

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

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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”, “^{99m}Tc-HDP”, “^{99m}Tc-MDP”, “^{99m}Tc-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. (www.actabiomedica.it)

Key words: total knee arthroplasty, scintigraphy, loosening, aseptic, septic, ^{99m}Tc 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 prosthesis 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-MDP", "99mTc-hydroxymethane diphosphonate", and "99m Tc-methylenediphosphonate", "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 ^{99m}Tc-methylene diphosphonate which accumulates on the surface of the bone mineral matrix. The uptake of ^{99m}Tc-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 decreased 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

of the prosthesis (43). 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 (44).

The lack of increased uptake in the first two phases is an important negative finding that would hamper the diagnosis of infection (45).

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 (46). The pattern of distribution of isotope is not sufficiently characteristic to predict loosening or infection (47,48).

Segura et al. (2004) (18) 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) (49) 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) (44) 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) (26) conducted a meta-analysis of 20 studies to determinate 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 (50).

In fact, the use of TPBS to evaluate TKA is an issue of debate. Bone scans are less helpful in evaluating loosening in TKAs than in THA (26).

Intense focal uptake after more than 6 months postoperatively suggests loosening or infection (51), 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 (33).

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 ^{67}Ga citrate scintigraphy and leukocyte scintigraphy to achieve better specificity.

• *^{67}Ga citrate scintigraphy*

Gallium-67 is another radionuclide initially used to detect cancer (52). Afterwards, gallium has been shown to accumulate in infection and inflammation (28). The exact reason why ^{67}Ga accumulates in infection is still not clear, probably, it binds to transferrin, lactoferrin, leukocytes and siderophores produced by bacteria, in inflammatory areas (31,53).

Several authors suggested to perform gallium imaging in addition to bone scintigraphy to improve the radionuclide diagnosis of the PJI.

^{67}Ga citrate scintigraphy along with TPBS reflect inflammation and osteoblast activity respectively.

In summary, ^{67}Ga citrate scintigraphy is diagnostic of PJI if gallium uptake is more extensive or exceeds the one of the TPBS (52).

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 (52).

Studies have shown that sequential technetium-gallium scans have a sensitivity for infection between 83% and 87% and a specificity between 30% and 79% (54,55).

The degree of gallium visualization varies with the intensity of the inflammatory response, and leukocyte accumulation is clearly the major determining factor (56). Findings on gallium scans can be positive in inflammatory lesions, both infectious and noninfectious, secondary to the accumulation of leukocytes (57).

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, ^{67}Ga has been replaced by other more specific radionuclide imaging techniques (31). ^{67}Ga 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 $^{99\text{m}}\text{Tc}$ -hexamethylpropylene amine oxine ($^{99\text{m}}\text{Tc}$ 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). ^{111}In - or $^{99\text{m}}\text{Tc}$ -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 $^{99\text{m}}\text{Tc}$ -sulfur colloid or $^{99\text{m}}\text{Tc}$ -nanocolloid.

Even if $^{99\text{m}}\text{Tc}$ -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-anti-granulocytescintigraphy (AGS). This scintigraphy is used as an alternative to autologous WBC scintigraphy in PJI 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 PJI 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 sen-

sitivity and specificity for PJI from 75-93% and 65-86% respectively. Combining ^{99m}Tc-sulesomab 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 PJI 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 PJI, 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%, 89%, 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 periprosthetic 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 diagno-

sis, 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).

^{67}Ga 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. Savarino 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 $^{99\text{m}}\text{Tc}$ -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 controlateral 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.

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