Bone scan in painful knee arthroplasty: obsolete or actual examination?

Giuseppe Niccoli¹, Domenico Mercurio¹, Fabrizio Cortese²
¹ Clinic of Orthopaedics, Academic Hospital of Udine, Udine, Italy; ² Orthopedics and Traumatology Department, Ospedale S. Maria Del Carmine of Rovereto, Rovereto (TN), Italy

Summary. Background: Complications and revision surgeries after Total Knee Arthroplasty (TKA) have increased. Aseptic loosening, instability and infection are the major causes of TKA failure. For many years, nuclear medicine (NM) imaging was helpful to frame a painful total joint arthroplasty. The differentiation of septic from aseptic prosthetic loosening is critical. The latest AAOS guidelines to detect periprosthetic joint infection (PJI) restrict the role of NM scintigraphy. On the other hand, several studies suggest that NM imaging plays an important role in the evaluation of patients with painful prosthesis, but its specificity in differentiating aseptic loosening from infection is low. Moreover, scintigraphic exams showed different diagnostic accuracy in TKA compared to total hip arthroplasty (THA).

Purpose: To assess and discuss current knowledges about the diagnostic value of the various scans in TKA failure alone.

Methods: We perform a pubmed/medline search to identify all papers published in the literature matching the following key words: “total knee arthroplasty”, “bone”, “scintigraphy”, “imaging”, “three-phase”, “triple-phase”, “99mTc-HDP”, “99mTc-MDP”, “99mTc-hydroxymethane diphosphonate”, and “99m Tc-methylenediphosphonate”, “leukocyte scanning”, “labeled leukocyte scintigraphy”, “antigranulocyte”, “nuclear medicine”, “septic loosening”, “aseptic loosening” and “infection”.

Results: Three phases bone scintigraphy results an early diagnostic screening test or part of the preoperative tests for painful TKA and when PJI is suspected. Instead, leukocyte/bone marrow scintigraphy is superior to other scintigraphic tools in diagnosis of TKA infections. Granulocyte scintigraphy, seems to be an excellent choice when the diagnosis is unclear. Moreover, nuclear diagnostic tests showed different diagnostic accuracy between TKA and THA.

Conclusions: Although nuclear diagnostic tests for THA failure are superior in diagnostic accuracy compared to TKA, NM scintigraphy is still an effective tool in the identification of chronic, low grade PJI. To date, scintigraphic exams have an higher levels of sensitivity, specificity and accuracy. Currently, leukocyte/bone marrow scintigraphy is considered the gold standard for this aim. Nevertheless, further studies are needed to assess and improve the accuracy of the scintigraphic exams in order to discriminate the causes of failure for painful TKA.

Key words: total knee arthroplasty, scintigraphy, loosening, aseptic, septic, 99mTc HDP, labeled leukocyte, antigranulocyte

Introduction

Total knee arthroplasty (TKA) is still rising. In the United States (US) the amount of primary TKA grew 1.7-fold from 135,992 to 237,645 between 1993 and 2005 (1,2).

Likewise, the total number of complications and revision surgeries, after TKA, has also increased (8%) (3). Aseptic loosening was cited, in 23-71% of the cases, as the most frequent reason of revision surgery; in 8.1-39% cases the cause was instability, and in 5-18.4% infection (4-6).
Although infections occur more rarely, they are one of the most feared, and potentially fatal, complications. The number of TKA infections diagnosed in the US is steadily rising, almost six-fold between 1990 and 2004 (7).

Usually laboratory tests, serology, aspiration of joint fluid and microbiological tests are the most common ways to differentiate these conditions, even if there is no test that shows 100% sensitivity and specificity (8-10).

If there are no clinical signs and symptoms, differentiation between aseptic and septic TKA loosening is very difficult (11). Therefore, an early and correct diagnosis is crucial to allow appropriate surgical planning and timely antimicrobial treatment (12).

To date, the most accurate method, considered the reference standard, to diagnose prosthetic infections is the isolation of one or more organism from tissues, even if false positive and false negative results could occur (13). Intraoperative histological examinations are a valuable method to define septic or aseptic mobilization during revision surgery, to decide the therapeutic approach to be adopted (14). Recently, Di Benedetto et al. (15) reported results achieved by other authors before, showing high specificity and sensitivity of the polymorphonuclear (PMN) leukocytes count of extemporaneous exam in presence of highly virulent pathogens.

In fact, accurate preoperative diagnostic criteria would be needed to add information in order to confirm or exclude infection.

For many years, nuclear medicine (NM) imaging was helpful, giving information on the painful joint replacement and its specific complications. But, the latest AAOS guidelines (2011) on the role of NM scintigraphy to detect periprosthetic joint infection (PJI) were flawed, ill-defined and limited (16,17).

On the other hand, several studies suggest that NM imaging plays an important role in the evaluation of patients with painful prosthesis, as well as nuclear imaging techniques in the evaluation of PJI should be considered among the hip and knee replacement failure. For these reasons, NM role should be re-evaluated, and its algorithms consequently adapted (17-20).

Parvizi et al. (2006) (21) suggested a diagnostic algorithm without drawing any distinction between hip and knee arthroplasty.

A wide variety of nuclear medicine procedures can be used. In general, it is accepted that a study without alterations is a strong indicator of no prosthetic joint infection, however, its specificity in differentiating aseptic loosening from infection is low (22-25).

Bone scintigraphy is useful especially in patients who underwent total hip arthroplasty (THA). Whereas scintigraphic exams showed different diagnostic accuracy in the TKA failure (26). In this review we decide to assess and discuss current knowledges about the diagnostic value of the various scans in TKA failure alone.

**Methods**

A pubmed/medline search was conducted in March 2017 to identify all randomized control trial, meta-analysis, systematic review, prospective and retrospective studies published in the literature. The MeSH terms (keywords) used in different combination were: “total knee arthroplasty”, “bone”, “scintigraphy”, “imaging”, “three-phase”, “triple-phase”, “99mTc-HDP”, “99mTc-99mTc-MDP”, “99mTc-hydroxymethane diphosphonate”, and “99m Tc-methylene diphosphonate”, “leukocyte scanning”, “labeled leukocyte scintigraphy”, “antigranulocyte”, “nuclear medicine”, “septic loosening”, “aseptic loosening” and “infection”. The searches were limited to English and German languages. The references of these studies and systematic reviews were also searched for inclusion of other relevant papers in this review. All relevant peer-reviewed articles were analyzed and all journals were considered. This has been designed as a comprehensive review, not a meta analysis neither systematic review.

**Results**

The literature search and cross-referencing resulted in a total of 83 articles retrieved with the search strategy eligible for this review.

A total of 25 studies eligible for this purpose were reviewed. A procedure of diagnostic algorithm for the use of scintigraphy was planned.

The results of the review are described below, dividing the different scintigraphic exams in: 1) Bone
scintigraphy (Technetium-99m(99Tc) labeled diphosphonate, Gallium-67 citrate); 2) Labeled leukocyte (in-vitro and in-vivo labeled white cells).

- 99m Tc-MDP

Three phases bone scintigraphy (TPBS) is the first method in NM widely available and easily performed in cases of suspected total joint arthroplasty infection (27).

Bone scintigraphy is usually performed with 99mTc-methylene diphosphonate which accumulates on the surface of the bone mineral matrix. The uptake of 99mTc-MDP depends on blood flow and rate of new bone formation. Fracture, heterotopic ossification, neoplasm, arthritis, aseptic loosening and infection cause increased bone turnover. These possibilities may give false positive results and decrease bone scintigraphy specificity (28-30).

Moreover, after total joint arthroplasty, bone scan may be positive for at least 2 years after THA and for 5 years after TKA due to physiological bone remodeling (31). In TKA, bone scintigraphy shows more than 60% of femoral components and nearly 90% of tibial component, demonstrating persistent periprosthetic activity even more than 12 months after implantation (32). In addition, although periprosthetic uptake generally decreases over time, there is considerable patient-to-patient variation (33-35).

Some papers showed variable results in sensitivity and specificity related to the definition PJI diagnosis with TPBS (19,26).

TPBS consists of the dynamic imaging sequence called as “the blood flow” or “perfusion phase” or “first phase”, the static images of the region of interest known as the “blood pool” or “soft tissue phase” or “second phase” and the late images known as “third phase” and consisting of planar static images of the area of interest, which are acquired 2-4 h after radiopharmaceutical injection (31).

The first phase demonstrates perfusion, the second shows the relative vascularity, and the third the relative osteoblastic activity and thus the bone turnover. A positive bone scan can be indicative of loosening, infection, or stress fracture. While a diffuse uptake may indicate the presence of a complex regional pain syndrome. The triple-phase bone scan has a high sensitivity but poor specificity (31).

Increased uptake on the first and second phases of the scan signifies hyperaemia and increased blood pool uptake respectively, but these findings are non-specific (36).

With 99m Tc-methylenediphosphonate, the ability to differentiate between tumours, activated osteoarthritis and noninfectious inflammatory lesions is often not possible (37).

The indications for the bone scans involve patients with TKA with anterior or unresolved knee pain, and suspected infection (38).

The concept of a “hot patella” on a bone scan was introduced by Sy and Smith, suggesting that it reflected a metabolic feature (39). Kipper et al. (40) defined a “hot patella” more specifically as a tracer uptake, on the third phase of the bone scan with Tc-99m-MDP, in the patella greater than in the ipsilateral distal femur or the proximal tibia. The incidence of this kind of features in patients without primary patellar resurfacing was 51% (28/55). Ninety-five percent of patients with anterior knee pain and 21% of patients with diffuse knee pain had a “hot patella” (38).

Studies have shown that bone scans have a higher sensitivity for the diagnosis of a high pressure patella compared to radiographs (41).

The explanations of increased patellar uptake could be due to osteoarthritis or to the intraosseous engorgement pain syndrome that had venous stasis or increased pressures in the bone marrow near the painful joint. Also, an increased stress across the patellofemoral joint and subsequent remodelling of the bone, impending fracture, and loosening of the patellar button explain increased patellar uptake. Patients with “hot patella” who underwent secondary patellar resurfacing had symptomatic relief of symptoms (38).

Aseptic loosening is an inflammatory reaction to the prosthetic components (42). Subsequently, the particulate debris activates tissue phagocytes but can not be broken down by cellular enzymes. The continued secretion of proinflammatory cytokines and proteolytic enzymes damages the bone and cartilage and further activates immune cells. The heightened inflammatory response leads to osteolysis and, eventually, loosening.
Bone scan in painful knee arthroplasty: obsolete or actual examination?

The ability of Tc-99m-MDP to distinguish loosening from infection is poor. In case of infected TKA, the characteristic findings show an increased uptake in all three phases of the scan. The lack of increased uptake in the first two phases is an important negative finding that would hamper the diagnosis of infection.

Conventional bone scintigraphy may reveal increased isotope uptake not only in infection, but also in the presence of mechanical loosening. Osteolysis from polyethylene wear debris usually gives rise to the same appearances on the bone scan as infection, which it may mimic clinically. The pattern of distribution of isotope is not sufficiently characteristic to predict loosening or infection.

Segura et al. (2004) reported a sensitivity of 100% but a specificity of 0% for bone scintigraphy in the diagnosis of PJI after THA or TKA. Reinartz et al. (2005) regarded TPBS diagnostic of periprosthetic hip infection, when the blood-pool and late phase only showed increased uptake of radioisotope and they reported a sensitivity of 68% and specificity of 76%. Also, Nagoya et al. (2008) diagnosed PJI of the hip when TPBS showed uptake of radioisotope in all phases. Their results showed a sensitivity of 88% and specificity of 90%.

Ouyang et al. (2014) conducted a meta-analysis of 20 studies to determine the TPBS utility in PJI diagnosis. They found a sensitivity of 0.83 (95% CI 0.72-0.90) and specificity of 0.73 (95% CI 0.65-0.80) for PJI detection using TPBS. But, TPBS demonstrated a substantial drop in sensitivity and specificity from 0.83 and 0.73 in hip and knee PJI to 0.75 (95% CI 0.40-0.95) and 0.55 (95% CI 0.24-0.83) in knee PJI alone. An explanation could be that, in asymptomatic patients, periprosthetic isotope uptake around TKA can often be found for several years and, since TKA disturbs the natural kinematics of the knee joint, it’s extremely variable.

Although the guidelines of IDSA (Infectious diseases Society of America) did not recommend routinely using of TPBS for the assessment of PJI, several studies indicate its diagnostic value, especially in hip.

Intense focal uptake after more than 6 months postoperatively suggests loosening or infection, but false-positive rates are high (up to 72%) (33). Sequential bone scans that show increasing radiotracer uptake are also suggestive of loosening, but they are not diagnostic, as the wide variability in uptake has been shown in asymptomatic patients followed with sequential scans.

In conclusion, currently TPBS alone has an important role in the painful TKA, but it is less used to detect PJI. TPBS is often combined with other functional radionuclide imaging techniques, such as 67Ga citrate scintigraphy and leukocyte scintigraphy to achieve better specificity.

• 67Ga citrate scintigraphy

Gallium-67 is another radionuclide initially used to detect cancer. Afterwards, gallium has been shown to accumulate in infection and inflammation. The exact reason why 67Ga accumulates in infection is still not clear, probably, it binds to transferring, lactiferrin, leukocytes and siderophores produced by bacteria, in inflammatory areas.

Several authors suggested to perform gallium imaging in addition to bone scintigraphy to improve the radionuclide diagnosis of the PJI. 67Ga citrate scintigraphy along with TPBS reflect inflammation and osteoblast activity respectively.

In summary, 67Ga citrate scintigraphy is diagnostic of PJI if gallium uptake is more extensive or exceeds the one of the TPBS.

Conversely, if gallium uptake is strictly concordant and lesser than the uptake on the bone scan, or there is no gallium uptake, the PJI diagnosis is excluded. PJI diagnosis is inconclusive if gallium uptake is concordant and of equal intensity on the two scans.

Studies have shown that sequential technetium-gallium scans have a sensitivity for infection between 83% and 87% and a specificity between 30% and 79%.

The degree of gallium visualization varies with the intensity of the inflammatory response, and leukocyte accumulation is clearly the major determining factor. Findings on gallium scans can be positive in inflammatory lesions, both infectious and noninfectious, secondary to the accumulation of leukocytes.
An unusual, infectious-like uptake in gallium-technetium scans, with incongruent hot areas in gallium scan has been observed in patient who developed severe metallosis due to metal-metal friction in TKA (55).

We analyzed the studies that showed bone/gallium imaging sensitivity, specificity and accuracy for PJI diagnosis. We found average values of sensitivity, specificity and accuracy of 58%, 84.5% and 78% respectively (27). No articles that show sensitivity specificity and accuracy for TKA infection alone has been found. Combined bone/gallium imaging offers only a modest improvement over bone scintigraphy alone, with an accuracy of about 65–80% (27).

To date, because of its low specificity in PJI diagnosis, 67Ga has been replaced by other more specific radionuclide imaging techniques (31). 67Ga scintigraphy remains reserved to diagnosing and monitoring of spinal infections (52).

Labeled leukocyte scintigraphy

White cells usually do not accumulate at sites of increased bone mineral turnover, in the absence of infection. Leukocyte labeling is performed with indium-111 (111-In) or 99m Tc-hexamethylene dicyclamine oxide (99m Tc HMPAO). The majority of leukocytes labeled are neutrophils. In the aseptic loosening of TJA neutrophils are generally absent. Heterotopic ossification, metastatic disease and degenerative arthritis did not accumulate labeled white cells (58).

In TJA infection, acute, subacute and chronic infection show different pattern of labeled leukocyte uptake. When bacteria start to secrete chemotactic factors, leukocytes come to the periprosthetic foci from the peripheral blood. In this case leukocyte scintigraphy is positive and allows to detect acute and subacute infection. While, in chronic infection, the bacterial biofilm retards the invasion of labeled leukocytes in the site of infection. For this reason, the late leukocyte imaging at 24h is more sensitive and more specific than routine leukocyte imaging at 2–4 h (31,53,59,60).

The great disadvantage of leukocyte scintigraphy is that leukocytes accumulate not only in the infected area but also in the bone marrow (31).

Palestro et al. (1990,1991) (23,61) reported a sensitivity of 100% and specificity of 23% using labeled leukocyte imaging for PHI diagnosis.

In TKA leukocyte scintigraphy, when periprosthetic activity shows a more intense signal compared to the controlateral knee, as the criterion of positive study, this technique has a sensitivity of 89% and an increase of specificity from 50% to 75% (23). 111In- or 99m Tc-HMPAO-leukocyte scintigraphy used alone with a grading system of periprosthetic uptake has showed sensitivity between 50-100% and specificity between 45–100% (62,63).

Schauwacker et al. (64) reported an average Tc-HMPAO sensitivity of 87% and an average Tc-HMPAO specificity of 81%. As reported by others, the relatively low levels of sensitivity, specificity and accuracy of labeled white blood cell (WBC) scintigraphy are mainly a consequence of the accumulation of leukocytes in the reticuloendothelial bone marrow (22,65).

To avoid radiotracer uptake by reticuloendothelial cells or fixed macrophages of the marrow, bone marrow imaging is performed with 99m Tc-sulfur colloid or 99m Tc-nanocolloid.

Even if 99m Tc-labeled sulfur colloid and labeled leukocytes have similar physiologic distribution in the bone marrow. Besides bone infection stimulate leukocytes accumulation but reduces sulfur colloid accumulation in the bone marrow, so it permits to discriminate infection-induced or surgery-induced leukocyte accumulation in this site (22,61,66).

Palestro et al. (1990) reported sensitivity, specificity, and accuracy of labeled leukocytes plus sulfur colloid bone marrow imaging in THA of 96%, 97%, and 97%, respectively (61). This result is superior compared to imaging with labeled leukocytes alone or in combination with routine bone scintigraphy (sensitivity 67%, specificity 78% in painful TKA) (23). In combined leukocyte/bone imaging, diphosphonates accumulate in bone, while labeled leukocytes accumulate in marrow. Therefore conditions that affect bone marrow may or may not affect bone and vice versa (67).

Regarding leukocyte and bone marrow scintigraphy in TKA infections only, we found in four studies (between 2001 and 2014) and 86 TKA the average values of sensitivity and specificity of 70.57% and 94.6% respectively (68–71).
Pelosi et al. (2004) (72), to avoid performing bone marrow scan, sought to increase the accuracy of labeled leukocytes scintigraphy alone, gaining images at multiple time points. So they added a semiquantitative evaluation to improve accuracy in a dual time point imaging depending of whether early images reflect labeled leukocyte uptake in marrow and late images reflect labeled leukocyte uptake in infection. The result was the increased in accuracy from 75% to 95%, but only about half patients in this series (THA and TKA) had surgical confirmation of their diagnosis.

To date, both methods, 111In- or 99m Tc-labeled leukocytes plus bone marrow scintigraphy have defined limitations: the time consuming and the high cost needed to complete the procedure, well-trained technicians, special facilities and need of in-vitro direct blood cell manipulation. The in vitro labeling process is labor intensive and involves direct handling of blood products, and therefore the risks of contaminating the final product with lethal pathogens and the potential for inter-patient misadministration (59,69).

A complete examinations requires a BM scans to localize the sites of red marrow which may be a source of false positive results on labeled white blood cell scans. Finally, it should be noted that this procedure involves higher levels of radiation exposure (73).

**Labeled leukocyte scintigraphy with antigranulocyte antibody**

Another scintigraphic method is 99m Tc-antigranulocytescintigraphy (AGS). This scintigraphy is used as an alternative to autologous WBC scintigraphy in PJII diagnosis, to avoid its disadvantages.

Unlike WBC scintigraphy, AGS is carried out “in vivo” labeled leukocytes by the use of monoclonal antibodies and antibody fragments against specific surface receptors on granulocytes (29,69). Besilesomab and sulesomab are the monoclonal antibodies most commonly used. The sensitivity and specificity of besilesomab for PJII range from 67-91% and 57-75%, respectively.

Linking bone imaging or semiquantitative analysis, AGS with besilesomab increases its sensitivity (from 67 to 100%) and specificity (from 84 to 100%) (74,75). Similarly, AGS with sulesomab reported sensitivity and specificity for PJII from 75-93% and 65-86% respectively. Combining 99m Tcsulesomab with 99m Tc-nanocolloid in bone marrow imaging the specificity increases to 100% (76,77).

Furthermore, dual time point imaging and time activity curve analysis may improve test accuracy (78,79). AGS is a promising diagnostic tool for PJII and overcomes the limitations of the in vitro labeling procedure (WBC scintigraphy). However, this method has also a disadvantage: since the antibodies used are murine-derived they could trigger a human antimurine antibody (HAMA) response. This risk ranges from less than 5%, in patients receiving a single dose of antibody, to more than 30% in patients receiving repeated injections (74).

Two meta-analysis available in literature (80,81) on the use of AGS in PJII, showed a sensitivity of 83% and specificity of 80%.

Conversely, Sousa et al. (82) obtained a higher sensitivity (100%) and a lower specificity (20%).

Specifically, we found two studies that assess the diagnostic utility of AGS in infected TKA. Gratz et al. (2009) (74) obtained sensitivity, specificity, positive and negative predictive value and accuracy using besilesomab alone of 91%, 66%, 76%, 85% and 80% for sepsis. A significant increase of these values to 94%, 88%, 99%, 95%, 89% respectively was observed with AGS plus TPBS.

Rubello et al. (2008) (83) published their results in diagnosis of infected TKA using sulesomab after a dual time imaging protocol. Sensitivity and specificity improve from 92.7 and 78.4 in early scans to 100% in delayed scans.

False positives in early scans were properly diagnosed as negative in the delayed imaging. The reason of this feature in early imaging is a non-specific mechanism of accumulation of this small diffusible compound in the infectious foci. If, instead, the early AGS imaging appears negative, delayed imaging is not necessary.

**Discussion**

The main role of scintigraphy in painful joint arthroplasty is diagnose the loosening causes, especially aseptic failure from infection. Periprosthetic joint infection is the most serious complication after hip or knee replacement.
Early detection of TKA infection may improve outcomes by enabling appropriate surgical planning and early antimicrobial treatment (26,36).

Classic clinical signs of infection are often not present and a gold standard for the preoperative diagnosis does not exist (8,9,84). Late infection in TKA continues to be a challenging problem.

If subclinical infection is not identified at the time of the first revision surgery, the infection could come back. Therefore, accurate preoperative diagnostic criteria should be established.

Intraoperative biopsies are needed to add information in order to confirm or exclude infection (14).

In TKA failure, tests showed different diagnostic accuracy and the investigative protocol, suggested by AAOS, excludes NM investigations in most cases. On the other hand AAOS has recommended that triphasic bone scintigraphy should be used in cases of suspected TKA infection, after negative cultures.

This rational approach avoids unnecessary radiation exposure, patient inconvenience, and costs (16).

Therefore, in the future a decision-making process for the scintigraphy value in preoperative diagnosis of TKA failure should be developed and validated.

TPBS is mainly a sensitive exam to detect increased periarticular bone turnover. Negative bone scintigraphy is a good indicator that an alternative cause of pain should be investigated. Whereas, positive bone scintigraphy is evidence of loosening, “hot patella”, wear-associated osteolysis, or PJI, justifying the further imaging. However, TPBS may give false positive results for several years after primary procedure, due to bone remodeling (26). The finding of a “hot patella” on a bone scan in patients with anterior knee pain following total knee replacement suggests a problem related to the patellofemoral joint (38).

The biological response to polyethylene (PE) wear debris, and the consequent development of osteolysis, is considered as the main factor for aseptic loosening of metal-on-PE TKA.

The pattern of distribution of isotope is not sufficiently characteristic to predict loosening or infection (36,46-48).

Even if, currently, the new prosthetic designs and surgical techniques have restricted mechanical failures. TPBS alone is not recommended for PJI diagnosis, but for its acceptable diagnostic capability, simplicity and cost-effectiveness TPBS is an early diagnostic screening test or part of the preoperative tests when PJI is suspected (26,85).

67Ga scintigraphy has proven to be a useful in addition to TPBS, but the accuracy to detect PJI is nearly 80% (62).

Leukocyte/bone marrow scintigraphy appears the best available imaging technique to detect infection in patients with suspicious PJI.

The reported average values of sensitivity and specificity are 70.57% and 94.6% respectively. Leukocyte/bone marrow scintigraphy is superior to other scintigraphic tools in diagnosis of TKA infections, but it has less diagnostic accuracy than leukocyte/bone marrow scintigraphy in THA infections diagnosis (68-71).

Synovial fluid culture, as well as a granulocyte scintigraphy, seems to be an excellent choice when performed in patients with doubtful diagnosis. Sarvarino et al. (2009) (12) integrate their algorithm with the granulocyte scintigraphy to diagnose a subclinical infection. If inflammation tests and granulocyte scintigraphy are positive, two stage surgical revision is scheduled and needle-aspirate is carried out to perform germ isolation and antibiotic resistance evaluation. Instead, if serological tests are positive but granulocyte scintigraphy is negative and vice versa, culture and leukocyte count on needle-aspirate are suggested to diagnose infection. AGS seems to have merits as a complementary diagnostic test to traditional diagnostic procedures such as biopsy or culture.

To date, NM is most valuable for determining whether or not a painful joint arthroplasty is infected. Currently, leukocyte/bone marrow scintigraphy is considered the gold standard for this aim (23,82). The addition of a semiquantitative evaluation of late and early images in 99m Tc-labeled leukocyte scintigraphy improves levels of sensitivity, specificity and accuracy similar to the results obtained using leukocyte/bone marrow scintigraphy (72).

Some articles agree in saying that the preoperative NM imaging should be re-evaluated and the algorithms adapted accordingly, in fact NM scintigraphy results an effective tool in the identification of chronic, low grade PJI (17-19).
Conclusions

In conclusion this manuscript is a comprehensive review of the evolution about the role of scintigraphy to assess TKA complications.

We summarize key-points that should be considered in painful TKA diagnosis.

- After TKA, bone scan may be positive for 5 years due to physiological bone remodeling (31).
- In TKA failure, nuclear diagnostic tests showed different diagnostic accuracy compared to THA (26).
- Additional and new investigations for painful TKA are needed to assess and improve the accuracy of the scintigraphic exams in order to discriminate the causes of failure. Besides, more researches is needed to overcome the disadvantages afflicting combined labeled leukocyte/bone marrow imaging and antigranulocyte scintigraphy.
- Bone marrow imaging and antigranulocyte scintigraphy are available in few Institutions (59, 69).
- To date, we can follow the algorithm proposed by Trevail et al. (17) for NM investigation of painful THA.

At the beginning, the patient with painful TKA may be submitted to TPBS. The exam is positive if there is increase periprosthetic uptake of tracer compared to the contralateral knee. Then, patients underwent labeled leukocytes scintigraphy. WCS results positive when it proves a pattern of uptake concordant with that of the initial bone scintigraphy; if WCS was negative, aseptic loosening is reported. Otherwise, if WCS results equivocal, the next step to do is TC-99m nanocolloid bone marrow scintigraphy.

References

1. Mota REM, Tarricone R, Ciani O, Bridges JFP, Drummond M. Determinants of demand for total hip and knee arthroplasty: a systematic literature review. BMC Health Serv Res 2012; 12: 225.
2. Tian W, et al. Looking upstream: factors shaping the demand for postacute joint replacement rehabilitation. Arch Phys Med Rehabil 2009; 90: 1260-8.
3. Kurtz S, et al. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. J Bone Joint Surg Am 2005; 87: 1487-97.
4. Mortazavi SMJ, Schwartzenberger J, Austin MS, Purtill JJ. Parvizi J. Revision Total Knee Arthroplasty Infection: Incidence and Predictors. Clin Orthop 2010; 468: 2052-9.
5. Dalury DF, Pomeroy DL, Gorab RS, Adams MJ. Why are total knee arthroplasties being revised? J Arthroplasty 2013; 28: 120-1.
6. Song SJ, Detch RC, Maloney WJ, Goodman SB, Huddleston JI. Causes of instability after total knee arthroplasty. J Arthroplasty 2014; 29: 360-4.
7. Kurtz SM, et al. Infection burden for hip and knee arthroplasty in the United States. J Arthroplasty 2008; 23: 984-91.
8. Barrack RL, Jennings RW, Wolfe MW, Bertot AJ. The Coventry Award. The value of preoperative aspiration before total knee revision. Clin Orthop 1997; 8-16.
9. Claassen L, Radtke K, Ettinger M, Plass C, von Lewinski G. Preoperative diagnostic for periprosthetic joint infection prior to total knee revision arthroplasty. Orthop Rev 2014; 6: 5437.
10. Greidanus NV, et al. Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty. A prospective evaluation. J Bone Joint Surg Am 2007; 89: 1409-16.
11. Kumar R, Kumar R, Kumar V, Malhotra R. Comparative analysis of dual-phase 18F-fluoride PET/CT and three phase bone scintigraphy in the evaluation of septic (or painful) hip prostheses: A prospective study. J Orthop Sci Off J Jpn Orthop Assoc 2016; 21: 205-210.
12. Savarino L, Tignani D, Baldini N, Bochicchio V, Giunti A. Pre-operative diagnosis of infection in total knee arthroplasty: an algorithm. Knee Surg Sports Traumatol Arthrosc Off J ESSKA 2009; 17: 667-675.
13. Mariani BD, Martin DS, Levine MJ, Booth RE, Tuan RS. The Coventry Award. Polymerase chain reaction detection of bacterial infection in total knee arthroplasty. Clin Orthop 1996: 11-22.
14. Bori G, et al. Usefulness of histological analysis for predicting the presence of microorganisms at the time of reimplantation after hip resection arthroplasty for the treatment of infection. J Bone Joint Surg Am 2007; 89: 1232-7.
15. Di Benedetto P, et al. The role of intraoperative frozen section in arthroplasty revision surgery: our experience. Acta Bio-Medica Atenei Parm 2016; 87 Suppl 1: 34-40.
16. Della Valle C, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: the diagnosis of periprosthetic joint infections of the hip and knee. J Bone Joint Surg Am 2011; 93: 1355-7.
17. Trevail C, Ravindranath-Reddy P, Sulkin T, Bartlett G. An evaluation of the role of nuclear medicine imaging in the diagnosis of periprosthetic infections of the hip. Clin Radiol 2016; 71: 211-9.
18. Segura AB, et al. What is the role of bone scintigraphy in the diagnosis of infected joint prostheses? Nucl Med Commun 2004; 25: 527-32.
19. Yue B, Tang, T. The use of nuclear imaging for the diagnosis
of periprosthetic infection after knee and hip arthroplasties. Nucl Med Commun 2015; 36: 305-11.

20. Palestro CJ. Radionuclide imaging of infection: in search of the grail. J Nucl Med Off Publ Soc Nucl Med 2009; 50: 671-673.

21. Parvizi J, Ghanem E, Menashe S, Barrack RL, Baeuer TW. Periprosthetic infection: what are the diagnostic challenges? J Bone Joint Surg Am 2006; 88 Suppl 4: 138-147.

22. Palestro CJ, Torres MA. Radionuclide imaging in orthopedic infections. Semin Nucl Med 1997; 27: 334-45.

23. Palestro CJ, Suyer AJ, Kim CK, Goldsmith, S. J. Infected knee prosthesis: diagnosis with In-111 leukocyte, Tc-99m sulfur colloid, and Tc-99m MDP imaging. Radiology 1991; 179: 645-8.

24. Magnuson JE, et al. In-111-labeled leukocyte scintigraphy in suspected orthopedic infection: comparison with other imaging modalities. Radiology 1988; 168: 235-9.

25. Rini JN, Palestro CJ. Imaging of infection and inflammation with 18F-FDG-labeled leukocytes. QJ Nucl Med Mol Imaging Off Publ Ital Assoc Nucl Med.AIMN Int Assoc Radiopharmacol IAR Sect Off Soc Of 2006; 50: 143-6.

26. Ouyang Z, Li H, Liu X, Zhai Z, Li X. Prosthesis infection: diagnosis after total joint arthroplasty with three-phase bone scintigraphy. Ann Nucl Med 2014; 28: 994-1003.

27. Love C, Marvin SE, Palestro CJ. Nuclear medicine and the infected joint replacement. Semin Nucl Med 2009; 39: 66-78.

28. Gemmel F, et al. Prosthetic joint infections: radionuclide state-of-the-art imaging. Eur. J Nucl Med Mol Imaging 2012; 39: 892-909.

29. Restrepo S, Vargas D, Riascos R, Cuellar H. Musculoskeletal infection imaging: Past, present, and future. Curr Infect Dis Rep 2005; 7: 365-72.

30. Palestro CJ, Love C, Miller TT. Diagnostic imaging tests and microbial infections. Cell Microbiol 2007; 9: 2323-3.

31. Gillemans AWJM, Galli F, Pacilio M, Signore A. Leukocyte and bacteria imaging in prosthetic joint infection. Eur Cell Mater 2013; 25: 61-77.

32. Rosenthal L, Lepanto L, Raymond F. Radiophosphate uptake in asymptomatic knee arthroplasty. J Nucl Med Off Publ Soc Nucl Med 1987; 28: 1546-9.

33. Hofmann AA, et al. Bone scans after total knee arthroplasty in asymptomatic patients. Cemented versus cementless. Clin Orthop 1990; 183-8.

34. Della Valle CJ, et al. Preoperative testing for sepsis before revision total knee arthroplasty. J Arthroplasty 2007; 22: 90-93.

35. Palestro CJ. Nuclear medicine, the painful prosthetic joint, and orthopedic infection. J Nucl Med Off Publ Soc Nucl Med 2003; 44: 927-9.

36. Love C, Tomas MB, Marvin SE, Pugliese PV, Palestro CJ. Role of nuclear medicine in diagnosis of the infected joint replacement. Radiogr Rev Publ Radiol Soc N Am Inc 2001; 21: 1229-38.

37. Modic MT, et al. Vertebral osteomyelitis: assessment using MR. Radiology 1985; 157: 157-66.

38. Ahmad R, Kumar GS, Katam K, Dunlop D, Pozo JL. Significance of a ‘hot patella’ in total knee replacement without primary patellar resurfacing. The Knee 2009; 16: 337-40.

39. Fogelman I, McKillop JH, Gray HW. The ‘hot patella’ sign: is it of any clinical significance? Concise communication. J Nucl Med Off Publ Soc Nucl Med 1983; 24: 312-5.

40. Kipper MS, Alazraki NP, Feiglin DH. ‘The ‘hot’ patella. Clin Nucl Med 1982; 7: 28-32.

41. Heijgaard N, Diemer H. Bone scan in the patellofemoral pain syndrome. Int Orthop 1987; 11: 29-33.

42. Rini JN, et al. PET with FDG-labeled leukocytes versus scintigraphy with 111In-oxine-labeled leukocytes for detection of infection. Radiology 2006; 238: 978-87.

43. Henkin RE, et al. Nuclear Medicine 2006.

44. Nagoya S, Kaya M, Sasaki M, Tateda K, Yamashita T. Diagnosis of peri-prosthetic infection at the hip using triple-phase bone scintigraphy. J Bone Joint Surg Br 2008; 90: 140-4.

45. Rosenthal L, Lisbona R, Hernandez M, Hadjipavlou A. 99mTc-PP and 67Ga imaging following insertion of orthopedic devices. Radiology 1979; 133: 717-21.

46. Math KR, Zaidi SF, Petchprapa C, Harwin SF. Imaging of total knee arthroplasty. Semin Musculoskelet Radiol 2006; 10: 47-63.

47. Smith SL, Wastie ML, Forster I. Radionuclide bone scintigraphy in the detection of significant complications after total knee joint replacement. Clin Radiol 2001; 56: 221-4.

48. Levitsky KA, et al. Evaluation of the painful prosthetic joint. Relative value of bone scan, sedimentation rate, and joint aspiration. J Arthroplasty 1991; 6: 237-44.

49. Reinaerts P, et al. Radionuclide imaging of the painful hip arthroplasty: positron-emission tomography versus triple-phase bone scanning. J Bone Joint Surg Br 2005; 87: 465-70.

50. Osmon DR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis Off Publ Infect Dis Soc Am 2013; 56: e1-e25.

51. Allen AM, Ward WG, Pope TL. Imaging of the total knee arthroplasty. Radiol Clin North Am 1995; 33: 289-303.

52. Cyeval C, Bourdon A. Imaging orthopedic implant infections. Diagn Interv Imaging 2012; 93: 547-57.

53. Palestro CJ, Love C. Radionuclide imaging of musculoskeletal infection: conventional agents. Semin Musculoskelet Radiol 2007; 11: 335-52.

54. McKillop JH, et al. Scintigraphic evaluation of the painful prosthetic joint: a comparison of gallium-67 citrate and indium-111 labelled leucocyte imaging. Clin Radiol 1984; 35: 239-41.

55. Worland RL, Arredondo J, Angles F, Jessup DE. Scintigraphic evaluation in total knee failure secondary to severe metallosis. J Arthroplasty 1998; 13: 116-9.

56. Reing CM, Richin PF, Kenmore PI. Differential bone-scanning in the evaluation of a painful total joint replacement. J Bone Joint Surg Am 1979; 61: 933-6.

57. Schneider R, Hood RW, Ranawat CS. Radiologic evalu-
Bone scan in painful knee arthroplasty: obsolete or actual examination?

72. Pelosi E, et al. 99mTc-HMPAO-leukocyte scintigraphy in the diagnosis of prosthetic joint infection. Nucl Med Commun 2001; 28: 288-93.

73. Rojas-Burke J. Health officials reacting to infection mishaps. J Nucl Med Off Publ Soc Nucl Med 1992; 33: 13N-14N, 27N.

74. Gratz S, et al. Nuclear medical imaging in case of painful knee arthroplasty. Radiol 2009; 49: 59-67.

75. Boubaker A, et al. Immunoscintigraphy with antigranulocyte monoclonal antibodies for the diagnosis of septic loosening of hip prostheses. Eur J Nucl Med 1995; 22: 139-147.

76. von Rothenburg T, Schoellhammer M, Schaffstein J, Koester O, Schmid G. Imaging of infected total arthroplasty with Tc-99m-labeled antigranulocyte antibody Fab’fragments. Clin Nucl Med 2004; 29: 548-51.

77. Pakos E, et al. Use of 99mTc-Sulesomab for the Diagnosis of Prosthesis Infection after Total Joint Arthroplasty. J Int Med Res 2007; 35: 474-481.

78. Rubello D, et al. Role of anti-granulocyte Fab’ fragment antibody scintigraphy (LeukoScan) in evaluating bone infection: acquisition protocol, interpretation criteria and clinical results. Nucl Med Commun 2004; 25: 39-47.

79. Gratz, S. et al. (99m)Tc-Fab’ fragments (sulesomab) for imaging septically loosened total knee arthroplasty. J Int Med Res 2007; 35: 54-67.

80. Xing D, et al. Use of anti-granulocyte scintigraphy with 99mTc-labeled monoclonal antibodies for the diagnosis of periprosthetic infection in patients after total joint arthroplasty: a diagnostic meta-analysis. PLoS One 2013; 8: e69857.

81. Pakos EE, Trikalinos TA, Fotopoulos AD, Ioannidis JPA. Prosthesis infection: diagnosis after total joint arthroplasty with antigranulocyte scintigraphy with 99mTc-labeled monoclonal antibodies—a meta-analysis. Radiology 2007; 242: 101-8.

82. Sousa R, et al. Diagnostic accuracy of combined 99mTc-sulesomab and 99mTc-nanocolloid bone marrow imaging in detecting prosthetic joint infection. Nucl Med Commun 2011; 32: 834-9.

83. Rubello D, et al. Diagnosis of infected total knee arthroplasty with anti-granulocyte scintigraphy: the importance of a dual-time acquisition protocol. Nucl Med Commun 2008; 29: 331-5.

84. Del Pozo JL, Patel R. Clinical practice. Infection associated with prosthetic joints. N Engl J Med 2009; 361: 787-94.

85. Palestro CJ. Nuclear medicine and the failed joint replacement: Past, present, and future. World J Radiol 2014; 6: 446-58.