PET with FDG-labeled Leukocytes versus Scintigraphy with ^{111}In-Oxine–labeled Leukocytes for Detection of Infection[1]

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Purpose: To compare prospectively the accuracy of positron emission tomography (PET) with leukocytes labeled in vitro with ^{18}F fluorodeoxyglucose (FDG) versus that of conventional scintigraphy with leukocytes labeled in vitro with ^{111}In oxine in patients suspected of having infection.

Materials and Methods: This HIPAA-compliant study had institutional review board approval; informed consent was obtained from all patients. Patients were 25 men and 26 women aged 32–86 years. In vitro labeling of autologous human leukocytes with FDG and ^{111}In-oxine was performed according to published methods. Labeling efficiencies and cell viability were determined. Imaging was performed 2.5–5.8 hours after injection of 196–315 MBq of FDG-labeled leukocytes and approximately 24 hours after injection of 17–25 MBq of ^{111}In-oxine–labeled leukocytes. Forty-three (20 men, 23 women; mean age, 59 years; range, 32–86 years) patients could be successfully imaged with both tracers. Six patients were not injected with FDG-labeled leukocytes because of low labeling efficiency (<35%). Two patients were injected with FDG-labeled leukocytes but were not imaged. One reader interpreted all results as positive or negative for infection. Imaging results were compared with final diagnoses. Labeling efficiencies and cell viabilities were compared by using the paired *t* test. Differences between PET and scintigraphy were determined by using the McNemar test.

Results: For the 43 patients who were imaged with both tracers, labeling efficiency of FDG was lower than that of ^{111}In oxine (72% ± 8 [standard deviation] vs 90% ± 5, $P < .001$). Viability of FDG-labeled leukocytes was not different from that of ^{111}In-oxine–labeled leukocytes (98% ± 1 vs 97% ± 3). There were no differences between FDG PET and ^{111}In scintigraphy in terms of sensitivity (87% vs 73%), specificity (82% vs 86%), or accuracy (84% vs 81%).

Conclusion: PET with FDG-labeled leukocytes was comparable to scintigraphy with ^{111}In-oxine–labeled leukocytes. Further investigation in a larger population with dedicated PET or PET/computed tomography seems warranted.

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Autologous human leukocytes labeled in vitro with indium 111 (^{111}In)-oxine are routinely used to evaluate patients suspected of having infection. Indications for labeled leukocyte imaging include evaluation of suspected infection of a prosthetic joint, orthopedic hardware, or vascular graft; suspected osteomyelitis; and identification of the source of infection in patients with fever of unknown origin, unexplained leukocytosis, or bacteremia at presentation (1).

Positron emission tomography (PET) with fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) is a sensitive, high-spatial-resolution technique that is widely used to image a variety of tumors. Although FDG, a glucose analogue, accumulates in sites of infection, it is a nonspecific tracer that also accumulates in areas of aseptic inflammation, as well as in malignant and benign neoplasms (2). Results of several studies have demonstrated the feasibility of labeling human leukocytes with FDG (3–5). Forstrom et al (5) found that whole-body and major organ dosimetry estimates for 225–250-MBq doses of in vitro FDG-labeled autologous human leukocytes were comparable to those obtained with ^{111}In-oxine–labeled leukocytes. Results of biodistribution studies performed in four healthy adult volunteers showed that FDG-labeled leukocyte uptake occurred predominantly within the reticuloendothelial system, as is seen with leukocytes labeled with other methods (5). These studies also revealed tracer activity in the brain (1.7% ± 0.4 at 6 hours) and urinary excretion consistent with the presence of free FDG, which probably resulted from elution following dephosphorylation within cells (5).

PET imaging of FDG-labeled leukocytes could have several important advantages over conventional scintigraphy of ^{111}In-oxine–labeled leukocytes. First, PET is intrinsically a tomographic technique and enables precise localization of potential sites of infection. Tomography, while possible with ^{111}In-oxine–labeled leukocytes, is a time-consuming procedure, and images are typically of poor quality. Second, semiquantitative analysis, which may be useful for differentiating infectious from noninfectious conditions and for monitoring patients' responses to therapy, is easily performed with PET but is less feasible with conventional scintigraphy. Finally, FDG-labeled leukocyte scan results are available more quickly than are ^{111}In-oxine–labeled leukocyte scan results because imaging can be performed 3–4 hours after FDG-labeled leukocytes are injected but is typically performed approximately 24 hours after ^{111}In-oxine–labeled leukocytes are injected.

The purpose of our study, therefore, was to compare prospectively the accuracy of gamma-camera PET with in vitro FDG-labeled leukocytes to that of conventional scintigraphy with in vitro ^{111}In-oxine–labeled leukocytes in patients suspected of having infection.

Materials and Methods

Patients

Fifty-one adult patients (25 men, 26 women; mean age, 59 years; range, 32–86 years) who were *(a)* suspected of having infection, *(b)* referred to our institution for ^{111}In-oxine–labeled leukocyte scintigraphy between August 2003 and August 2004, and *(c)* likely to undergo subsequent histopathologic, microbiologic, and/or intraoperative procedures for confirmation of the final diagnoses were enrolled in this prospective investigation. Reasons for referral included suspected musculoskeletal infection ($n = 47$), vascular graft infection ($n = 3$), and fever of unknown origin ($n = 1$). The institutional review board granted ethical approval for this study, and written informed consent was obtained from all patients prior to participation. The study was compliant with the Health Insurance Portability and Accountability Act.

Labeling Procedures

All leukocyte labeling was performed by a radiochemist (K.K.B.) with 15 years of experience in labeling leukocytes. ^{111}In labeling of autologous human leukocytes was performed according to standard methods (6,7). FDG labeling of autologous human leukocytes was performed according to a modification of the procedure published by Forstrom et al (4).

In summary, by using a 20-gauge needle, 36 mL of blood was withdrawn into a color-coded 60-mL syringe that contained 5 mL of heparin sodium, 1000 U/mL. Seven milliliters of hetastarch (Abbott Laboratories, North Chicago, Ill), a settling agent, was added to the syringe, which was kept in a vertical position in a hood (Class IIA/B3 Biological Safety Cabinet; Forma Scientific, Marietta, Ohio) for 1.0–1.5 hours. A 19-gauge butterfly needle was attached to the syringe, and plasma was slowly ejected into two conical 10-mL plastic tubes. The plasma was centrifuged (Marathon 8K; Fisher Scientific, Springfield, NJ) at 450 *g* for 10 minutes. The plasma was separated from the leukocyte pellet, and 5 mL of sterile saline containing 2% heparin was added to the leukocyte button. Cells were gently resuspended and centrifuged again at 450 *g* for 5 minutes. The supernatant was removed, and 18–20 mCi (660–740 MBq) of FDG in 1.5 mL of saline was added to the cell suspension. The mixture was incubated for 30 minutes at 37°C. At the end of incubation, the mixture was centrifuged again at 450 *g* for 5 minutes. The supernatant was removed, and cells were resuspended in 5 mL of saline containing 2% heparin. The mixture was again centrifuged at 450 *g* for 5 minutes. The supernatant was then removed again, and FDG-la-

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Abbreviation:
FDG = fluorodeoxyglucose

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beled cells were resuspended in 4 mL of saline. The wash and cells were assayed in the dose calibrator to determine the activity associated with the wash and with the cells.

Determination of Labeling Efficiency

The radiochemist (K.K.B.) calculated the labeling efficiency *(E)* for the ^{111}In-oxine–labeled and the FDG-labeled leukocytes by using the formula $E = C/(C + W) \cdot 100$, where C is the activity associated with the cells and W is the activity associated with the wash. If labeling efficiency was less than 35% for the FDG-labeled leukocytes, the patient was not injected with the radiopharmaceutical because there was insufficient activity to enable the acquisition of diagnostic-quality images; the patient therefore was excluded from further analysis.

Determination of Cell Viability

For patients who were injected with FDG-labeled leukocytes, viability of ^{111}In-oxine–labeled and FDG-labeled leukocytes was determined by using the trypan blue dye exclusion technique (4). A nuclear physician (G.G.T.) with 3 years of experience performed microscopic examination of aliquots of ^{111}In-oxine–labeled leukocytes and FDG-labeled leukocytes mixed with 0.4% trypan blue dye immediately after the labeling procedures. Cell viability (CV) was calculated for ^{111}In-oxine–labeled and FDG-labeled leukocytes by using the following formula: $CV = V/(V + B) \cdot 100$, where V is the number of viable cells and B is the number of trypan blue–defective cells.

Imaging Protocol and Final Patient Study Group

Among the 51 patients who were enrolled in the study, a total of eight were excluded from analysis and follow-up because of FDG-labeled leukocyte labeling efficiency of less than 35% ($n = 6$), camera malfunction ($n = 1$), or patient inability to cooperate with imaging ($n = 1$). The final study group therefore included 43 patients (20 men, 23 women; mean age, 59 years; range, 32–86 years). PET of FDG-labeled leukocytes and conventional scintigraphy of ^{111}In-oxine–labeled leukocytes were performed no more than 10 days apart. Forty-one of the 43 patients included in the final study group underwent both studies within 24 hours of each other, one patient underwent both studies within 4 days of each other, and one patient underwent both studies within 10 days of each other. Thirty patients underwent FDG-labeled leukocyte PET first, and 13 patients underwent ^{111}In-oxine–labeled leukocyte scintigraphy first. There was no randomization with respect to the order of the two studies; the order was based on logistic issues. On the basis of the patients' clinical status, interval biopsy procedures and/or treatment were not performed between the two studies.

For PET, patients were injected with a mean of 7.7 mCi (285 MBq) (range, 5.3–8.5 mCi [196–315 MBq]) of FDG-labeled autologous human leukocytes. Imaging was performed 2.5–5.8 hours (mean, 3.6 hours) after injection by using a dual-head coincidence-detection gamma camera (Solus MCD/AC; ADAC Laboratories, Milpitas, Calif) with which attenuation maps were obtained by using a cesium 137 (^{137}Cs) source. Emission and transmission imaging were performed of the suspected site of infection or from the top of the ear to the upper thigh when the site was unknown. For emission imaging, 64 projections (32 projections per detector) at 40 seconds per projection (corrected for radioactive decay) were acquired by using 128 × 128 matrixes. A 20% window centered on the 511 keV photopeak of ^{18}F and a 30% window centered on the Compton centerline (310 keV) were used. For transmission imaging, 96 projections at 2 seconds per projection were acquired by using 128 × 128 matrixes, with a 20% window centered on the 665 keV photopeak of ^{137}Cs. Emission and transmission imaging were performed in an alternating sequence without moving the gantry. Data were reconstructed by using an iterative method (ordered-subset expectation maximization). In-plane tomographic spatial resolution at full width half maximum was 4.8 mm (according to the manufacturer).

For ^{111}In-oxine–labeled leukocyte scintigraphy, patients were injected with a mean of 561 μCi (21 MBq) (range, 450–680 μCi [17–25 MBq]) of ^{111}In-oxine–labeled autologous leukocytes. Ten-minute static images of the suspected site of infection were obtained approximately 24 hours later with a dual- or single-detector gamma camera (Solus, Genesys, or Argus; ADAC Laboratories) that was equipped with a medium-energy collimator by using a 20% window centered on 173 and 247 keV and 128 × 128 matrixes. Single photon emission computed tomography (SPECT) was performed as part of our routine clinical practice in one patient who was suspected of having malignant external otitis and was also performed (on the basis of the judgment of one of the investigators [C.J.P.]) in another patient to enable further localization of an abnormality that was evident on planar images. For dual-detector gamma cameras, SPECT acquisition parameters consisted of a 128 × 128 × 16 matrix with 128 projections (64 projections per detector) at 60 seconds per projection. For the single-detector gamma camera, SPECT acquisition parameters consisted of a 128 × 128 × 16 matrix with 64 projections at 60 seconds per projection.

All 20 patients who had been referred for evaluation of suspected infection of prosthetic joints or orthopedic hardware also underwent marrow scintigraphic imaging. These patients were injected with 10 mCi (370 MBq) of technetium 99m (^{99m}Tc)–sulfur colloid after the acquisition of ^{111}In-oxine–labeled leukocyte images. Approximately 30 minutes later, static images were obtained in the anterior and posterior views and in both lateral views by using the dual-isotope acquisition mode.

Image Interpretation

A single experienced nuclear physician (C.J.P.) with 22 years of experience prospectively reviewed (in the order in which the studies were acquired) all attenuation-corrected transverse, coronal, sagittal, and three-dimensional volume FDG-labeled leukocyte PET images and ^{111}In-oxine–labeled leukocyte pla-

nar and SPECT images by using a computer workstation (Pegasys; ADAC Laboratories). The reader interpreted each study independently while blinded to the results of all other imaging studies and the final diagnosis and classified all studies as yielding positive or negative results for focal infection.

Results of studies performed in patients suspected of having infection in prosthetic joints or orthopedic hardware were interpreted in conjunction with ^{99m}Tc–sulfur colloid marrow scans by using previously described criteria (8). Briefly, these studies were classified as yielding positive results for infection if the distribution of labeled leukocytes and the distribution of ^{99m}Tc–sulfur colloid were spatially incongruent.

Studies performed in patients suspected of having pedal osteomyelitis were classified as yielding positive results for infection if focally increased tracer activity in the forefoot was equally intense on the dorsal and plantar views from ^{111}In-oxine–labeled leukocyte scintigraphy (9) and if activity appeared to conform to the location of bone on FDG-labeled leukocyte tomograms. For all nonosseous infections, both studies were classified as yielding positive results for infection if labeled leukocyte activity was identified outside the normal biodistribution of the agent.

Reference Standard

Imaging study interpretations were compared with final diagnoses, which were considered the reference standard.

Final diagnoses were established in consultation with an infectious disease specialist (C.S.) with 25 years of experience on the basis of review of all available histopathologic findings, microbiologic examination results, and intraoperative findings and/or on the basis of findings at clinical follow-up. Histopathologic evidence of osteomyelitis, gross purulence at surgery, and positive cultures obtained from blood or other sterile sites (including bone) were considered to indicate the presence of infection. Final diagnoses were available only for the 43 patients who were imaged successfully with both FDG-labeled leukocytes and ^{111}In-oxine–labeled leukocytes. For 30 of the 43 patients, the final diagnosis was based on histopathologic, microbiologic, and/or intraoperative findings, while for the remaining 13 patients, the final diagnosis was determined clinically.

Statistical Analysis

Labeling efficiencies and cell viabilities were compared by using the paired t test. Sensitivity, specificity, accuracy, positive predictive, and negative predictive values were calculated for the entire study population and for the following three patient subgroups: patients with histopathologic, microbiologic, and/or intraoperative confirmation of the final diagnoses (group 1); patients who had been referred for evaluation of suspected osteomyelitis in the hands or feet (group 2); and patients suspected of having infection in a prosthetic joint (group 3). The significance of differences between FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy was determined by using the McNemar test. Analysis of proportions was used to determine whether there were any significant differences in results between patient subgroups in this investigation and to compare results of this investigation with those of previous studies performed by other investigators. $P < .05$ was considered to indicate a statistically significant difference. Statistical analysis was performed by using a software package (MedCalc, version 7.5.0.0 for Windows XP; Mariakerke, Belgium).

Results

Patients

The 43 patients had been referred for the following reasons: suspected infection of a prosthetic joint ($n = 17$ [10 hip prostheses and seven knee prostheses]) or an item of orthopedic hardware ($n = 4$), suspected osteomyelitis ($n = 18$), suspected infection in a vascular graft ($n = 2$), suspected psoas abscess ($n = 1$), and fever of unknown origin ($n = 1$) (Table 1). Final diagnoses were available for all 43 patients. For 30 of the 43 patients, the final diagnosis was based on histopathologic, microbiologic, and/or intraoperative findings (group 1), and for 13 patients, the final diagnosis was determined clinically. Fifteen of the 43 patients were found to have infection, including infection in a prosthetic joint ($n = 3$ [one hip prosthesis and two knee prostheses]) or item of orthopedic hardware ($n = 1$), osteomyelitis ($n = 7$), septic arthritis ($n = 1$), vascular graft infection ($n = 2$), and psoas abscess ($n = 1$).

Labeling Efficiency and Cell Viability

For the 43 patients who comprised the study group, mean labeling efficiency (Table 2) of FDG-labeled leukocytes was significantly lower than that of ^{111}In-oxine–labeled leukocytes (72% ± 8 vs 90% ± 5, $P < .001$ [paired t test]). For the six patients in whom the labeling efficiency of FDG-labeled leukocytes was less than 35%, the mean labeling efficiency of ^{111}In-oxine–labeled leukocytes was 90% ± 2 (range, 89%–93%).

Mean FDG-labeled leukocyte cell viability (Table 2) was not significantly different from mean ^{111}In-oxine–labeled leukocyte cell viability (98% ± 1 vs 97% ± 3, $P > .05$ [paired t test]).

Imaging Results

Forty-one patients underwent both FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy within 24 hours of each other, one patient underwent both studies within a 4-day interval, and one patient underwent both studies within a 10-day interval. For 11 of 41 patients, the FDG-labeled leukocyte and ^{111}In-oxine–labeled leukocyte studies were performed on the same day. For 30 of 41 patients, FDG-labeled leukocyte PET was performed on the day before but within 24 hours of ^{111}In-oxine–labeled leukocyte scintigraphy.

SPECT imaging was performed in two patients: one patient who was suspected of having malignant external otitis (patient 12) and one patient who had left hip pain and fever (patient 8). Patient 12 had negative results at planar and SPECT imaging, and the final diagnosis was negative for malignant external otitis. At planar imaging, patient 8

Table 1

Patient Characteristics, Labeling Efficiencies, and Imaging Results

Patient No./ Sex/Age (y)	Indication(s) for Imaging	Basis of Final Diagnosis	Labeling Efficiency (%)		Imaging Results*	
			FDG	^{111}In-Oxine	FDG	^{111}In-Oxine
1/M/80	Fever of unknown origin	Clinical	68	92	TN	TN
2/F/68	Osteomyelitis in knee	Histopathologic and microbiologic	56	88	TN	TN
3/M/55	Pedal osteomyelitis	Histopathologic and microbiologic	55	93	TN	FP
4/M/68	Vascular graft infection	Histopathologic	80	87	TP	TP
5/F/56	Infected prosthetic joint†	Clinical and microbiologic	80	89	TN	TN
6/M/59	Infected prosthetic joint‡	Clinical	75	90	TN	TN
7/F/33	Osteomyelitis in ankle	Clinical	81	93	TN	TN
8/F/44	Psoas abscess	Clinical and microbiologic§	91	91	TP	TP
9/F/50	Osteomyelitis in fourth digit of right hand	Histopathologic and microbiologic§	63	88	TP	FN
10/M/32	Infected orthopedic hardware	Surgical and microbiologic‖	85	88	TP	TP
11/M/61	Pedal osteomyelitis	Histopathologic and microbiologic#	79	93	TP	TP
12/M/83	Malignant otitis externa	Clinical	78	99	FP	TN
13/F/47	Infected prosthetic joint‡	Histopathologic and microbiologic	85	92	FP	TN
14/F/50	Infected orthopedic hardware	Surgical	75	92	TN	TN
15/F/53	Vascular graft infection	Surgical and microbiologic§	74	90	FN	FN
16/M/66	Pedal osteomyelitis	Histopathologic	70	87	TP	TP
17/M/57	Pedal osteomyelitis	Histopathologic and microbiologic§	61	94	TP	TP
18/M/62	Infected prosthetic joint‡	Surgical and microbiologic	61	93	TN	TN
19/F/83	Infected prosthetic joint	Clinical	62	70	TN	TN
20/F/51	Pedal osteomyelitis	Histopathologic and microbiologic	70	92	FP	FP
21/M/63	Pedal osteomyelitis	Histopathologic and microbiologic§	72	89	TP	TP
22/F/50	Infected orthopedic hardware	Surgical and microbiologic#	81	86	TP	TP
23/M/57	Osteomyelitis in pelvis	Clinical	80	89	TN	TN
24/F/64	Infected prosthetic joint‡	Clinical	74	87	TN	TN
25/F/81	Infected prosthetic joint‡	Clinical	79	83	TN	TN
26/M/51	Infected prosthetic joint‡	Surgical and microbiologic	75	92	TN	TN
27/F/40	Osteomyelitis in femur	Clinical	67	92	TN	TN
28/F/75	Pedal osteomyelitis	Histopathologic	79	93	TP	FN
29/M/63	Pedal osteomyelitis	Surgical	80	83	FN	FN
30/M/40	Infected orthopedic hardware	Surgical	68	96	TN	TN
31/M/86	Infected prosthetic joint†	Clinical	71	78	TN	TN
32/M/65	Infected prosthetic joint†	Clinical	67	93	TN	TN
33/F/48	Infected prosthetic joint†	Surgical	71	88	TN	TN
34/F/77	Infected prosthetic joint†	Clinical and microbiologic	63	90	TN	TN
35/F/69	Infected prosthetic joint†	Surgical	56	85	TP	TP
36/M/40	Pedal osteomyelitis	Histopathologic	85	93	TN	TN
37/F/57	Pedal osteomyelitis	Histopathologic	67	91	FP	FP
38/F/43	Pedal osteomyelitis	Histopathologic	70	91	FP	FP
39/F/52	Infected prosthetic joint†	Microbiologic#	77	90	TP	TP
40/M/60	Infected prosthetic joint‡	Surgical	61	94	TN	TN
41/M/56	Infected prosthetic joint‡	Surgical and microbiologic**	64	94	TP	TP
42/F/57	Pedal osteomyelitis	Clinical	63	90	TN	TN
43/F/82	Infected prosthetic joint‡	Clinical	66	92	TN	TN

* FN = false-negative, FP = false-positive, TN = true-negative, TP = true-positive.

† Total knee replacement.

‡ Total hip replacement.

§ Blood culture was positive for *Staphylococcus aureus.*

‖ Blood culture was positive for *Streptococcus intermedius.*

Blood culture was positive for *Staphylococcus epidermidis.*

** Blood culture was positive for *Serratia marcescens.*

had an abnormality in the left sacroiliac joint region that was localized to the psoas region at tomography; this abnormality was consistent with the final diagnosis of psoas abscess.

FDG-labeled leukocyte and ^{111}In-oxine–labeled leukocyte scans were accurate in 36 and 35 of the 43 patients, respectively (Table 3). Both imaging studies yielded concordant and correct results in 33 patients: 11 patients had true-positive results at both studies, and 22 patients had true-negative results at both studies. Among the 11 patients with true-positive results at both studies, one had an infected hip prosthesis, two had infected knee prostheses, one had infected orthopedic hardware, four had osteomyelitis, one had septic arthritis, one had a vascular graft infection (Fig 1), and one had a psoas abscess. Both studies yielded concordant and incorrect results in five patients: Three patients (all of whom had diabetes with pedal ulcers and all of whom had undergone bone biopsies whose results were negative for osteomyelitis) had false-positive results at both studies, and two patients had false-negative results at both studies. Of the latter two patients, one had diabetes and surgical confirmation of calcaneal osteomyelitis that had been misinterpreted as soft-tissue infection on imaging studies, and the other was receiving hemodialysis and had surgical and microbiologic confirmation of an infected hemodialysis graft.

Study results were discordant in five patients. Two patients had false-positive results at FDG-labeled leukocyte PET: One patient had a femur fracture adjacent to a right hip prosthesis but no evidence of infection at histopathologic or microbiologic examination, and one patient had otitis externa (Fig 2) that was misinterpreted as osteomyelitis and resolved with the administration of antibiotic ear drops. One patient had false-positive results at ^{111}In-oxine–labeled leukocyte scintigraphy; this patient had a diabetic pedal ulcer and negative bone biopsy results (Fig 3). Last, two patients had false-negative results at ^{111}In-oxine–labeled leukocyte scintigraphy: One patient had histopathologically confirmed osteomyelitis in the fourth digit of the right hand (Fig 4), and one patient had histopathologically confirmed osteomyelitis in the third digit of the right foot.

Table 2

Labeling Efficiency and Cell Viability

Parameter	FDG	^{111}In-Oxine
Labeling efficiency (%)*	72 ± 8 (55–91)	90 ± 5 (70–99)
Cell viability (%)	98 ± 1 (94–99)	97 ± 3 (88–99)

Note.—Data are mean values ± standard deviations, with ranges in parentheses.

* $P < .001$.

Table 3

Summary of Imaging Results in 43 Patients

	FDG				
^{111}In-Oxine	TP	TN	FP	FN	Total
TP	11	0	0	0	11
TN	0	22	2	0	24
FP	0	1	3	0	4
FN	2	0	0	2	4
Total	13	23	5	2	43

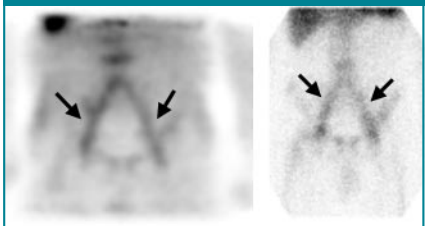
Note.—FN = false-negative, FP = false-positive, TN = true-negative, TP = true-positive.

Statistical and Subgroup Analyses

For all 43 patients studied, the sensitivity, specificity, and accuracy, respectively, of the two modalities were as follows: 87% (13 of 15), 82% (23 of 28), and 84% (36 of 43) for FDG-labeled leukocyte PET and 73% (11 of 15), 86% (24 of 28), and 81% (35 of 43) for ^{111}In-oxine–labeled leukocyte scintigraphy (Table 4). According to results of the McNemar test, there were no significant differences in sensitivity, specificity, accuracy, positive predictive value, or negative predictive value for any comparison of FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy in the total patient population or in any of the patient subgroups.

For the subset of patients in group 1 ($n = 30$), the accuracies of FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy were 80% and 73%, respectively (Table 5). All patients in group 2 ($n = 13$) had diabetes mellitus: One was suspected of having osteomyelitis in a finger, and 12 were suspected of having pedal osteomyelitis. Twelve of the 13 patients in group 2 had histopathologic, microbiologic, and/or intraoperative confirmation of the final diagnosis. Seven of the 13 patients had a final diagnosis of osteomyelitis. For group 2, accuracies of FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy were 69% and 46%, respectively (Table 5).

Figure 1



a. b.

Figure 1: Patient 4. Coronal images in 68-year-old man with end-stage renal disease who had undergone aortobifemoral bypass 6 years previously. **(a)** Maximum intensity projection from FDG-labeled leukocyte PET and **(b)** ^{111}In-oxine–labeled leukocyte scintigraphic planar anterior view show diffuse tracer uptake around the graft (arrows). Fine-needle aspiration biopsy revealed abscess formation.

Figure 2

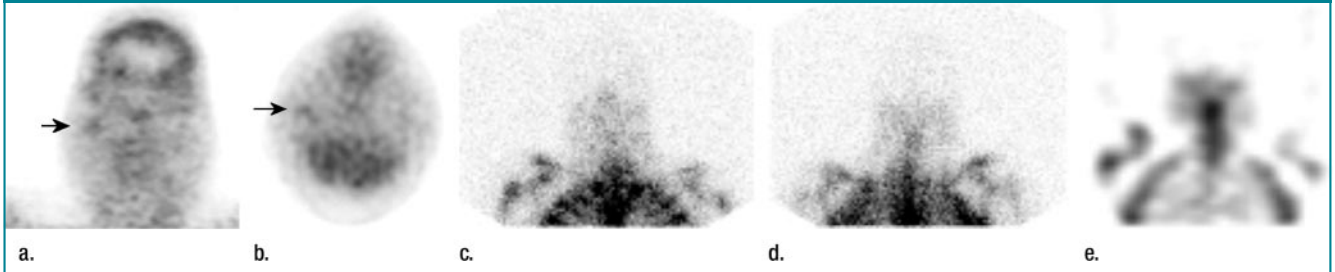


Figure 2: Patient 12. Images in 83-year-old man with diabetes and possible malignant otitis externa. **(a)** Coronal and **(b)** transverse FDG-labeled leukocyte PET images show faint uptake (arrow) in region of right temporal bone; this uptake was interpreted as indicating osteomyelitis. **(c)** Anterior and **(d)** posterior static views and **(e)** coronal tomograms from ^{111}In-oxine–labeled leukocyte scintigraphy do not show findings of infection. The patient's ear infection resolved after administration of topical antibiotics alone. Therefore, findings at FDG-labeled leukocyte PET were classified as false-positive, while those at ^{111}In-oxine–labeled leukocyte scintigraphy were classified as true-negative. Note the faint cerebral activity seen on **a** and **b**; this activity reflects free FDG.

Group 3 (n = 17) included 10 patients with hip prostheses and seven patients with knee prostheses. Nine of the 17 patients had histopathologic, microbiologic, and/or intraoperative confirmation of the final diagnosis. Three of the 17 prostheses (one hip prosthesis and two knee prostheses) were infected. Microbiologic and/or intraoperative confirmation of infection was available for all three infected prostheses. For six of the 14 uninfected prostheses there was histopathologic, microbiologic, and/or intraoperative confirmation of the final diagnosis. For group 3, accuracies of FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy were 94% and 100%, respectively (Table 5).

According to results of analysis of proportions, there were no significant differences in the sensitivity, specificity, or accuracy of FDG-labeled leukocyte PET between any pair of subgroups. The only significant differences observed between pairs of calculations were those between the specificity of ^{111}In-oxine–labeled leukocyte scintigraphy in group 2 and that in group 3 (33% vs 100%, P = .005) and between the specificity of ^{111}In-oxine–labeled leukocyte scintigraphy in group 2 and that in all patients (33% vs 86%, P = .002) (Tables 4 and 5).

Comparison of Study Data with Those Reported in Literature

In comparing the sensitivity of FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy in our group 2 with the sensitivity of ^{111}In-labeled leukocyte scintigraphy for osteomyelitis previously reported by Newman et al (9), we found that the sensitivity of FDG-labeled leukocyte PET in our group of 13 patients (86% [six of seven]) was not significantly different from that of ^{111}In-labeled leukocyte scintigraphy in the group of 41 patients examined by Newman et al (89% [23 of 26], P = .62). In addition, the sensitivity of ^{111}In-labeled leukocyte scintigraphy in our group 2 patients (57% [four of seven]) was not significantly different from that in the group of patients examined by Newman et al (89% [23 of 26], P = .19).

In comparing the accuracy of FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy in our group 3 with the accuracy of ^{111}In-labeled leukocyte scintigraphy previously reported by Palestro et al (8), who eval-

Figure 3

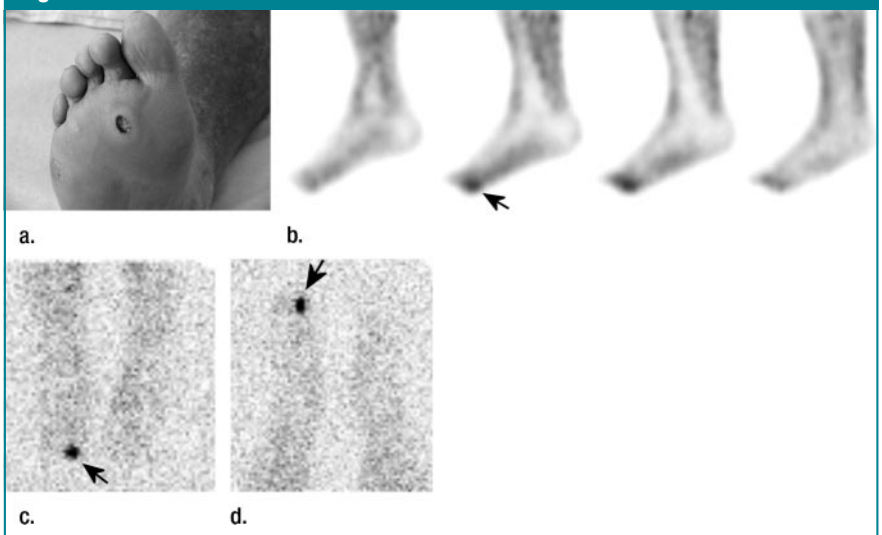


Figure 3: Patient 3. Images in 55-year-old man with diabetes and **(a)** an ulcer overlying the second metatarsal bone of the right foot. **(b)** Sagittal tomograms from FDG-labeled leukocyte PET show uptake (arrow) in the soft tissue of the right forefoot but no evidence of osteomyelitis. **(c)** Dorsal and **(d)** plantar views from ^{111}In-oxine–labeled leukocyte scintigraphy show intense focal tracer uptake (arrow) that is equally well seen on both views and was interpreted as being consistent with osteomyelitis. Resection of the second metatarsal bone of the right foot revealed no evidence of osteomyelitis and no other abnormalities.

uated total hip replacements with combined labeled leukocyte and sulfur colloid imaging, we found that the accuracy of FDG-labeled leukocyte PET in our group of 17 patients suspected of having infection in a prosthetic joint (94% [16 of 17]) was not significantly different from that of ^{111}In-labeled leukocyte scintigraphy in the 50 patients with total hip prostheses examined by Palestro et al (98% [49 of 50], $P = .99$). In addition, the accuracy of ^{111}In-labeled leukocyte scintigraphy in our group 3 patients (100% [17 of 17]) was not significantly different from that in the group of patients examined by Palestro et al (98% [49 of 50], $P = .57$).

Discussion

The results of our study indicate that the labeling efficiency for FDG-labeled leukocytes was significantly lower than that for ^{111}In-oxine–labeled leukocytes. The mean labeling efficiency for FDG-labeled leukocytes (72%) was the same as that reported by Forstrom et al (4) in healthy volunteers whose leukocytes were labeled with 74 MBq of FDG. However, the six (12%) of 51 patients originally enrolled in our study who were subsequently excluded from analysis had FDG-labeled leukocyte labeling efficiencies that were less than 35%, which precluded imaging. These six patients nevertheless had ^{111}In-oxine–labeled leukocyte labeling efficiencies that were comparable to those in the remainder of the study population. Although the explanation for this phenomenon requires further investigation, the uptake of FDG, which probably depends on leukocyte glucose transporters, may have been influenced by factors such as the expression of leukocyte glucose transporters, serum glucose levels, and the presence of receptor-blocking substances, including intrinsic proteins and receptor-blocking medications such as angiotensin-receptor blockers. In contrast, uptake of ^{111}In-oxine, a lipophilic molecule that enters cells by means of passive diffusion, should be independent of any receptor-mediated effect.

In the present study, the mean cell viability of FDG-labeled leukocytes, according to results of use of the trypan blue dye exclusion technique, was 98%, which is comparable to what Forstrom et al (4) reported for FDG-labeled leukocytes (100%) and to the mean cell viability we observed for ^{111}In-oxine–labeled leukocytes (97%). Thus, the use of FDG as the label for leukocytes did not affect cell viability.

In general, there was good agreement between FDG-labeled leukocyte PET images and ^{111}In-oxine–labeled leukocyte scintigraphic images. Results at ^{111}In-oxine–labeled leukocyte scintigraphy in our study were similar to those previously reported for patients with a variety of conditions (10). The accuracy of both agents was lowest in our study for the subgroup of patients ($n = 13$) suspected of having osteomyelitis in the hands or feet (group 2). FDG-labeled and ^{111}In-oxine–labeled leukocytes performed similarly in this setting. For the accuracy of FDG-labeled leukocyte PET (69%) to have been significantly better than that of ^{111}In-oxine–labeled leukocyte scintigraphy (46%) in this patient group, the number of patients would have had to have been more than 50. In this setting, both FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy had low specificity (50% and 33%, respectively). False-positive results occurred because soft-tissue infections and physiologic accumulation of labeled leukocytes in granulating wounds were not accurately differentiated from underlying bone uptake of tracers. Although tomography helped enable the differentiation of soft-tissue uptake from bone uptake, it may be possible, with dedicated PET or PET/computed tomography (CT), to make this distinction more consistently.

With respect to the sensitivity of FDG-labeled leukocyte PET versus that of ^{111}In-oxine–labeled leukocyte scintig-

Figure 4

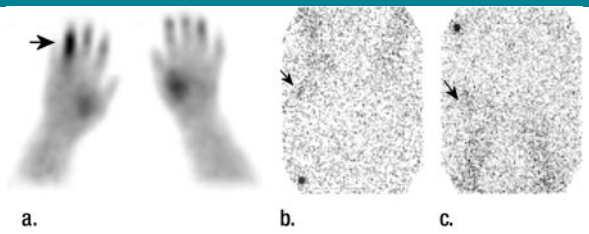


Figure 4: Patient 9. Images in 50-year-old woman with diabetes and with cellulitis that involved the fourth digit of the right hand. **(a)** Maximum intensity projection image from FDG-labeled leukocyte PET shows intense tracer uptake in the fourth digit (arrow) that was classified as being consistent with osteomyelitis. **(b)** Dorsal and **(c)** palmar views from ^{111}In-oxine–labeled leukocyte scintigraphy show ill-defined, faint tracer uptake (arrow) that is best seen on the dorsal view and was classified as soft-tissue infection. Excisional biopsy of the distal interphalangeal joint revealed bone necrosis with inflammatory cells in marrow spaces, a finding indicative of osteomyelitis. Culture was positive for heavy growth of *Staphylococcus aureus*.

Table 4

Results of Statistical Analysis of Imaging Findings in 43 Patients

Parameter	FDG	^{111}In-Oxine
Sensitivity (%)	87 (13/15)	73 (11/15)
Specificity (%)	82 (23/28)	86 (24/28)
Accuracy (%)	84 (36/43)	81 (35/43)
Positive predictive value (%)	72 (13/18)	73 (11/15)
Negative predictive value (%)	92 (23/25)	86 (24/28)

Note.—Data in parentheses were those used to calculate the percentages.

raphy in the detection of osteomyelitis, there was no statistically significant difference in our study. The sensitivity for osteomyelitis observed in our series for FDG-labeled leukocyte PET (86%) was similar to the 89% sensitivity Newman et al (9) observed at ^{111}In–labeled leukocyte scintigraphy performed 24 hours after tracer injection. We observed a lower sensitivity for ^{111}In-oxine–labeled leukocyte scintigraphy (57%) than previously reported, but our sample (n = 7) was too small to reveal statistically significant differences. The possible discrepancy between our results and those of Newman et al may be due to the fact that they examined a population that was larger (35 patients with 41 foot ulcers vs 12 patients with 12 foot ulcers and one patient with cellulitis of a finger) and had a higher prevalence of osteomyelitis (68% [28 of 41] vs 54% [seven of 13]).

Group 2 in our study included one patient who had false-negative results at both FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy. This patient had surgically confirmed calcaneal osteomyelitis that was misinterpreted as soft-tissue involvement at both studies. There were two patients who had false-negative results at ^{111}In-oxine–labeled leukocyte scintigraphy and true-positive results at FDG-labeled leukocyte PET. These patients had histopathologically confirmed osteomyelitis in a finger and in a toe. A possible explanation for these discrepancies is that with FDG-labeled leukocytes, we were imaging hyperemia or possibly free FDG resulting from elution following dephosphorylation within the cells rather than a true uptake of labeled leukocytes.

Although less likely, it is possible that there was washout of ^{111}In-oxine–labeled leukocytes by 24 hours. Newman et al (9) found that ^{111}In-labeled leukocyte scintigraphy had a higher sensitivity at 24 hours (89%) than at 4 hours (77%). Nevertheless, future investigations with FDG-labeled leukocyte PET and ^{111}In-oxine–labeled leukocyte scintigraphy should include dual–time point imaging of ^{111}In-oxine–labeled leukocytes, with early imaging performed 2–4 hours after injection and delayed imaging performed 24 hours after injection. With respect to the interval between injection and imaging, it is notable that we did not encounter a problem demonstrating the localization of FDG-labeled leukocytes 3–5 hours after injection: No patient in our series had a false-negative FDG-labeled leukocyte scan and a true-positive ^{111}In-oxine–labeled leukocyte scan; if this had occurred, we could have ascribed the discrepancy to a shorter interval for localization of leukocytes at FDG-labeled leukocyte PET.

For group 3, overall accuracies (when results were interpreted in conjunction with those of marrow scanning) were 94% for FDG-labeled leukocyte PET and 100% for ^{111}In-oxine–labeled leukocyte scintigraphy. There were no incorrect results with ^{111}In-oxine–labeled leukocyte scintigraphy in this group. There was a single incorrect result (a false-positive result in a patient with surgical confirmation of an aseptic femoral shaft fracture) in this group with FDG-labeled leukocyte PET. It is conceivable that the mild periprosthetic uptake seen at the fracture site in this patient reflected free FDG accumulating in an area of aseptic inflammation. Nevertheless, results obtained with both agents in our small sample (n = 17) were similar to the 98% accuracy previously reported for ^{111}In-labeled leukocyte scintigraphy of 50 total hip replacements (8).

Although imaging results obtained with FDG-labeled leukocyte PET were comparable to those obtained with ^{111}In-oxine–labeled leukocyte scintigraphy in our study, there were a few limitations (in addition to differences in labeling efficiencies) that warrant further consideration. First, we did not study the rate of elution of FDG from leukocytes over time. Images of FDG-labeled leukocytes that included the brain or the bladder showed free FDG, but exactly how much is not known. Pio et al (11), however, found that the patterns of distribution of FDG and FDG-labeled leukocytes were distinct and provided complimentary information in the evaluation of inflammation. In our series,

Table 5

Results of Statistical Analysis of Imaging Findings in Patient Subgroups

Patient Subgroup and Parameter*	FDG	^{111}In-Oxine
Group 1 (n = 30)		
Sensitivity (%)	87 (13/15)	73 (11/15)
Specificity (%)	73 (11/15)	73 (11/15)
Accuracy (%)	80 (24/30)	73 (22/30)
Positive predictive value (%)	76 (13/17)	73 (11/15)
Negative predictive value (%)	85 (11/13)	73 (11/15)
Group 2 (n = 13)		
Sensitivity (%)	86 (6/7)	57 (4/7)
Specificity (%)	50 (3/6)	33 (2/6)†
Accuracy (%)	69 (9/13)	46 (6/13)
Positive predictive value (%)	67 (6/9)	50 (4/8)
Negative predictive value (%)	75 (3/4)	40 (2/5)
Group 3 (n = 17)		
Sensitivity (%)	100 (3/3)	100 (3/3)
Specificity (%)	93 (13/14)	100 (14/14)
Accuracy (%)	94 (16/17)	100 (17/17)
Positive predictive value (%)	75 (3/4)	100 (3/3)
Negative predictive value (%)	100 (13/13)	100 (14/14)

Note.—Data in parentheses were used to calculate the percentages.

* Group 1 included patients with histopathologic, microbiologic, and/or intraoperative confirmation of final diagnosis; group 2, patients suspected of having osteomyelitis in the hands or feet; and group 3, patients suspected of having infection in a prosthetic joint.

† $P < .05$ for imaging with ^{111}In-oxine–labeled leukocytes in group 2 versus that in group 3 and that in all patients.

there were two patients who had false-positive FDG-labeled leukocyte PET results and true-negative ^{111}In-oxine–labeled leukocyte scintigraphic results: One patient had otitis externa, and the second had an aseptic femur fracture occurring in the setting of a hip prosthesis. Both patients had very mild uptake of FDG-labeled leukocytes that may have represented free FDG. Future investigators should consider measuring the in vivo rate of elution of FDG from leukocytes over time.

Also, for convenience, we did not randomize the order in which the FDG-labeled leukocyte and ^{111}In-oxine–labeled leukocyte studies were performed and evaluated.

Another limitation was the short physical half-life of ^{18}F, which presents a series of logistic challenges not encountered with ^{111}In-oxine–labeled leukocytes. These include coordinating the delivery of FDG with patient arrival in the department in the absence of an on-site cyclotron, challenges related to the labeling procedure, and camera availability. However, the short half-life of ^{18}F also affords a lower radiation dose per millicurie or megabecquerel of injected activity.

Despite limitations, results obtained with FDG-labeled leukocyte PET were comparable with those obtained with ^{111}In-oxine–labeled leukocyte scintigraphy. Because FDG-labeled leukocytes have several intrinsic advantages over ^{111}In-oxine–labeled leukocytes, use of this agent warrants further investigation in a larger series, ideally with dedicated PET or PET/CT.

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