed no changes on PET but did show increased uptake in the neck and greater trochanter. The second patient with steroid-induced ON who underwent decompression of a Stage II lesion which was excluded from the study showed no evidence of increased uptake on PET but still showed MRI changes consistent with Stage II disease.

All patients had MRI findings of ON in the femoral head. (Table 3). Bone scans did not reveal ON in either femoral head in five of six hips when compared with the MRI. The findings were comparable to (Kappa = 0.88) the PET imaging findings. When the PET and MRI scans for

Table 3. Presence of imaging findings in femoral head and acetabulum in MRI and PET scan*

Patient	MRI femoral head right/left	PET scan femoral head right/Left	MRI acetabulum right/left	PET scan acetabulum right/left
1	1/1	0/0	0/0	0/0
2	1/NA	1/NA	0/NA	0/NA
3	1/1	1/1	0/0	1/0
4	NA/1	NA/1	NA/0	NA/1
5	NA/1	NA/1	NA/0	NA/1
6	1/1	1/1	0/0	1/1
7	1/1	1/1	0/0	0/1
8	1/1	1/1	0/0	1/0
9	1/1	1/1	0/0	1/0
10	1/NA	1/NA	0/NA	1/NA
11	1/NA	1/NA	0/NA	0/NA

*Presence is indicated by a 1 and absence by a 0.

NA = Not Applicable due to previous surgery.

right-sided ON of the femoral head were compared, an agreement of 88.9% (95% CI = 51.8 to 99.7) was determined. PET versus MRI for the left side of the femoral head revealed an agreement of 87.5% (95% CI = 47.4 to 99.7).

PET F-18 fluoride imaging studies in 9 hips (8 patients) revealed signal changes in the region of the acetabulum not detected on MRI (Figs. 1 and 2, Table 3). Comparison of these findings resulted in poor agreement with a Kappa of 0.36.

Discussion

In this study we sought to determine if agreement between more traditional imaging modalities and PET F-18 fluoride scans existed in patient with atraumatic ON of the femoral head and also whether the PET scan modality provided any further areas about the hip joint where activity was recorded that MRI and SPECT scan did not detect. Standard diagnostic techniques (MRI or technetium bone scan) for ON do not always provide prognostic information. Traditionally, PET scans, in addition to MRI and SPECT scans, have been utilized to determine vascularity and uptake changes in patients with tumor progression; however, PET scans may be more sensitive in detecting early changes compared to MRI and these changes might predict subsequent progression. We hypothesized F-18 fluoride PET scan imaging would match the traditional “gold standard” imaging studies of MRI and SPECT modalities but would also provide further information not seen with standard imaging modalities.

Our study is limited by the sample size and the possible bias in the sample population. We did record good agreement of the PET scan with MRI findings in the femoral head and also identified increased activity in the acetabulum of several patients with the PET scan modality which was not apparent in the MRI or bone scan. This resulted in poor agreement on the acetabular side of the joint and a low Kappa score. In this small pilot study it may be difficult to determine the implication of the acetabular findings. With a large number of patients identified who met the inclusion criteria (60), but a small fraction (11) agreeing to participate, we experienced a major limitation that is

Fig. 1A–E (A) A female patient with polycythemia vera remains asymptomatic with early-onset ON visible in this radiograph. (B) MRI reveals changes in the femoral head with no acetabular

involvement. Positron emission tomography scan results at (C) 5 to 10 minutes, (D) 15 to 20 minutes, and (E) 35 to 40 minutes reveal increased acetabular uptake outlined by arrows.

Fig. 2A–D A female patient with ON secondary to steroid use had undergone left THA. She remains (A) asymptomatic on the right side as shown in this radiograph. (B) MRI reveals changes in the femoral head with no acetabular involvement. Positron emission tomography scan results at (C) 25 to 30 minutes and (D) 35 to 40 minutes reveal increased acetabular uptake outlined by the arrow.

difficult to overcome. Because the PET scan image readings were performed by a single reader, this may be viewed as a limitation as well, despite utilizing an objective criterion. The ilium of each patient acted as a normal baseline, allowing the different timelines to be more objectively reported. It is difficult to rate the sensitivity and specificity of our findings due to the fact it is uncertain if they indicate a pathological process or adaptation.

Osteonecrosis of the femoral head is a disease process for which progression is difficult to predict. Given the various etiologies this should not be surprising. However, despite the various causes the end result is often the same [14, 18]. In our limited series we found a portion of patients with good agreement of findings compared to MR imaging, but a subset of patients having acetabular changes in early stages of ON was identified only by PET imaging. These findings had no correlation to findings in this region on MRI or SPECT. In the later stages, degenerative arthritis confounds the accuracy of all the imaging modalities, especially at the articular surface [3, 9, 10]. However, in early disease, the presence of changes on both sides of the joint may lead to greater acceleration of degenerative changes. The acetabular blood supply comes primarily from the superior gluteal, inferior gluteal, and obturator arteries. The blood supply for the femoral head arises from branches of the profunda femoris [1]. These vessels are clearly from different sources, but the changes seen on PET were still recorded in both in the femoral head and acetabulum.

Fink et al. [3] described acetabular findings on MRI in 9.5% of patients with femoral head ON. We observed acetabular changes on PET scans in patients with ON without corresponding MRI changes. All bone scans showed increased uptake of both the acetabulum and femur, but we were unable to distinguish between the two

given the poor resolution of the images. Interestingly, the patient with HIV who had undergone core decompression 3 weeks previously had no improvement in flow relative to the nonoperative side included in the study, whereas the patient who underwent core decompression 2 years previously did not show PET evidence of ON but continues to have MRI changes on the hip that was excluded from the study due to previous surgery.

Further study is needed to ascertain whether acetabular ON predicts progression of the disease. Furthermore, if the early presence of acetabular metabolic changes as indicated on F-18 fluoride PET can predict outcome in nonoperative treatments, then it may serve as an important role in the future [7, 11]. With the advent of PET computed tomography combined with labels such as fluorodeoxyglucose, we may gain considerable insight into the pathophysiology of ON as well. Drawing conclusions from this small sample size is difficult, and our observations have raised more questions. However, the results serve as a starting point for future investigation to determine if the presence of a positive signal on the acetabular side of the joint is a prognostic indicator for success or failure of progression of the disease. The results, however, may suggest an expanded vascular and anatomic role of ON extending into the acetabulum than previously believed.

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