Role of Nuclear Medicine in Prosthesis Surveillance

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Mauro Liberatore

The materials of which the prostheses are made are studied extensively elsewhere in this book. A brief mention to this subject, however, must also be made in this chapter, because some constitutive characteristics of the prostheses have important reflexes on scintigraphic findings. Prostheses are usually made of metal (cobalt–chromium or titanium) and plastic (high molecular weight polyethylene). The attachment of this hardware to the bone can be assured by surgical cement (polymethylmethacrylate) or by new bone formation itself around the prosthesis, avoiding the use of the cement. The latter condition requires application of hydroxyapatite to the prosthetic surface or, alternatively, the use of prosthetic materials with a porous coating. In cemented prostheses, normal marrow cells are observed at the cement–bone interface, while in cementless porous-coated prostheses, most of the pore space is occupied by endostal bone and the remainder by normal marrow cells. In the cementless nonporous-coated prostheses, a partially mineralized fibrous tissue can be found around the prosthesis [1].

Nowadays, joint replacement is a widely used surgical procedure that has led to improved quality of life for a large number of people suffering from advanced joint diseases. It has been estimated that about 700,000 hip and knee arthroplasties are performed every year in the United States alone [2]. Furthermore, it is reasonable to presume a further increase in this number due to increased life expectancy in the Western countries. While these surgical procedures, in the vast majority of cases, are successful, some complications can occur, such as aseptic loosening, dislocation, infection, fracture, and hardware failure. A number of these complications are relatively rare and easily diagnosed by plain radiography, while differentiation between aseptic loosening and infection can be more difficult. Symptoms and signs of early infection are not specific: the erythrocyte sedimentation rate, increased leukocyte count, and protein C-reactive levels are neither sensitive nor specific, and the standard radiographic appearance of infection can mimic that of aseptic loosening. Although joint aspiration with Gram staining and culture is considered the definitive diagnostic test, its sensitivity is variable ranging from 28 to 92 %. Its specificity is more reliable ranging from 92 to 100 % [2, 3]. Plain radiographs are neither sensitive nor specific, and computed tomography and magnetic resonance imaging, even if more sensitive for detecting osteolysis, can be limited by the artefacts caused by the implanted metallic prosthesis. Since clinical and radiographic signs of the two conditions may overlap in a significant number of cases, radionuclide imaging

M. Liberatore (✉)
Department of Radiological,
Oncological and Anatomo-Pathological Sciences,
University of Rome "La Sapienza",
Viale Regina Elena, 324, 00161 Rome, Italy
e-mail: maurlib@tin.it

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plays a significant role in the study of these complications.

Aseptic loosening of the prothesis is the most common reason for revision surgery. About 25 % of all prostheses demonstrate, sooner or later, evidence of loosening [2]. Inappropriate mechanical load, fatigue failure at the bone–prosthesis or cement–prosthesis interface, and implant motion can cause this complication. However, the most frequent cause of this complication is an inflammatory reaction caused by the fragmentation of prosthetic components [4]. The shedding of microscopic particles of these materials, due to the wear of hardware, probably attracts and activates phagocytic tissues cells. However, enzymatic digestion of these particles is particularly difficult, leading to a continuous inflammatory stimulus, which produces secretion of pro-inflammatory cytokines and proteolytic enzymes responsible for bone and cartilage damages. The development of a pseudo-membrane with a variable cellular composition has been reported: histiocytes are the most common isolated cells (95 % of specimens), but also giant cells are very frequent (80 %) as well as lymphocytes and plasma cells (25 %), while neutrophils are present only in about 10 % of specimens [5–8]. A similar condition leads to osteolysis, corresponding to radiographic appearance of periprosthetic lucency, loss of supporting osseous tissues, and eventually loosening of the prosthesis.

Infection is the third most common reason for revision arthroplasty, but is, perhaps, the most serious complication. Its frequency ranges from 1 to 2 % for primary implants and from about 3 to 5 % for revision implants [9]. This complication can develop within the first months, but also years after surgery. From the histopathological point of view, the inflammatory reaction found in the infected prosthesis can be similar to that present in aseptic loosening except for the presence of neutrophil leukocytes, which are almost absent in aseptic loosening and always abundantly present in infection.

Distinguishing infection from aseptic loosening of a prosthesis is extremely important, since infection often requires multiple admission (removal of infected hardware followed by a long course of antibiotic treatment and a revision arthroplasty), while aseptic loosening requires only one hospital admission and a single surgical intervention (single-stage exchange arthroplasty). Thus, a false-positive case (lack of specificity of the diagnostic tool) can produce unnecessary, multiple, and expensive surgical procedures, while a false-negative case (lack of sensitivity of the diagnostic tool) results in additional surgical intervention, since undiagnosed infection will turn into failure of the revision implant. Radionuclide imaging usefully contribute to the evaluation of symptomatic prosthesis suspected of infection by several scintigraphic methods.

7.1 Bone Scintigraphy

Bone scintigraphy is based on the administration and the study of skeletal uptake of phosphates and phosphonates labeled with 99mTc. This uptake reflects bone turnover and, therefore, bone metabolic activity. This scan is an easily available and inexpensive diagnostic tool, and its role in the evaluation of painful joint replacements has been extensively studied over the years. This scan is extremely sensitive for detecting bone changes around prosthetic joints, since, like all scintigraphic methods, it provides functional rather than anatomic information. Several authors reported that bone scan is a useful method for detecting joint replacement failure, but that it is not sufficiently specific for assessing the cause of the failure. Aliabadi et al. found that bone scintigraphy can accurately detect prosthetic loosening, but cannot distinguish aseptic from infected loosening [10]. Some investigators based their attempt to differentiate aseptic loosening from infection on the periprosthetic uptake patterns of the radiopharmaceutical [11]: focal uptake was considered indicative of aseptic loosening, while diffuse periprosthetic uptake around the femoral and acetabular component was associated with infection. Different results were obtained by other authors, who found diffuse periprosthetic

uptake associated with both the conditions [12] or reported that a similar uptake pattern was sufficiently specific, but insensitive to infection [13]. It has been reported (and could be concluded) that, focusing the analysis only on aseptic, loosened prosthesis, bone scan can be considered both sensitive and specific [14]. In reality, the problem is more complex, because the uptake of the radiopharmaceutical depends on bone mineral turnover, which increases in a number of conditions besides infection, producing increased periprosthetic activity. Furthermore, it is well known that asymptomatic hip replacements are associated with several uptake patterns of the radiopharmaceutical. These patterns partially depend on the time elapsed from surgery and also on the modality of attachment of prosthetic implant. Usually, up to about one year from surgery, the periprosthetic uptake is very variable independently of the presence of surgical cement. After this period, while the majority of asymptomatic patients with cemented hip replacement have a normal uptake pattern, about 10 % of these patients present increased periprosthetic uptake [15] (Fig. 7.1). This increased uptake beyond one year from surgery is even more frequent when porous-coated hip prostheses are implanted [16, 17].

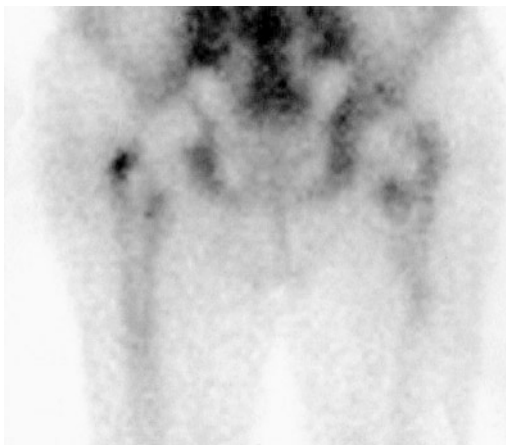

Fig. 7.1 Bone scintigraphy in posterior view. Aseptic loosening of the right hip prosthesis. The left prosthesis was painless. Significant uptake of the radiopharmaceutical can be seen around both the prostheses

The study of total knee replacement by bone scintigraphy is perhaps more problematic than that of hip prosthesis. In fact, it has been reported that 60 % of femoral and 90 % of tibial components show increased periprosthetic uptake more than 12 months after surgery [18, 19]. Serial bone scans performed in asymptomatic patients for a period of two years after implantation of total knee prostheses demonstrate that even if periprosthetic activity generally decreased over time, there was significant variability patient-to-patient [19]. These authors proposed the use of serial scans to actually asses the significance of increased periprosthetic uptake.

On this basis, the results obtained by further studies showing low accuracy of bone scan in assessing infection of total knee replacement are not surprizing [20, 21].

Bone scintigraphy can also be performed evaluating not only late images (reflecting bone osteometabolic activity) but also early phases of the scan (vascular and blood pool phases). A similar study is currently called 3-phase bone scan. This different approach does not seem to produce better results in diagnosing prosthetic infection, as reported in Table 7.1.

As can be seen, the clinical usefulness of bone scintigraphy in the evaluation of painful prosthetic joints can be considered low, due to the low values of its diagnostic accuracy. It does not seem possible with a single scan to differentiate aseptic loosening from either infection or normal post-operative appearance. For both cemented and porous-coated hip and knee replacements, bone scan is more useful in excluding prosthetic pathology when it is clearly negative. Due to its high negative predictive value, this scintigraphy can be used as a screening test or in association with other radionuclide studies.

7.2 Combined Bone/Gallium Scintigraphy

The property of gallium-67 of accumulating in both septic and aseptic inflammations has been known for about 40 years. Early investigations

Table 7.1 Reliability of 3-phase bone scintigraphy in the assessment of prosthetic infection

Author and year	Type of prosthesis	N° of prostheses	Sensitivity (%)	Specificity (%)	Accuracy (%)
Magnuson et al. [41]	Hip and knee	49	100	18	53
Levitsky et al. [42]	Hip and knee	72	30	86	68
Palestro et al. [20]	Knee	41	67	76	–
Love et al. [21]	Hip and knee	150	76	51	62*

* In the same study, the accuracy value of simple bone scintigraphy was 50 %

regarding the role of this radionuclide in musculo-skeletal infections showed variable values of accuracy. In 1979, Reing et al. carried out a study on 79 joint replacements, comparing bone and gallium-67 scintigraphies in diagnosing infection [22]. The sensitivity and specificity values obtained for bone and gallium-67 scans were 100, 15, and 95, 100 %, respectively. These findings suggested that gallium-67 imaging may significantly increase the accuracy of radionuclide diagnosis of infected joint replacement. Rushton et al. in a comparative study of bone and gallium-67 scans reported that gallium-67 accumulated in all the 13 infected prostheses they studied, whereas none of the 18 patients with aseptic loosening of prosthesis showed abnormal gallium-67 uptake (100 % accuracy) [23]. Other authors found 80 % accuracy values [13, 24], while Aliabadi et al. reported that gallium-67 scan is only 37 % sensitive, but 100 % specific [10]. In order to improve the accuracy of both bone and gallium-67 scans, the two studies are often interpreted together according to standardized criteria [25]. According to this approach, the scan is positive for infection when the spatial distribution of the two tracers is incongruent or when this distribution is spatially congruent but the gallium-67 uptake is higher than that found on the bone scan. The test is negative for infection when the gallium-67 scan is normal, independently from the bone scan results or when the spatial distribution of the two tracers is congruent, but the gallium-67 uptake is lower than that found on bone scan. Finally, the scans have to be considered dubious for infection when spatial distribution and intensity of uptake of the two radiotracers are congruent.

This combined interpretation, however, does not significantly increase the accuracy over either study alone. In fact, while Tehranzadeh et al. reported a 95 % accuracy for combined studies [26], the majority of the authors found less satisfactory results, as shown in Table 7.2.

In conclusion, on the basis of the above reported accuracy values, it can be affirmed that combined bone/gallium-67 imaging interpretation, produces only a slight accuracy improvement in comparison with bone scan alone.

7.3 Labeled Leukocyte Scintigraphy

From the physio-pathological point of view, indium-111-labeled leukocytes should be the most specific tracer for detecting infection, since they are always abundantly present in the histopathological specimen drawn at the site of prosthetic joint infection. Most of the early reported results, however, can be considered disappointing. A possible explanation of similar contradictory results may be found in the different methods used for image interpretation. All the methods shown in Table 7.3 are based on a comparison of intensities between periprosthetic region and another region used as reference point or merely on the presence of any periprosthetic activity. Labeled leukocytes accumulate in bone marrow, and even if bone marrow is more present in axial skeleton and proximal humeri and femurs, its distribution is characterized by significant inter-individual variability. Furthermore, orthopedic hardware can give rise to localized marrow expansion [27–29], and other systemic diseases can also cause generalized bone marrow

Table 7.2 Reliability of combined bone/gallium-67 scintigraphy in the assessment of prosthetic infection

Author and year	Sensitivity (%)	Specificity (%)	Accuracy (%)
Merkel et al. [43]	66	81	77
Gomez-Luzuriaga et al. [44]	70	90	80
Kraemer et al. [45]	38	100	81
Love et al. [21]	75	59	66

expansion. Thus, similar conditions can make it difficult to correctly distinguish eventual alteration of marrow distribution from uptake really due to infection. Poor accuracy of above-mentioned results depends on the fact that the intensity of labeled leukocyte accumulation is not a useful criterion to obtain a correct diagnosis of infection.

In order to improve accuracy of labeled leukocyte scans, combined leukocyte/bone scan was tested, assuming incongruent images with the two tracers as positivity criterion. As shown in Table 7.4, inconsistent results were obtained. In particular, some authors reported a significant increase in sensitivity (from 45 % with leukocyte scan to 85 % with leukocyte/bone imaging) against a slight drop in specificity (from 100 to 85 %) [30]. Further experiences gave similar results, showing higher specificity values of combined scans in comparison with leukocyte scan alone (95 vs. 50 %) and only small decrease of sensitivity (88 vs. 100 %) [31].

On the other hand, lower accuracy of the combined scintigraphies was found by other investigators. Studying total knee replacements, Palestro et al. reported that sensitivity and specificity of combined scans were not significantly better than those of a leukocyte scan alone (67 vs. 89 % and 78 vs. 75 %) [20]. Only slight improvement of accuracy was obtained with combined leukocyte/bone scintigraphy by Love et al. (from 64 % with leukocyte scan to 70 % with leukocyte/bone imaging) [21]. Furthermore, incongruent leukocyte/bone images were observed in 15 % of asymptomatic patients with porous-coated hip arthroplasties [16]. Such

Table 7.3 Diagnostic reliability of labeled leukocyte scintigraphy in the assessment of prosthetic infection

Author and year	Type of prosthesis	Criteria for classifying images as positive	Sensitivity (%)	Specificity (%)
Pring et al. [46]	Hip and knee	Periprosthetic activity at least as intense as normal marrow	100	89.5
Magnuson et al. [41]	Hip and knee	As above	88	73
McKillop et al. [24]	Hip and knee	Any type of periprosthetic activity	50	100
Wukich et al. [30]	Hip and knee	Focal increase of activity compared with adjacent bone marrow activity	100	45
Johnson et al. [31]	Hip and knee	Any type of periprosthetic activity	100	50
Palestro et al. [32]	Hip	Any type of periprosthetic activity, regardless of intensity	100	23
Palestro et al. [32]	Hip	Periprosthetic activity more intense than the controlateral hip	23	63
Palestro et al. [20]	Knee	Any type of periprosthetic activity, regardless of intensity	89	50
Palestro et al. [20]	Knee	Periprosthetic activity more intense than the controlateral hip	89	75

Table 7.4 Reliability of combined leukocyte/bone scintigraphy in the assessment of prosthetic infection

Author and year	Type of prosthesis	Sensitivity (%)	Specificity (%)
Mulamba et al. [47]	Hip	92	100
Merckel et al. [48]	Hip and knee	86	100
Pring et al. et al. [49]	Hip and knee	100	66
Palestro et al. [20]	Knee	67	78
Cuckler et al. [50]	Hip and knee	60	73

incongruence, not dependent on the presence of an infection, is probably due to the different distribution of the tracers (marrow uptake for leukocyte and bone uptake for diphosphonate). Several conditions can affect both these distributions or only one of these, with unforeseeable effects.

Labeled colloids used for bone marrow imaging (such as 99mTc-Sulfur colloid) and labeled leukocyte have a very similar distribution in the bone marrow in normal subjects and also in patients with marrow abnormalities. Combining bone marrow with leukocyte imaging, congruent images are obtained, except in the case of osteomyelitis, which strongly attracts white blood cells, producing incongruent uptake patterns. On the basis of these criteria, Palestro et al. used leukocyte/marrow imaging in patients with painful hip replacement, obtaining a sensitivity of 100 % and a specificity of 98.7 % for the diagnosis of infection [32]. These authors in another study, regarding painful knee prostheses, found that these combined scans produce more accurate results than bone scintigraphy alone, leukocyte imaging alone, and combined leukocyte/bone imaging in diagnosis of infection [20]. Love et al. studied, with leukocyte/marrow imaging, 59 painful lower extremity joint replacements and reported sensitivity, specificity, and accuracy values for prosthetic joint infection of 100, 91, and 95 %, respectively [33]. These authors, more recently, investigating 150 failed joint prostheses, found that sensitivity, specificity, and accuracy of leukocyte/marrow imaging were 96, 87, and 91 %, respectively. Furthermore, the test resulted more accurate than bone (50 %) bone/gallium-67 (66 %), and leukocyte/bone imaging (70 %). From a practical point of view, leukocyte scan should be performed first, since if no periprosthetic activity is found on this scan, the marrow scan need not be performed. Alternatively, simultaneous dual-isotope acquisitions can also be performed, with significant advantages from the point of view of the comparison and interpretation of the images.

In addition to the 111-Indium,, leukocytes can be labeled with technetium-99m with satisfactory results. This method, avoiding the execution of bone marrow imaging, contemplates the acquisition of images at various time points. The early images should reflect the uptake of leukocytes in the marrow, while late images reflect the uptake due to the infection (Fig. 7.2). With this approach Pelosi et al. obtained satisfactory results, with an accuracy of 75 % using a visual analysis and of 95 % using a semi-quantitative analysis [34]. If one were to perform, however, even after technetium-99m-labeled leukocyte scan, the bone marrow scintigraphy, it is necessary to carry out marrow imaging at least 72 h after leukocyte scintigraphy. In conclusion, scintigraphy with labeled leukocytes, if based on a positivity criterion that takes into account the normal distribution of bone marrow rather than the intensity leukocyte uptake, is the most reliable method for diagnosis of prosthetic infection. This scan can be performed labeling cells with indium-111 and comparing the findings with bone marrow imaging obtained by technetium-99m-sulfur colloid. Alternatively, the labeling can be performed with technetium-99m, evaluating normal marrow activity and infection by multiple time-point analysis.

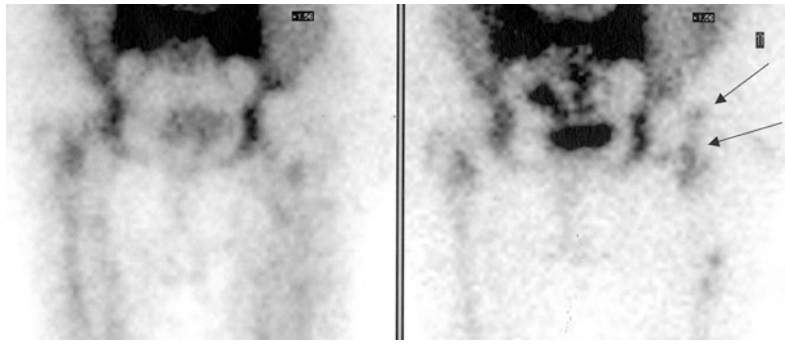

Fig. 7.2 99mTc-labeled leukocyte scan at 30 min (*left*) and 20 h (*right*) after labeled cells administration, in a patient with infection of left hip prosthesis. The appearance of two areas of increased uptake of the radiopharmaceutical (*arrows*), which was not present in the *left image*, can be seen on the *right image*

7.4 Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography

In recent years, fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG) has been widely utilized in diagnosing prosthetic joint infection due to its advantageous characteristics (high resolution of PET images, availability, and rapid completion of the examination) and some disadvantages of leukocyte imaging (time-consuming separation and labeling of cells, direct contact with blood). The obtained results, however, seem to be inconclusive, mainly because of differing methods for image interpretation. In fact, some authors have used as a criterion of positivity, the increased uptake at the bone prosthesis interface, resulting in sensitivity, specificity, and accuracy values of 90, 89.3, and 89.5 %, respectively, for prosthetic hip infection and of 90.9, 72 and 77.8 %, respectively, for prosthetic knee infection [35]. Other authors have argued that accuracy of the test does not depend on the intensity of the uptake, but on the location of the uptake. In particular, the presence of activity at the bone–prosthesis interface along the shaft of the femoral component of a hip prosthesis is sensitive (92 %) and specific (97 %) for infection [36]. Further experiences confirmed that periprosthetic uptake patterns on PET images are able to differentiate infection from aseptic loosening, while intensity of uptake does not permit such a diagnosis [37]. On the contrary, Manthey et al. found that differential diagnosis between aseptic loosening and infection is possible by analyzing both intensity and pattern of uptake (96 % accuracy) and that the presence of activity around the femoral head and neck (the exact opposite of what was stated by others) are suggestive of infection [38]. Considering only intense periprostatic activity, Stumpe et al. found 18F-FDG-PET significantly sensitive, but not specific, with an overall accuracy of 69 %, which resulted in lower than that obtained with bone scan [39].

Using several different criteria for interpretation of 18F-FDG images, Love et al. reported that the most accurate criteria (71 %) for diagnosing infection is the presence of activity on the bone–prosthesis interface, with a target to background ration greater than 3.6:1 for hip replacement and 3.1:1 for knee replacement [33]. This study, however, demonstrates that the accuracy of leukocyte/marrow imaging in the same patients was 95 %, showing that 18F-FDG cannot replace leukocyte/marrow imaging in differentiating aseptic loosening from infection. Similar results were obtained by Mayer-Wagner et al., who, with 18F-FDG, found sensitivity and specificity values of 67 and 83 %, respectively, for the diagnosis of prosthetic infection [40].

7.5 Conclusions

In the evaluation of painful joint replacements, nuclear medicine plays essentially the role of differentiating aseptic loosening from infection of the prosthesis. Some partial analogies between the pathophysiological frameworks of these two conditions make nonspecific tracers of inflammation unreliable. The bone scan, due to its excellent negative predictive value, can be used as an initial screening test, since no tracer uptake reliably excludes infection. Labeled leukocyte scan combined with marrow imaging or based on multiple time-point analysis to evaluate the normal marrow activity is the scintigraphic method of choice for diagnosing infection.

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