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REVIEW

Nuclear medicine and the failed joint replacement: Past, present, and future

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Abstract

Soon after the introduction of the modern prosthetic joint, it was recognized that radionuclide imaging provides useful information about these devices. The bone scan was used extensively to identify causes of prosthetic joint failure. It became apparent, however, that although sensitive, regardless of how the images were analyzed or how it was performed, the test was not specific and could not distinguish among the causes of prosthetic failure. Advances in anatomic imaging, notably cross sectional modalities, have facilitated the diagnosis of many, if not most, causes of prosthetic failure, with the important exception of infection. This has led to a shift in the diagnostic paradigm, in which nuclear medicine investigations increasingly have focused on diagnosing infection. The recognition that bone scintigraphy could not reliably diagnose infection led to the development of combined studies, first bone/gallium and subsequently leukocyte/bone and leukocyte/marrow imaging. Labeled leukocyte imaging, combined with bone marrow imaging is the most accurate (about 90%) imaging test for diagnosing joint arthroplasty infection. Its value not withstanding, there are significant disadvantages to this test. *In-vivo* techniques for labeling leukocytes, using antigranulocyte antibodies have been explored, but have their own limitations and the results have been inconsistent. Fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) has been extensively investigated for more than a decade but its role in diagnosing the infected prosthesis has yet to be established. Antimicrobial peptides bind to bacterial cell membranes and are infection specific. Data suggest that these agents may be useful for diagnosing prosthetic joint infection, but large scale studies have yet to be undertaken. Although for many years nuclear medicine has focused on diagnosing prosthetic joint infection, the advent of hybrid imaging with single-photon emission computed tomography (SPECT)/electronic computer X-ray tomography technique (CT) and the availability of fluorine-18 fluoride PET suggests that the diagnostic paradigm may be shifting again. By providing the anatomic information lacking in conventional radionuclide studies, there is renewed interest in bone scintigraphy, performed as a SPECT/CT procedure, for detecting joint instability, mechanical loosening and component malpositioning. Fluoride-PET may provide new insights into periprosthetic bone metabolism. The objective of this manuscript is to provide a comprehensive review of the evolution of nuclear medicine imaging of joint replacements.

Key words: Bone scintigraphy; Positron emission tomography; ^{18}F-fluorodeoxyglucose; F-18; Fluoride-positron emission tomography; Gallium; Infection; Labeled leukocytes; Prosthetic joint

Core tip: Advances in anatomic imaging, notably cross sectional modalities, have facilitated the diagnosis of many, if not most, causes of prosthetic failure, with the important exception of infection. This has led to a shift in the diagnostic paradigm, in which nuclear medicine investigations increasingly have focused on diagnosing infection. This article is a comprehensive review of

the evolution of nuclear medicine imaging of joint replacements. In addition to conventional planar imaging studies such as bone, gallium, and labeled leukocyte imaging, single-photon emission computed tomography/electronic computer X-ray tomography technique and positron emission tomography imaging with ^{18}F-fluorodeoxyglucose and ^{18}F (NaI) are covered.

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INTRODUCTION

Contemporary joint arthroplasty procedures began less than 75 years ago, when the predecessor of the modern day hip replacement was introduced. A total hip arthroplasty includes both femoral and acetabular components; a hemiarthroplasty consists of only the femoral component. These prostheses are anchored to bone by various methods including polymethylmethacrylate and osseous ingrowth into the device's surface. Some devices are coated with hydroxyapatite which induces new bone formation and attaches to newly produced periprosthetic osseous tissue. The acetabular component can be forced into the acetabulum or secured by screws[1].

The predecessor of the contemporary knee prosthesis, developed about 40 years ago, consisted of a metallic femoral component, together with plastic patellar and tibial components. Today's devices provide improved range of motion and greater durability of the components[1].

The vast majority of lower extremity joint replacement surgeries are successful; complications like infection, fracture, dislocation, and heterotopic ossification are uncommon. At the present time the most common cause of prosthetic failure is aseptic loosening, which develops in more than a quarter of these devices and frequently results from an inflammatory reaction instigated by prosthetic components[2,3]. The debris created by component breakdown activates and draws surrounding leukocytes, triggering secretion of cytokines and enzymes damaging osseous tissues and leading to prosthetic loosening. The cellular response is characterized by an influx of various types of leukocytes. Neutrophils, however, rarely are present[4-6]. Most cases of aseptic loosening are treated with one surgery, the single stage exchange arthroplasty.

Infection, which occurs in up to 2% of primary implants, and up to 5% of revision implants is an uncommon complication of prosthetic joint surgery. Risk factors for infection include operative suite characteristics, surgical complexity, condition of the osseous tissue surrounding the prosthesis, and immune status of the patient.

Bacteria bind to most joint replacement components and once attached they secrete a protective biofilm[3]. Organisms commonly encountered in infected joint replacements include *Staphylococcus epidermidis* and *Staphylococcus aureus*. *Streptococcus viridans*, *Escherichia coli*, *Enterococcus faecalis*, and *group-B Streptococcus* are occasionally identified[4]. Early prosthetic joint infections occur by three months after implantation, while delayed infections develop within three months to one year after implantation. Late infections are defined as infections that occur more than one year after surgery. Early and delayed infections are thought to be due to organisms introduced at surgery; late infections are more likely to be due to hematogenous spread[7].

The infected joint replacement is accompanied by an inflammatory reaction characterized by a neutrophilic response, often intense[6]. Management of the infected joint replacement consists of removal of the device, a lengthy course (weeks to months) of antibiotic treatment, and eventually a reimplantation procedure[8].

The correct therapeutic approach often depends on the accurate differentiation of aseptic loosening and infection. This differentiation is not always obvious. Signs and symptoms, except for pain, frequently are lacking. Laboratory tests may be suggestive, but are not diagnostic, of infection. Joint aspiration with culture, the definitive preoperative test is specific, but sensitivity is variable[9,10]. Plain radiographs are not specific and prosthesis related artifacts limit, to some degree, cross sectional imaging studies.

Nuclear medicine procedures have, for many years, contributed useful information about the painful joint replacement. This manuscript is a comprehensive review of the evolution of nuclear medicine imaging of joint replacements.

LITERATURE SEARCH

An electronic search with no language restrictions was conducted in the bibliographic database PubMed using the terms infection, osteomyelitis, arthroplasty, joint replacement, prosthetic joint, bone scintigraphy, bone marrow scintigraphy, gallium, labeled leukocytes, besilesomab, sulesomab, sulfur colloid, antimicrobial peptides, positron emission tomography, positron emission tomography (PET), fluorodeoxyglucose (FDG), fluoride and ^{18}F. The list of articles generated was augmented by crosschecking the reference lists of the retrieved papers. This was designed as a comprehensive review, not a meta analysis, of the failed joint replacement and therefore neither specific inclusion criteria nor any evidence based quality assessment tools were used to select the included articles.

RADIONUCLIDE IMAGING

Bone scintigraphy

The first, and undoubtedly the most extensively investigated, radionuclide procedure used for imaging joint arthroplasties was bone scintigraphy. Technetium-99m (^{99m}Tc) labeled diphosphonates, usually methylene di-

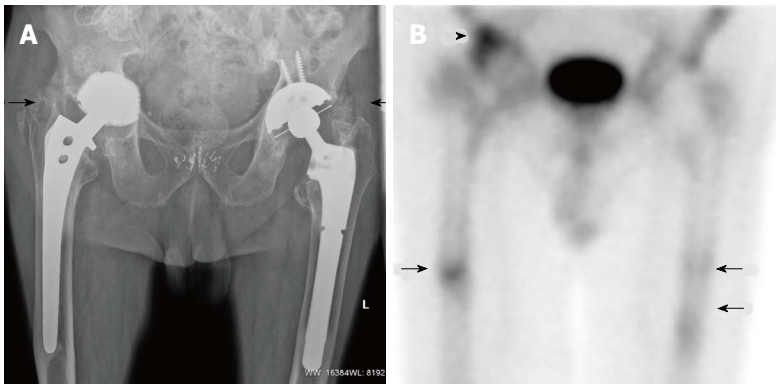

Figure 1 Aseptically loosened right hip arthroplasty. A: X-ray reveals medial protrusion of the acetabular component of a painful 15 year old hip replacement. There is heterotopic ossification around both greater trochanters (arrows); B: On the ^{99m}Tc-methylene diphosphonate bone scan, there is focally increased radiopharmaceutical accumulation at the distal tip of the femoral component (arrow) of the right hip replacement and lateral to the femoral neck (arrowhead) corresponding to the heterotopic bone seen on the X-ray. An aseptically loosened prosthesis was revised. Focally increased radiopharmaceutical accumulation is present at the tip of the femoral component of the asymptomatic left hip arthroplasty (double arrows) which also was 15 years old.

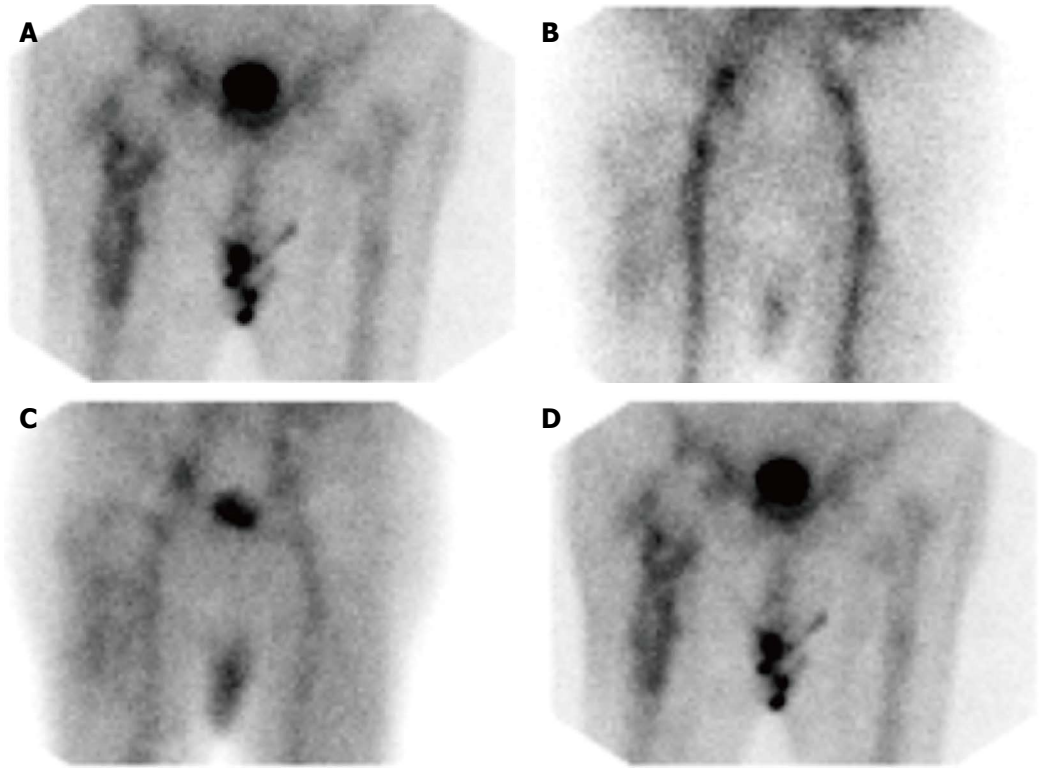

Figure 2 Infected right hip arthroplasty. A: On the ^{99m}Tc-methylene diphosphonate bone scan, there is irregularly increased radiopharmaceutical accumulation around the entire femoral component of the 2 years old cementless (revision) prosthesis, a pattern which some investigators have reported as specific for infection; B-D: On the ^{99m}Tc-MDP bone scan, there is diffuse hyperperfusion, and hyperemia around the prosthesis on the flow and blood pool images, and diffusely increased periprosthetic radiopharmaceutical on the delayed, bone image (same patient illustrated in Figure 2A); B: Flow; C: Blood pool; D: Bone.

phosphonate (MDP), are used for this study. Radiopharmaceutical incorporation into the bone depends on perfusion and rate of new bone formation. Imaging usually is performed two to fours after injection. The procedure also can be performed as a three phase bone scan: the flow or perfusion phase, acquired immediately after radiopharmaceutical injection, followed immediately by the soft tissue or blood pool phase. The third, or bone, phase is performed between two and four hours later.

Gelman *et al*[10] reported that bone scintigraphy was 85% accurate for prosthetic hip loosening. Weiss *et al*[11] reported that bone scintigraphy accurately identified prostheses requiring surgical intervention. Another group of investigators, however, observed that bone scintigraphy cannot determine the cause of the failure, information critical to patient management[12].

In an effort to enhance its specificity, investigators have studied periprosthetic uptake patterns on bone scans. Williamson *et al*[13] suggested that focal periprosthetic uptake indicated loosening and diffuse uptake indicated infection (Figures 1, 2A). Williams *et al*[14] reported that diffuse periprosthetic uptake was sensitive (100%), but not specific (54%) for infection. Another group of investigators came to the opposite conclusion: diffuse periprosthetic uptake was specific, but not sensitive, for infection[15]. Aliabadi *et al*[16] reported that bone scintigraphy did not differentiate septic from aseptic loosening (Figure 3A).

Further confounding the analysis of periprosthetic uptake is the numerous uptake patterns present around

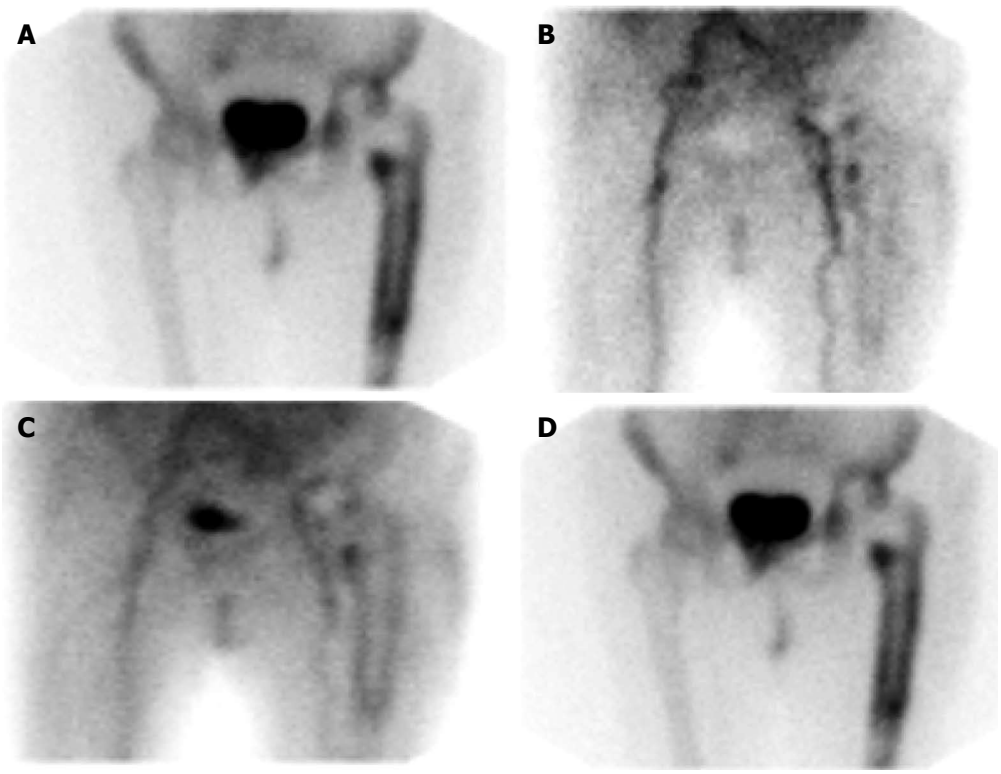

Figure 3 Aseptically loosened left hip replacement. A: On the ^{99m}Tc-MDP bone scan, there is diffusely increased radiopharmaceutical accumulation around the femoral component of the cemented 2 years old prosthesis. Compare with Figure 2A; B-D: On the ^{99m}Tc-MDP bone scan, there is diffuse hyperperfusion, and hyperemia around the prosthesis on the flow and blood pool images, and diffusely increased periprosthetic radiopharmaceutical on the delayed, bone image (same patient illustrated in Figure 3A), B: Flow; C: Blood pool; D: Delayed. The scan appearance is nearly identical to that of the infected prosthesis in Figure 2B.

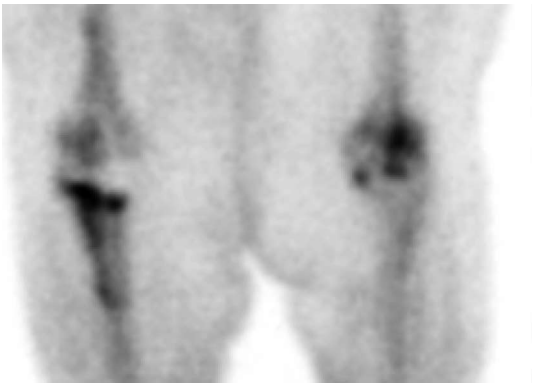

Figure 4 Asymptomatic right knee arthroplasty. On the ^{99m}Tc-MDP bone scan, there is irregular, intense radiopharmaceutical accumulation around the long stemmed tibial component of a three year old right knee replacement. The femoral component is unremarkable. The patient had a history of breast carcinoma and bone scintigraphy was performed as part of a routine evaluation for metastatic disease.

asymptomatic devices. For up to 12 m after insertion of a hip prosthesis, periprosthetic uptake is very variable; after this time ten percent of asymptomatic cemented hip prostheses still demonstrate uptake[17]. Increased periprosthetic uptake is even more frequent in cementless devices[18-20].

Gallo *et al*[21] studied 27 hydroxyapatite coated hip replacements, observing that while a normal study excluded aseptic loosening with a high degree of certainty, a positive study was not reliable for diagnosing either loosening or infection. Complicating matters further is the paucity of data on radionuclide bone imaging of hybrid and bipolar prostheses.

Assessment of knee replacements also is challenging. In one investigation periprosthetic activity was seen around more than sixty percent of femoral components and nearly 90% of tibial components of asymptomatic devices for up to several years[22] (Figure 4). In an investigation of asymptomatic knee replacements with serial bone scans periprosthetic activity generally diminished over time after implantation. There was considerable variation among patients. The authors stated, in order to determine the significance of periprosthetic activity, serial scans need to be performed[23] (Figure 5A). Another group of investigators reported that bone scintigraphy does not accurately diagnose the infected knee arthroplasty[24].

Performing radionuclide bone imaging as a three-phase study has been advocated to enhance its specificity[25]. Nagoya *et al*[26] reported that the test was 88% sensitive and 90% specific for hip replacement infection. Most other investigations, however, have reported low sensitivity, low specificity, or both[24,27-30] (Figures 2B and 3B).

Regardless of how bone scintigraphy is performed, its accuracy for diagnosing complications of lower extremity joint prostheses is about 50%-70%. At the present time this test is used primarily for screening purposes. A nor-

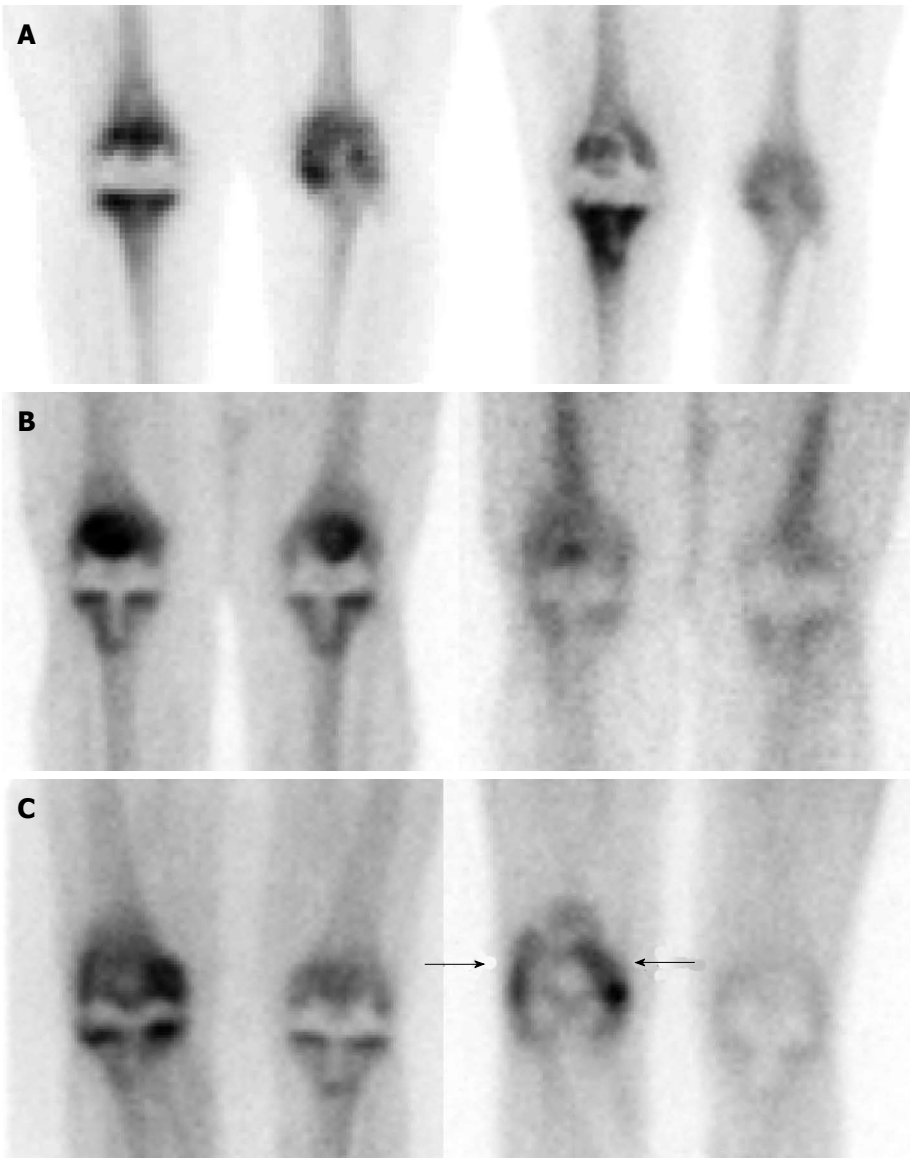

Figure 5 Aseptically loosened right knee arthroplasty. A: On the ^{99m}Tc-methylene diphosphonate (MDP) bone scan, performed about 6 mo after implantation (left), shows mildly increased radiopharmaceutical accumulation around the femoral and tibial components. On the repeat study, performed 9 mo later (15 mo after implantation), there is intensely increased radiopharmaceutical accumulation around the tibial component, while activity around the femoral component has resolved. An aseptically loosened tibial component was revised; B: On the ^{99m}Tc-MDP bone scan (left) there is increased radiopharmaceutical accumulation around the tibial component of both the symptomatic right and asymptomatic left knee prostheses. There is normal periprosthetic distribution around both prostheses on the gallium-67 image (right), and the combined study is negative for infection; C: On the ^{99m}Tc-MDP bone scan (left) there is increased radiopharmaceutical accumulation around the tibial component of the symptomatic right and faintly increased accumulation around the tibial component of the asymptomatic left knee prosthesis. On the gallium-67 image (right), in contrast to the bone scan, there is increased radiopharmaceutical accumulation around the femoral component (arrows) of the right knee replacement, while activity around the tibial component is normal. There is normal periprosthetic gallium activity around the asymptomatic left prosthesis. The distribution of activity around the right knee prosthesis on the bone and gallium studies is spatially incongruent and the combined study is (false) positive for infection. Aseptic loosening of joint replacements often is accompanied by an intense inflammatory response and gallium cannot reliably differentiate infection from inflammation.

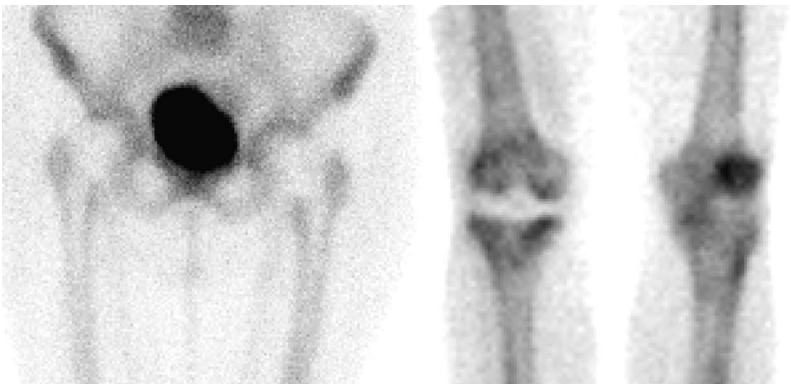

Figure 6 Normal ^{99m}Tc-methylene diphosphonate bone scans of bilateral hip (left) and right knee (right) prostheses. A normal bone scan is defined as a scan in which periprosthetic activity is indistinguishable from adjacent, non-articular bone. The bone scan has a high negative predictive value and therefore a normal study makes it very unlikely that the patient's symptoms are related to the prosthesis.

mal study makes it very unlikely that the patient's symptoms are related to the prosthesis (Figure 6).

Gallium scintigraphy

Over the years various techniques designed to overcome the limitations inherent in bone scintigraphy have been investigated. One of the earliest was gallium-67 citrate (gallium) imaging. Gallium uptake in infection likely is due to several factors including increased blood flow and vascular membrane permeability at inflammatory sites, lactoferrin binding and siderophore and bacterial uptake of gallium. Some gallium may be transported by leukocytes. Imaging typically is performed two to three days after injection[31].

Reing *et al*[32] observed that bone scintigraphy was sensitive (100%), but not specific (15%), while gallium was sensitive (95%) and specific (100%). Other investigators have reported similar results[15,33,34]. Aliabadi *et al*[16], in contrast, found, for the infected hip replacement, gallium scintigraphy was specific (100%) but insensitive (37%).

While some investigators have evaluated gallium imaging alone, other investigators have interpreted bone and gallium imaging together. Standardized criteria for interpretation of the combined study have been developed. The test is positive for osteomyelitis when distribution of the two tracers is different or, when their distribution is the same and the relative intensity of gallium uptake exceeds that of the bone agent. The test is equivocal for osteomyelitis when the distribution of the two radiotracers is the same, both spatially and in intensity. The test is negative for osteomyelitis when the gallium images are normal, regardless of the bone scan findings, or, when the distribution of the two tracers is the same and the relative intensity of gallium uptake is less than that of the bone agent (Figure 5B and 5C)[1].

Tehranzadeh *et al*[35] reported that bone/gallium imaging was 95% accurate for prosthetic joint infection. In most other series the test has been less successful. In 30 patients the test identified only 50% of the infected joint replacements[14]. Gómez-Luzuriaga *et al*[36] found that bone/gallium imaging was 80% accurate for prosthetic joint infection. Kraemer *et al*[37] reported that the combined test was 38% sensitive, and 100% specific for hip replacement infection. Merkel *at al*[38,39] evaluated bone/gallium imaging in an animal investigation and in patients and reported similar results.

Over the years the use of gallium for joint replacement infection has declined, and it has been replaced in most circumstances by labeled leukocyte imaging.

Labeled leukocyte scintigraphy

The accumulation of *in-vitro* labeled white cells at a site of infection depends on chemotaxis, the quantity and sorts of leukocytes labeled, and the primary cellular response in a particular situation. Neutrophils usually comprise the majority of leukocytes labeled and consequently sensitivity of WBC imaging is highest for neutrophil-mediated inflammatory processes[40]. When indium-111 is the radiolabel, images are acquired 18-30 h after administration. When technetium-99m is the radiolabel, imaging usually is performed four to six and repeated 18 to 30 h after administration.

One would anticipate that, because neutrophils invariably are present labeled leukocyte (WBC) imaging would accurately diagnose prosthetic joint infection. Interestingly, for quite some time, the value of the test was a subject of controversy.

In a canine study, Merkel *et al*[38] reported that WBC imaging was 94% sensitive and 86% specific for prosthetic infection. Pring *at al*[41] found that WBC imaging was 100% sensitive and 89.5% specific for the infected prosthetic joint. In another investigation, Pring *et al*[42] observed that WBC activity around infected prostheses was always significant. Rand *et al*[43] found that sensitivity and specificity for prosthetic knee infection was 83% and 85% when moderately to markedly increased periprosthetic activity was present. Magnuson *et al*[27], in an investigation of 98 patients reported sensitivity and specificity for WBC imaging of 88% and 73% respectively, for lower extremity joint replacement infection.

In some studies, WBC imaging was specific, but not sensitive for prosthetic joint infection, while in others the test was sensitive but not specific[15,34,44,45].

Poor sensitivity has been ascribed to the chronicity of the process; *i.e.*, presumably the neutrophilic response had ceased, or at least waned, by the time the patient underwent imaging. Neutrophils, however, almost always are present in the infected joint replacement, regardless of the duration of symptoms, so chronicity does not explain low sensitivity.

Poor specificity often has been attributed to nonspecific inflammation. It was thought that false positive results were secondary to labeled leukocyte accumulation in aseptic inflammation. Although aseptic inflammation around a prosthetic joint replacement is often accompanied by an intense leukocyte response, neutrophils rarely are present. In most situations, primarily neutrophils are labeled and the sensitivity of WBC imaging is greatest for detecting infections characterized by a neutrophilic response. The test is not at all sensitive, however, for detecting inflammation that is not neutrophil mediated[40]. Given the lack of a neutrophilic response in the aseptically inflamed prosthesis, inflammation cannot be the sole explanation for poor specificity.

What is the reason for the variable and often contradictory observations? WBC images usually are interpreted by comparing intensity of periprosthetic uptake to intensity of uptake in some predefined reference point, typically an area of presumably normal bone marrow. Studies in which intensity of labeled leukocyte activity in the area of interest exceeds intensity of activity in the reference point are classified as positive for infection; otherwise the study is negative. The likelihood of infection, however, is not related to intensity of periprosthetic activity (Figures 7A and 8A). In one investigation[46] the accuracy of the test varied with the manner in which the studies were interpreted. The mere presence of periprosthetic activity, regardless of intensity, was 100% sensitive and 23% specific. Using periprosthetic activity exceeding activity in the contralateral extremity as the criterion for infection, sensitivity was 65%, specificity was 61%[46].

There is another problem inherent in the interpretation of WBC images. Leukocytes, labeled or otherwise, accumulate in bone marrow, the normal distribution of which can be variable. Generalized, as well as localized, marrow expansion alter the "normal" distribution of marrow making it difficult to differentiate labeled leukocyte uptake in unusually located, but normal, marrow from uptake in infection[47].

In a manner analogous to bone/gallium imaging, it

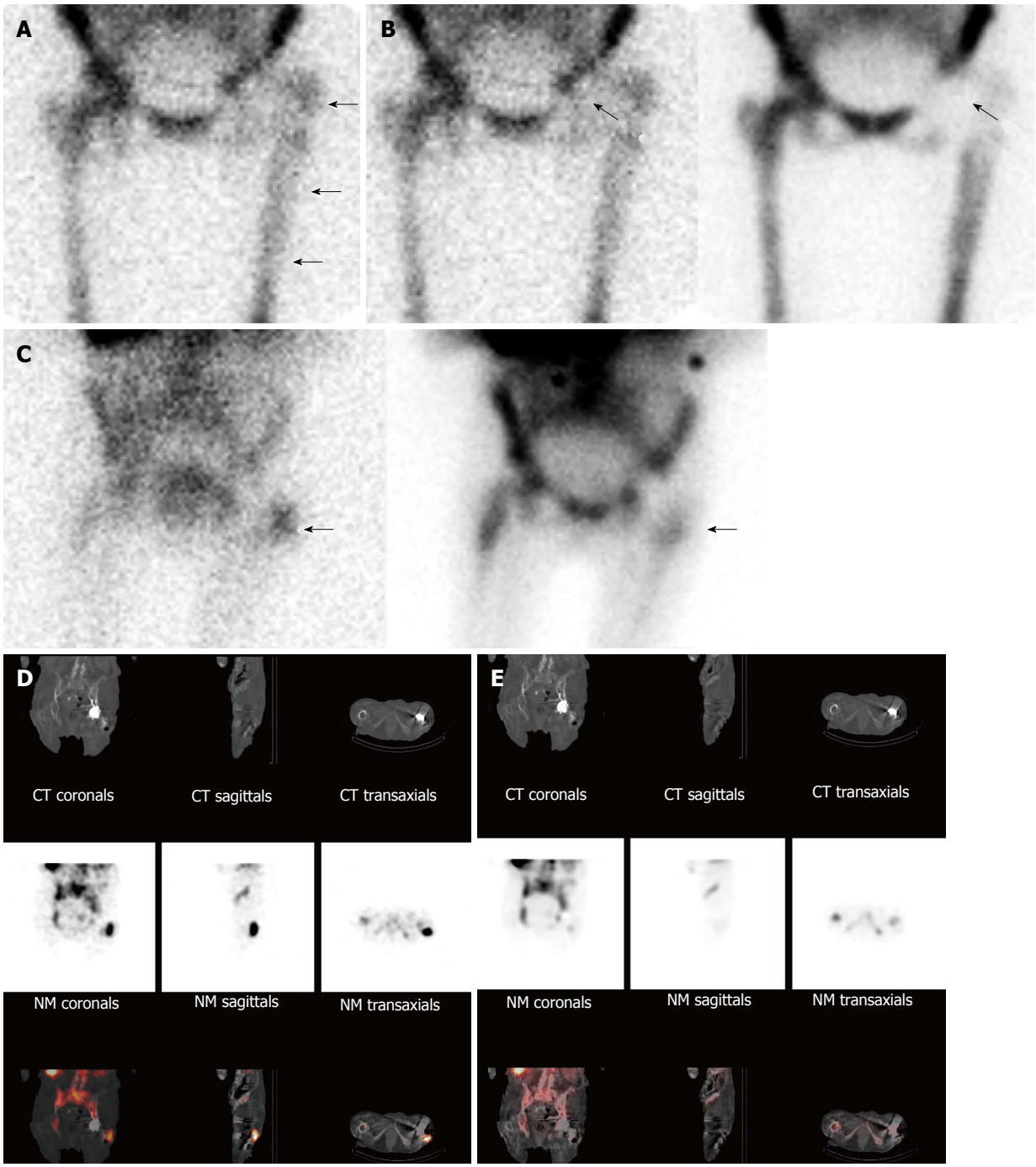

Figure 7 Infected left hip arthroplasty. A: On this anterior image from an indium-111 labeled leukocyte study, periprosthetic activity (arrows) is similar in intensity to activity in the contralateral lower extremity and less intense than pelvic activity, areas typically used as reference points when interpreting these studies. Because studies in which the intensity of labeled leukocyte activity in the region of interest does not exceed intensity of activity in the reference point, this study could be erroneously interpreted as negative for infection; B: The distribution of periprosthetic activity on the labeled leukocyte (left, ^{111}In-WBC) and sulfur colloid bone marrow (right, ^{99m}Tc-SC) images is spatially incongruent (arrows), *i.e.*, there is activity in the left hip joint on the labeled leukocyte image, but not on the bone marrow image. The combined study is positive for infection. (Same patient illustrated in Figure 7A); Although the planar combined indium labeled leukocyte/bone marrow study (C, left, ^{111}In-WBC; right, ^{99m}Tc-SC) is positive for infection (arrows), precise information about the location and extent of infection is lacking. On the fused images (bottom row) from the labeled leukocyte SPECT/CT (D) the location of the abnormal labeled leukocyte accumulation (arrows) can clearly be seen adjacent and extending to the prosthesis at the level of the greater trochanter. Note also the adjacent hypodense area in the soft tissues, consistent with abscess. Bone marrow SPECT/CT images (E) acquired simultaneously with the labeled leukocyte images in 16a confirm that the activity on the labeled leukocyte component of the examination is due to infection. Whether or not the bone marrow component of the SPECT/CT study contributes additional information beyond what planar imaging provides remains to be determined.

has been suggested that interpreting WBC images together with bone scans improves results. In one study, WBC imaging alone was 45% specific for prosthetic joint infection, but improved to 85% with the addition of bone imaging[44]. Johnson *et al*[45] observed that the combined test was more specific and only slightly less sensitive than

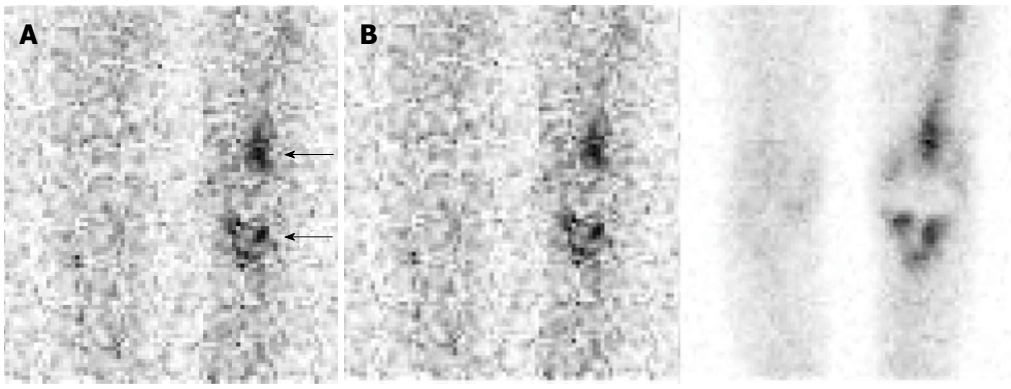

Figure 8 Aseptically loosened left knee arthroplasty. A: On this anterior image from an indium-111 labeled leukocyte study, there is intense periprosthetic activity around both the tibial and femoral components (arrows), while there is no activity around the contralateral knee. The study could be interpreted erroneously as positive for infection. Compare the intensity of activity around this prosthesis with the intensity of activity around the infected hip arthroplasty in Figure 7A. As these two cases illustrate, the intensity of labeled leukocyte activity around a prosthetic joint is not a reliable criterion for determining the presence or absence of infection; B: The distribution of periprosthetic activity on the labeled leukocyte (left, ^{111}In-WBC) and sulfur colloid bone marrow (right, ^{99m}Tc-SC) images is virtually identical (spatially congruent) and the combined study is negative for infection. The periprosthetic activity on the labeled leukocyte image is due to marrow, not to infection. Performing complementary bone marrow imaging eliminates the two major difficulties inherent in the interpretation of labeled leukocyte images: variable intensity of periprosthetic activity and differentiating bone marrow activity from infection. Same patient illustrated in Figure 8A.

WBC imaging for hip replacement infection.

Palestro *et al*[24] observed that the addition of bone imaging did not increase the accuracy of WBC imaging for knee arthroplasty infection. In another investigation, the accuracy of the combined test for lower extremity joint replacement infection was only 76%[48]. In an investigation of patients with asymptomatic cementless hip replacements, using standard interpretive criteria, WBC/bone imaging would have been classified as positive for infection 15% of the time[18].

Another approach to WBC imaging of the prosthetic joint is to combine the test with bone marrow imaging, which usually is performed with ^{99m}Tc sulfur colloid. Both radiopharmaceuticals accumulate in the reticuloendothelial cells of the bone marrow. The distribution of marrow activity on WBC and bone marrow images parallel one another in most situations. The one exception is osteomyelitis, in which the distribution of these two agents differs, *i.e.*, the images are spatially incongruent (Figures 7B and 8B)[47].

Mulamba *et al*[49] reported 92% sensitivity and 100% specificity for prosthetic hip infection. Palestro *et al*[24,46] reported similar results for infected hip and knee arthroplasties. Love *et al*[50] studied 59 lower extremity joint prostheses and reported that WBC/marrow imaging was 95% accurate for infection. El Espera *et al*[51] reported 91% accuracy for lower extremity prosthetic joint infection.

Virtually all of the investigations published to date indicate that WBC/marrow imaging is specific for joint replacement infection. In most of the investigations the test has proved to be sensitive as well. Joseph *et al*[52] however, reported that although test was 100% specific, the test was only 66% sensitive. Pill *et al*[53] reported similar results. It is unfortunate indeed that no illustrations of false negative studies, the salient point of these investigations, were provided in either publication.

There are some data that indicate performing WBC imaging at more than one time point could obviate the need for marrow imaging. The hypothesis is that images acquired shortly after injection represent marrow while images acquired later represent infection. Difference in uptake patterns over time is indicative of infection. The accuracy of the test improved from about 75% when images were interpreted visually, to about 95% when semiquantitative analysis was performed[54].

There are, unfortunately, disadvantages to WBC/marrow imaging. The leukocyte labeling procedure is demanding, not routinely available, and involves contact with blood products. Labeling enough leukocytes to produce diagnostically useful studies can be difficult in immunocompromised individuals. Image quality, especially when using indium-111, is not ideal. The need to perform marrow imaging is another disadvantage. Radiolabeled antigranulocyte antibodies and antibody fragments have been explored as alternatives.

Besilesomab is a murine monoclonal G_1 immunoglobulin that binds to Normal Cross-reactive Antigen-95 on leukocytes[55]. Using visual image analysis the sensitivity and specificity for joint replacement infection range from 67%-91% and 57%-75%, respectively. By performing complementary bone imaging or semiquantitative analysis, sensitivity ranged from 67% to 100%; specificity ranged from 84% to 100%[56-59].

Sulesomab is a fragment antigen binding (Fab') portion of a murine monoclonal G1 immunoglobulin that binds to Nonspecific Cross-reactive Antigen-90 on leukocytes[55]. Reported sensitivity and specificity for prosthetic joint infection have ranged from 75% to 93% and 65% to 86%, respectively[60-62]. Dual time point imaging and time activity curve analysis may improve test accuracy[63-65].

Somewhat surprisingly, even though *in-vivo* labeled leukocytes accumulate in the marrow, in much the same way that *in-vitro* labeled leukocytes do, scant attention has

been paid to combining these studies with bone marrow imaging. In one of the few investigations in which complementary bone marrow imaging was performed, Sousa *et al*[66] reported that the specificity of ^{99m}Tc-sulesomab increased from 20% to 100%, when complementary marrow imaging was performed.

Using *in-vivo* labeled leukocytes overcomes the limitations of the *in-vitro* labeling procedure. Based on published data however, an additional study, either bone or marrow imaging probably still needs to be performed. Furthermore, besilesomab, which is a murine antibody, incites a human antimurine antibody (HAMA) response in up to 30% of patients[57]. Patients should be screened for HAMA and a positive result is a contraindication to the procedure. Because of immunogenicity concerns, patients should not undergo repeat studies with this agent. Not surprisingly, *in-vivo* labeled WBC imaging, using antigranulocyte antibodies, has not gained wide acceptance in the diagnostic workup of the painful joint replacement.

^{18}F-fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (FDG) is transported into cells *via* glucose transporters and phosphorylated to ^{18}F-2'-FDG-6 phosphate but is not metabolized. FDG uptake depends on cellular metabolic rate and the number of glucose transporters. Activated leukocytes demonstrate increased expression of these transporters with increased affinity for FDG in the presence of cytokines and growth factors. There are several advantages to FDG. The procedure is completed within two hours after injection. Target to background ratio is high. Images obtained with positron emission tomography (PET) have much higher resolution than those obtained with conventional agents[67].

Several investigators have studied the role of FDG-PET for evaluating painful lower extremity joint prostheses. Zhuang *et al*[68] evaluated 74 lower extremity joint prostheses and reported that increased activity along the bone prosthesis interface was 89.5% and 77.8 % for diagnosing infection of hip and knee arthroplasties, respectively. Accuracy depended on location, not intensity, of FDG uptake. Using similar criteria Chacko *et al*[69] reported that the test was 92% sensitive and 97% specific for hip replacement infection. Infection could not be differentiated from aseptic loosening based on intensity of periprosthetic uptake.

Reinartz *et al*[29] studied 92 hip prostheses with three phase bone scintigraphy and FDG-PET. Sensitivity, specificity and accuracy of three phase bone scintigraphy were 68%, 76% and 74% *vs* 94%, 95%, and 95%, respectively, for FDG-PET. Activity around the acetabular component and proximal aspect of the femoral component on FDG-PET images was not associated with infection. Pattern, but not intensity, of periprosthetic uptake was useful for differentiating infection from aseptic loosening. Cremerius *et al*[70] reported that FDG was 89% accurate for hip replacement infection. Gravius *et al*[71] reported similar results. Pill *et al*[53] studied 92 painful hip prostheses, including 21 infected devices, and reported that FDG was 95% sensitive and 93% specific for diagnosing infection. Fifty one of the prostheses, including ten infected devices, also were studied with WBC/marrow imaging. The sensitivity and specificity of WBC/marrow imaging in this subgroup were 50% and 95.1%, respectively.

Manthey *et al*[72] reported that FDG was 96% accurate for prosthetic joint infection. They also reported that activity around the femoral head and neck indicated synovitis plus infection, observations that contradict those of previous investigations[68,69].

Stumpe *et al*[30] observed that, in patients with painful hip replacements, intense bone prosthesis interface activity was reasonably specific (81% for reader 1 and 85% for reader 2), but not sensitive (33% for reader 1, 56% for reader 2) for diagnosing infection (33% for reader 1, 56% for reader 2). The accuracy of the test, for both readers, was 69%. Bone scintigraphy was more accurate than FDG-PET (80% *vs* 69%) in this investigation.

Van Acker *et al*[73] studied 21 patients with suspected prosthetic knee infection. FDG-PET was 100% sensitive and 73% specific. Sensitivity and specificity of WBC/bone imaging was 100% and 93%, respectively. Vanquickenborne *et al*[74] reported similar results.

García-Barrecheguren *et al*[75] studied 24 hip replacements. FDG-PET was neither sensitive (64%) nor specific (67%) for infection. Delank *et al*[76] studied 27 patients with failed hip and knee replacements and concluded that FDG-PET could not reliably differentiate between infection and aseptic inflammation.

Love *et al*[50] evaluated 59 failed lower extremity joint prostheses with FDG-PET and WBC/marrow imaging. Among the criteria used for image interpretation, bone prosthesis interface activity, with a target to background ratio greater than 3.6 for hip replacements and 3.1 for knee replacements was the most accurate (71%) for diagnosing infection. The accuracy of WBC/marrow imaging, in contrast, was 95%.

In a met analysis sensitivity and specificity of FDG-PET for prosthetic joint infection were 82% and 87% respectively[77]. In view of the large number of inconsistent and contradictory results that have been reported to date, the place of FDG-PET in the assessment of the prosthetic joint remains to be determined.

Infection-specific tracers

Given the dramatic differences in the management of aseptic loosening and infection of prostheses, the importance of accurately differentiating between these two conditions cannot be overstated. The development of an infection specific imaging agent would be a welcome improvement over the current procedures.

The potential of radiolabeled antibiotics as "infection-specific" radiopharmaceuticals has been explored. The hypothesis is that the radiolabeled antibiotic enters, and is metabolized by, bacteria and could be used to accurately localize infection. Although the results of initial studies were encouraging, subsequent investigations raised significant doubts about the validity of this concept and

enthusiasm for radiolabeled antibiotics has faded[78-81].

Antimicrobial peptides bind to the bacterial cell membrane. Their expression may be constant or induced on contact with microbes. They also can be transported *via* leukocytes[82]. ^{99m}Tc-UBI 29-41, a radiolabeled synthetic fragment of the naturally occurring human antimicrobial peptide ubiquicidin, appears to be able to differentiate between infection and sterile inflammation[83]. Recent data suggest that this agent is both sensitive and specific for prosthetic joint infection[84,85].

FUTURE

Initial data suggest that single-photon emission computed tomography (SPECT)/electronic computer X-ray tomography technique (CT) may contribute useful information to the evaluation of the failed joint arthroplasty. For example, nuclear arthrography often is performed as a dual isotope procedure, in which the bone scan provides "anatomic detail" and another radiopharmaceutical, often an indium-111 labeled complex, is used for the arthrographic component. A potential alternative to the dual isotope technique is SPECT/CT arthrography, in which the CT component provides the anatomic landmarks necessary for radiopharmaceutical localization. In one investigation SPECT/CT was significantly better than planar imaging for the acetabular cup of hip prostheses[86]. For knee arthroplasties, SPECT/CT offered a significant improvement over planar imaging for detecting femoral component loosening. SPECT/CT also was better than planar imaging for detecting tibial component loosening but statistical significance was not reached.

Hirschmann *et al*[87] reported that SPECT/CT could detect mechanical loosening, joint instability, component malposition, and patellofemoral problems in patients with knee arthroplasties. In another investigation of knee arthroplasties, SPECT/CT significantly altered the working diagnosis and proposed treatment, and changed the initial intention to revise or treat the patients non-surgically. The diagnosis made with SPECT/CT was correct in all patients who underwent surgery[88].

Graute *et al*[89] evaluated the contribution of SPECT/CT as an adjunct to planar scintigraphy with ^{99m}Tc-besilesomab for diagnosing and localizing low-grade prosthetic joint infection. Planar imaging was 66% sensitive, and 60% specific for infection. Combining planar imaging with SPECT/CT, sensitivity and specificity improved to 89% and 73%, respectively.

The potential impact of SPECT/CT extends well beyond diagnosing infection. In patients with a positive study, for example, the examination could provide information about the extent of infection as well as other abnormalities involving the native bone and the prosthesis (Figure 7C-E); joint aspiration and culture could be performed at the same time. In patients with negative studies the CT component could provide information about other causes of prosthetic failure. In such a scenario patients would be spared the need to undergo multiple imaging tests at different times and possibly different locations, and a diagnosis could be made more expeditiously.

Flourine18-fluoride-PET (fluoride-PET) bone imaging shows great promise in the evaluation of joint arthroplasties. Some investigators have used this test in a manner analogous to that of conventional bone scintigraphy. Sterner *et al*[90] compared the results of fluoride-PET bone scans to plain radiographs in 14 patients with painful knee arthroplasties. Sensitivity, specificity, and accuracy of the fluoride PET study for detecting aseptic loosening were 100%, 56%, and 71%, respectively. Sensitivity, specificity, and accuracy of plain radiographs were 43%, 86%, and 64%, respectively.

Other investigators have explored the potential of fluoride-PET for studying bone metabolism. An important concern in patients undergoing hip resurfacing arthroplasty is the viability of the remaining femoral head, and the risk of postoperative fracture or avascular necrosis. Conventional radiographs are of limited utility, because the femoral head is obscured by the overlying metallic components of the device. Ullmark *et al*[91] reported that fluoride PET correctly identified aseptic necrosis in three of fourteen patients with a hip resurfacing arthroplasty. Radiographs were negative in all cases. These investigators concluded that fluoride-PET is useful for evaluating bone metabolism at resurfacing arthroplasty. In another investigation, Ullmark *et al*[92] studied bone mineralization around the femoral component of cementless hip arthroplasties. They concluded that fluoride-PET is a valuable tool for analysis of bone mineralization patterns around uncemented femoral stems and together with the modified Polar Map system could be useful to study metabolic bone responses to prosthetic implants.

There are recent data that suggest that Fluoride-PET is a valuable tool to analyse bone formation and secondary stabilization of a press-fit acetabular cup in patients undergoing total hip arthroplasty[93].

CONCLUSION

At the moment, nuclear medicine is most valuable for determining whether or not a painful joint prosthesis is infected. WBC/marrow imaging, currently, is the best available imaging test for this purpose. Preliminary data suggest that SPECT/CT, in addition to providing information about the presence and extent of infection, may be able to provide additional information about other conditions that cause joint replacements to fail. Fluoride-PET also may provide hitherto unknown insight into periprosthetic bone metabolism.

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