The role of nuclear medicine techniques in differentiation between septic and aseptic loosening of total hip and knee arthroplasty

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Abstract

Jansen JA, Smit F, Pereira Arias-Bouda LM. The role of nuclear medicine techniques in differentiation between septic and aseptic loosening of total hip and knee arthroplasty.

This article gives an overview of nuclear imaging techniques, which can be used to diagnose (a)septic loosening in joint replacements. The pathophysiology of loosening and the differences between septic and aseptic loosening with its therapeutical consequences are discussed.

An overview is given of the advantages and limitations of frequently used techniques as triple-phase bone scanning and white blood cell scintigraphy. The additional value of SPECT/CT and the possible role of FDG PET/CT in the diagnosis of prosthetic joint infection is discussed.

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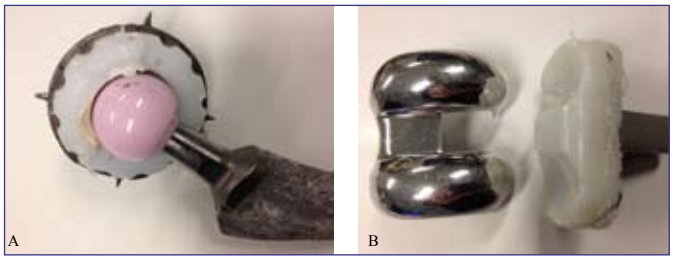

Figure 1. Pictures of retrievals showing wear of the bearing surfaces of total hip (A) and total knee (B) prosthesis, causing wear and small particle disease that can lead to aseptic loosening.

Introduction

A growing number of total hip and knee replacements are performed annually with a very good outcome in the majority of cases giving relief of arthritic pain and improved function. In some patients though complications occur of which loosening and infection are the most common (1-3).

The reason for approximately seventy percent of all re-operations in joint arthroplasty is loosening of the prosthesis. Symptoms of loosening are usually quite nonspecific with persistent pain at the arthroplasty site especially on weight bearing, and reduced mobility of the patient and the prosthesis (3,4). When prosthetic loosening is caused by infection it is classified as septic loosening, and in case of aseptic loosening it will be due to wear of the bearing surfaces (figure 1).

Infections occur in 2 to 3 percent of all primary joint replacements, and in 5 to 8 percent of revision joint replacement patients (5,6). About one third of the infections are directly post-operative, about one third are early infections within a year, and about one third are late infections more than one year after surgery (7). Infections are frequently caused by staphylococci from the skin, which can cause fulminant infections with purulent discharge from the operation wound in the early stage. Late onset and low grade infections usually have less specific infective signs though, but can also cause loosening on long term as well. It can be very difficult to distinguish between septic and aseptic loosening, as both may be accompanied by similar symptoms (8).

Recent improvements in tribology of bearing surfaces and prosthetic coatings have influenced the incidence of aseptic prosthetic loosening. The highly cross-linking of polyethylene inserts in acetabular cups and knee liners has diminished wear and occurrence of small particle disease. The cross-linking process has improved wear resistance of polyethylene liners without impairment of other significant material properties (9). Also through hydroxyapetite coating or plasma-porous spraying of femoral and tibial prosthetic stems bony ingrowth and early stabilization of implants can be stimulated.

As an alternative to standard cobalt-chrome on polyethylene bearings also aluminium oxide ceramic bearings have been developed in order to improve performance and longevity. Alumina ceramic is entirely biostable and bioinert material with good mechanical properties. Through more precise manufacturing and contact surface geometry the fracture risk of the ceramic heads and liners has been reduced, but squeaking still remains a concern in ceramic-on-ceramic bearings (10). More recently metal-on-metal bearings have received a lot of media attention. Although these hard-on-hard

bearings offer the potential use of large heads especially in resurfacing hips, recent studies have shown increased metal wear especially in cases of high inclined cups with edge wear resulting in formation of pseudotumors and high metal ion serum levels (11). Because of the increased complication rate, lack of superiority, greater cost and potential for adverse medical effects, the Dutch Orthopaedic Society has recently given a negative advice for the use of metal-on-metal bearings especially given more recent publications (12,13).

Diagnosis of prosthetic loosening and prosthetic joint infection

Because septic and aseptic loosening require different treatments, clinical differentiation between these causes is very important. In septic loosening it is necessary to treat the infection before revision. In a first stage this will be done by removal of the prosthesis and replacement by an antibiotic loaded cement spacer and intravenous antibiotics. After discharge the antibiotics are continued orally for six week in total. The second procedure will be planned after antibiotic treatment is stopped and inflammatory markers are normalised. Usually a couple of months after the first procedure the definitive surgery will be performed, during which the cement spacer is removed and replaced by the revision prosthesis (6,14). Revision in case of aseptic loosening can be done in a single procedure with removal of the loosened prosthesis and replacement by the revision prosthesis in the same procedure. This allows quicker mobilisation, a shorter hospital admission, has fewer complications and less costs.

On plain radiographs prosthetic loosening can frequently be recognised by the occurrence of progressive radiolucency in the bone-prosthesis interface or by migration of the implant. In many cases, especially in early stages of loosening, the radiographs are indeterminate or even false negative. The important difference between prosthetic joint infection (PJI) and aseptic, mechanical loosening can also not be seen on radiographs (3).

A very useful test for diagnosis of infection is pre-operative joint aspiration followed by prolonged culture. Especially in low-grade infections pre-operative aspiration frequently renders a negative culture result though, so even with a negative bacteriology culture result the diagnosis of infection cannot be excluded (15). Although the specificity is very high (>90%), the value of aspiration and culture is limited due to the variable sensitivity, ranging from 28 to 92 percent (16,17). Other laboratory tests with inflammatory markers as erythrocyte sedimentation rate, C-reactive protein, and peripheral white blood cell count are more sensitive but not very specific for an infected prosthesis (18).

Additional imaging with cross-sectional imaging techniques as computed tomography (CT) and magnetic resonance imaging (MRI) is not very useful due to imaging artefacts by the metallic implants.

In contrast to these techniques nuclear medicine examinations are not impaired by the metallic implants. Unfortunately, there is no true consensus about the gold standard technique since each radionuclide modality has its drawbacks and limitations. The triple-phase bone scan (TPBS) still is a frequently used diagnostic procedure in case of a painful joint replacement. It is sensitive for identifying the failed joint replacement, but cannot differentiate between infection and aseptic loosening. Bone scintigraphy has been used in combination with gallium scintigraphy to increase accuracy. Augmentation with a gallium scan can detect infection with an accuracy of 65 to 80 percent (19). However, gallium uptake is mainly related to inflammation and not to infection specifically (6,20). In addition, the suboptimal imaging characteristics of gallium, the high radiation dose and the need for multiple imaging sessions over several days are disadvantages to the technique. White blood cell (WBC) imaging is also used for diagnosing complications of arthroplasty, and in combination with bone marrow scintigraphy its accuracy can be improved (6,14,16,20,21). More recently, positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG PET) is increasingly used in patients with suspected infection of joint replacements (22,23). The main limitation of functional imaging though is the lack of structural delineation of the pathology. The use of hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) and PET/CT scans gives both functional and anatomical data. This combination registers the precise anatomical location of bone and joint lesions, and in this way the accuracy of the nuclear imaging can be improved (24). A better localisation of increased radiotracer uptake allows a more precise differentiation between soft tissue and bone infection, which can improve choice of treatment and outcome (25).

Triple-phase bone scan

Triple-phase bone scintigraphy (TPBS) using bone seeking tracers such as ^{99m}Tc-labelled diphosphonates MDP or HDP is the mainstay of nuclear medicine around the world in orthopaedic nuclear medicine. There is a large body of evidence for its usefulness in all kinds of orthopaedic problems (26-28). This includes the scanning of prosthetic problems like loosening, infection and inflammation. Uptake is related to blood flow and the rate of new bone formation. In case of a prosthesis enhanced uptake can be seen in areas of osteolysis induced by polyethylene wear debris. In fact, any cause of accelerated new bone formation, including postoperative physiological bone remodelling, as well as pathological conditions such as heterotopic ossification, aseptic loosening and infection may show increased periprosthetic activity. This explains the low specificity of this modality for detection of loosening. Although specificity can be improved significantly by adding SPECT/CT (29), the interpretation of the images remains difficult due to the variable periprosthetic uptake related to the physiological response in the first year after implantation. And this is exactly

the period in which most prosthetic joint complications occur. Although a completely normal TPBS excludes loosening and infection with high certainty, one should keep in mind that loosening still can be present under these circumstances. Our experience is that this can be due to loosening at the cement bed - prosthesis interphase, which not necessarily leads to bone reaction (unpublished data).
In addition to the limitations mentioned above, TPBS alone cannot differentiate between aseptic loosening and infection. Although the presence of infection almost always goes hand in hand with pathological findings in the arterial flow and soft tissue phase of the TPBS (figure 2), the specificity of these findings is low, meaning that also in uninfected cases pathological findings can be present in the early phases (30). In view of these findings, it appears that TPBS alone has only limited value in diagnosing joint replacement infections. Some investigators suggest that bone scintigraphy should be used as a screening test only, while others believe the diagnosis of infection should be based on the combined interpretation of findings from bone scintigraphy and other radionuclide techniques like WBC imaging or gallium scintigraphy.

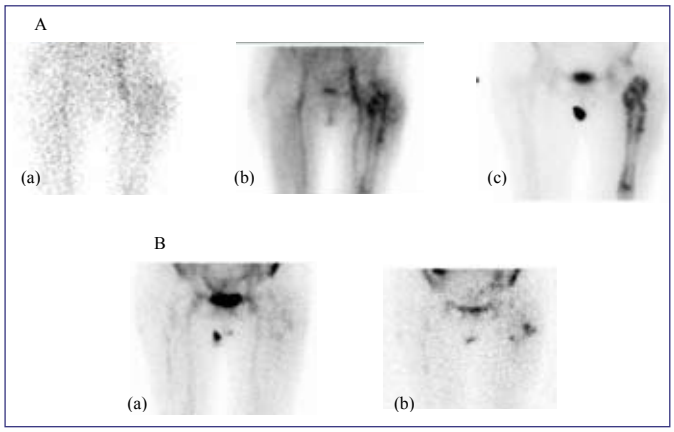

Figure 2. A patient with PJI of the left hip. (A) TPBS with anterior images of (a) arterial phase, (b) soft tissue phase and (c) static phase: the early phases show marked hyperaemia and soft tissue uptake around the femoral component of the hip prosthesis and diffuse patchy uptake around the femoral component in the static phase, suspicious of PJI. The WBC scan (B) with anterior images at 4 hours after injection (a) and 24 hours after injection (b) show moderate pathological uptake around the proximal part of the stem, increasing in time and therefore suspicious of infection. Note the spatially non-congruent distribution compared to the bone scan.

White blood cell scintigraphy

White blood cell (WBC) scintigraphy or scintigraphy with anti-granulocyte antibodies like Scintimun® have shown in selected studies a high sensitivity in detecting bacterial infection of the bone, including the infected prosthesis (31,32). There is enough evidence that WBC scanning with ex vivo labelled autologous leucocytes, either with ^{111}In-oxine- or ^{99m}Tc-hexamethypropyleneamineoxime (HMPAO), can be a useful adjunct to the abnormal bone scan for differentiation between aseptic and septic loosening.
The most challenging diagnostic situation however, is the patient with persistent pain after surgery. In these circumstances, the distinction between delayed (chronic) infection and failure related to prosthetic wear debris can be very difficult. Unfortunately, sensitivity of WBC in low grade, chronic infections is decreased, probably due to a less degree of neutrophil-influx under these circumstances. Other causes of decreased sensitivity are the formation of a protective membrane called glycocalyx or biofilm by bacteria in bone infection (33) and the negative influence of administered antibiotics (34). On the other hand, specificity is hampered by the presence of non-specific inflammation and interference of ectopic bone marrow induced by prosthetic surgery. As with bone scintigraphy, specificity of WBC scintigraphy increases when SPECT/CT is added. Fillippi and Schillaci showed both high sensitivity and specificity using ^{99m}Tc-WBC SPECT/CT in patients with suspected orthopaedic implant infection (35).

Improvement of the accuracy of radionuclide diagnosis of prosthetic joint infection

Combination of WBC imaging with bone scintigraphy

It has been suggested that radionuclide diagnosis of infection could be enhanced by combination of WBC imaging with bone scintigraphy. In this situation positive findings for infection are usually defined as the presence of non-congruent bone and leucocyte uptake, either in spatial distribution or in intensity (figure 2). However, this combined interpretation of both modalities doesn't seem to improve the accuracy for detecting PJI, as was shown by Teller et al (36). On the contrary, van Acker and co-workers managed to improve specificity from 53 to 93 percent when only lesions that were identified on a bone scan were taken into account, without affecting sensitivity (37).

Combination of WBC imaging with bone marrow scintigraphy

WBC imaging can be combined with bone marrow imaging to deal with the interference of ectopic bone marrow induced by prosthetic surgery, which can lead to false positive findings when interpreting the WBC scan alone. Both WBC imaging and bone marrow imaging with ^{99m}Tc-sulphur colloid reflect radiotracer accumulation in the reticuloendothelial system of the marrow. In patients without infection the images of WBC and bone marrow scans are congruent (figure 3), in contrast to patients with PJI in whom WBC and bone marrow scans are spatially incongruent due to the fact that infection stimulates uptake of leucocytes but suppresses uptake of sulphur colloid. The reported results using this combination of modalities consistently show a high accuracy, with sensitivity and specificity rates over ninety percent (38,39).

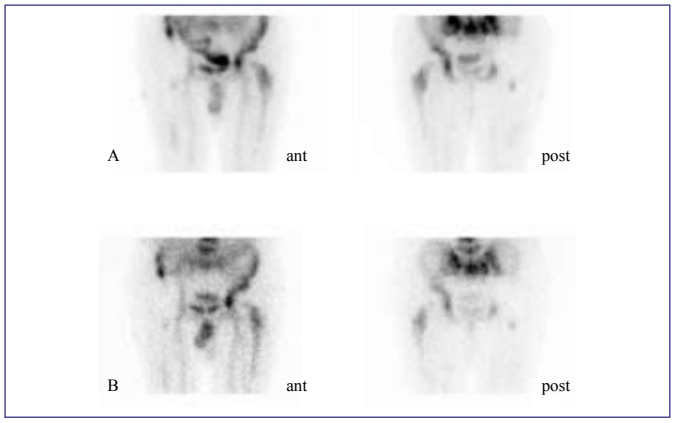

Figure 3. (A) WBC scintigraphy and (B) bone marrow scintigraphy of a patient with bilateral hip arthroplasty and persisting complaints of the left upper leg. The WBC images show diffuse uptake along the stem at the left side, and more discrete focal uptake at the right side. This is related to ectopic bone marrow rather than migration of leucocytes, as was confirmed by the bone marrow scan showing spatially congruent images.

Multiphase WBC imaging

Since the accumulation of neutrophils at the site of infection is a dynamic process, interpretation of the scan may be improved by comparing early and delayed images (40). Findings are classified as positive for infection if an increase in uptake intensity is observed with time (figure 2 and 4). Dual- or multiphase imaging leads to an increase in both sensitivity and specificity, especially if semi-quantitative evaluation is added (30,41).

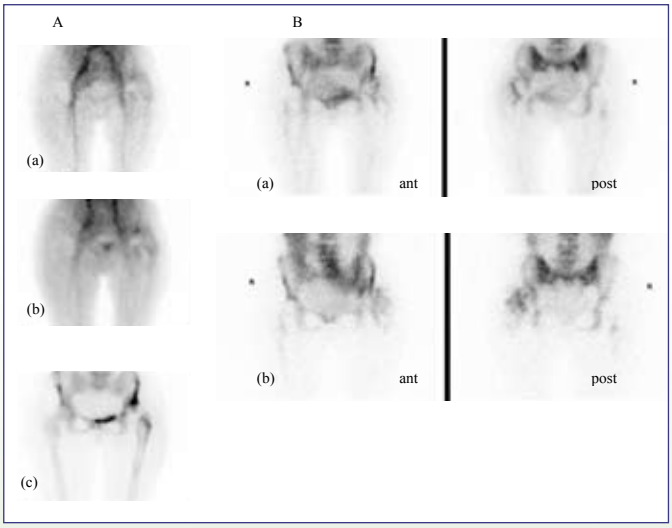

Figure 4. TPBS (A) and WBC scan (B) of a patient with persisting pain at the left hip after arthroplasty. The anterior images of the bone scan show only mild hyperaemia (a) and soft tissue uptake (b) at the left side of the hip and increased bone activity at the cranial acetabular part and mild activity around the (proximal) stem (c). The WBC images at four hours post-injection (a) show pathological uptake at the proximal part of the prosthesis, with increasing intensity with time (b, 24 hours post-injection). Per-operative cultures revealed Enterobacter cloacae colonies around the stem of the prosthesis.

Positron emission tomography with ^{18}F-fluorodeoxyglucose

^{18}F-FDG is a non-specific metabolic tracer, transported into cells by glucose transporters. FDG accumulates in cells with high glucose consumption, like tumour cells, but also in activated inflammatory cells such as lymphocytes, neutrophils and macrophages.

Investigators have reported inconsistent results on the performance of FDG PET/CT in diagnosis of prosthetic loosening and PJI (42-44). In our opinion this is mainly due to selection bias and non-uniform interpretation criteria. However, there are some consistent findings that are worthwhile to mention. In the first six months after arthroplasty surgery a non-specific periprosthetic uptake of FDG can be found due to post-operative remodelling, making the images difficult to interpret in the post-operative period. On the other hand, with a negative PET result PJI can be ruled out due to its high sensitivity. One should be aware of the possibility of false-negative results in pure mechanical loosening when the loosening occurs between the cement bed and the prosthesis. Since there are no cellular elements in this area, no enhanced periprosthetic glucose uptake is found (44). As mentioned before, we had the same experience using bone scintigraphy.

Differentiation between PJI and aseptic loosening and/or inflammation is difficult, since activated neutrophils and macrophages in inflamed tissue can show high glucose consumption, as high as in case of an infection. There is a high degree of overlap of intensity of the periprosthetic uptake in these conditions. This is particularly the case in patients with signs of polyethylene and metal-wear-induced chronic inflammation followed by periprosthetic osteolysis (42,44). In these patients often intense FDG accumulation is found in the joint capsule and around the prosthesis neck (44,45). The fact that FDG PET/CT has a high sensitivity for detecting small particle disease could be of high clinical value, since it could predict loosening in an early phase.

Since it is impossible to differentiate PJI from aseptic loosening by qualitative or quantitative assessment of the intensity of periprosthetic FDG uptake, investigators attempted to define uptake patterns to increase specificity. A well-known uptake pattern classification for hip prostheses was introduced by Reinartz (46) (table 1). Even so, using this uptake pattern classification Delanke and co-workers found a high degree of overlap between the patterns present in septic loosening and aseptic, abrasion-caused inflammation (pattern 4a-c and 5) (44). It has been proposed that combined reading of FDG PET/CT and the bone scan could be helpful in differentiating PJI from inflammation, defining only congruent pathological uptake positive for infection (37). Figure 5 shows an example of the patterns found on bone scan, PET/CT and

Table 1. Patterns of FDG PET findings and their clinical correlates in patients with a THA. Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery (46).

Pattern	Description	Clinical correlation
1	No increased uptake of FDG in the prosthesis-tissue interface	
2	Increased uptake of FDG in the area of the femoral neck	
3a	Increased uptake of FDG in the area of the femoral neck and in parts of the prosthesis-bone interface of the acetabular cup without covering the whole cup	No loosening
3b	Increased uptake of FDG in the area of the femoral neck and in parts of the proximal stem	
3c	Pattern 3a and 3b	
4a	Increased uptake of FDG in the area of the femoral neck and in the whole prosthesis-bone interface of the acetabular cup	
4b	Increased uptake of FDG in the area of the femoral neck and in wide parts of the prosthesis-bone interface of the stem	Loosening
4c	Pattern 4a and 4b	
5	Uptake of FDG in the periprosthetic soft tissue	Infection

WBC imaging in a patient with bilateral hip arthroplasty and persisting complaints at the right hip.
FDG PET/CT has a limited role in evaluating patients with persistent pain after total knee replacement; a diffuse uptake in the synovia is often encountered even without infection. Several investigators reported a worse performance of FDG PET/CT in total knee replacement compared to total hip replacement (43,44).

Conclusions

An increasing number of hip and knee replacements is performed annually with an excellent outcome in the majority of cases. If complications do occur though, infections and loosening are most common and the cause of more than 70 percent of all re-operations. Symptoms of septic and aseptic loosening can be very non-specific with pain on weight bearing and reduced mobility. Because both require a different treatment, it is very important to differentiate between the two causes of loosening.
Although radionuclide imaging plays an important role in the diagnostic work-up, there is no true consensus about the gold standard technique since each radionuclide modality has its drawbacks and limitations. At this moment dual phase WBC scintigraphy and WBC SPECT/CT combined with bone marrow scintigraphy seems to be the imaging modality of choice, showing the highest accuracy. The exact role of FDG PET/CT is not yet fully established. A normal scan rules out PJI with high certainty. Differentiation between PJI and loosening or inflammation is difficult however, even when using specific uptake pattern classifications. This is particularly the case in patients with signs of polyethylene and metal-wear-induced chronic inflammation. On the other hand, the high sensitivity of FDG PET/CT for small particle disease could be of high clinical value as an early predictor of loosening. Combined reading of FDG PET/CT and the bone scan could be helpful to differentiate PJI from abrasion-caused inflammation. The role of FDG PET/CT in patients with persistent pain after total knee replacement seems to be limited.

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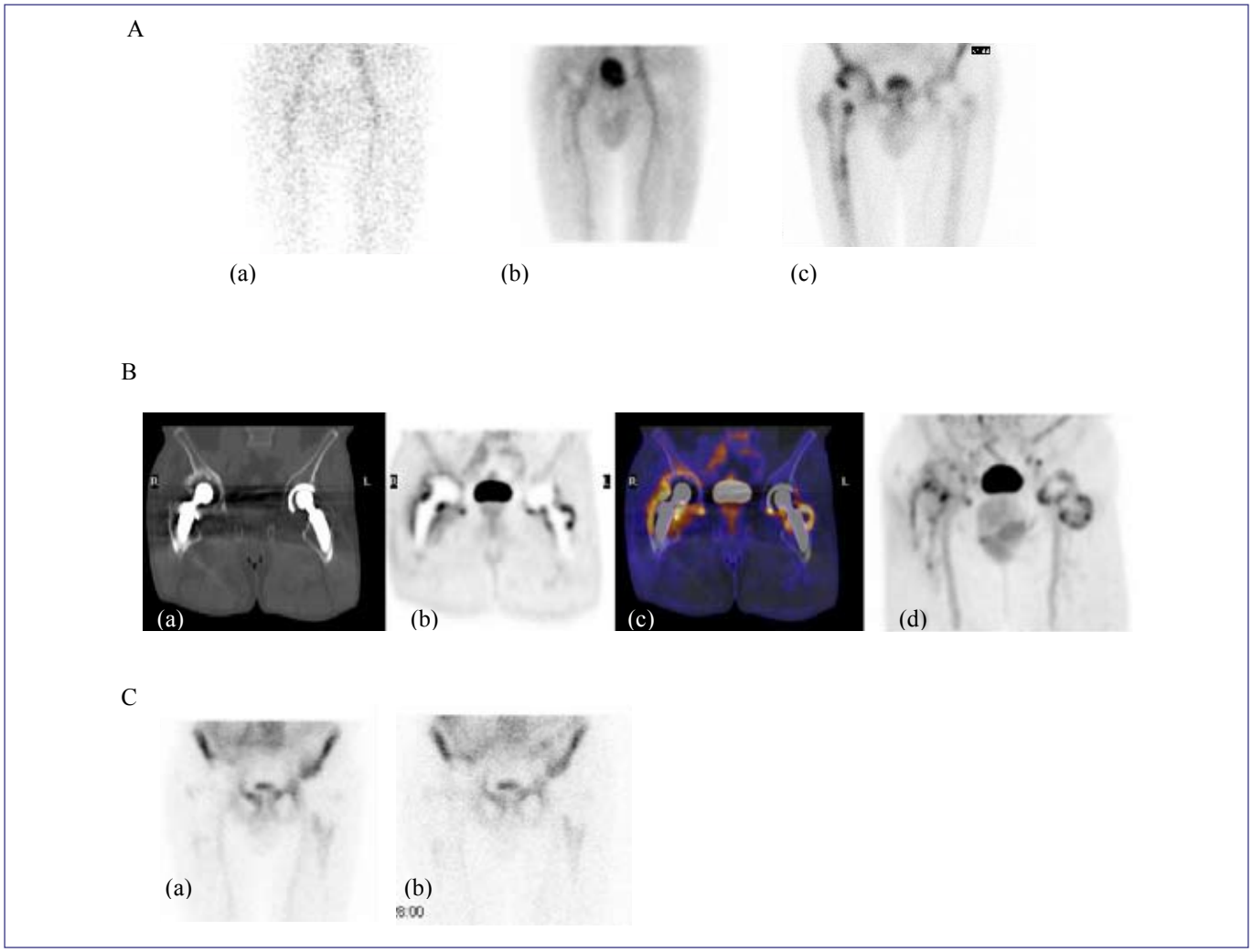

Figure 5. A patient with bilateral hip prostheses and persisting complaints at the right side. TPBS (A) shows no hyperaemia (a) and only subtle soft tissue uptake (b) around the cup and stem of the prosthesis at the right side and patchy uptake in these regions in the static phase (c). Normal findings at the left side. PET/CT images (B) with (a) coronal CT (b) coronal PET, (c) fused coronal images and (d) maximum intensity projection revealed high glucose consumption at wide parts of the bone – prosthesis interface of the stem and in the whole bone-prosthesis interface of the acetabular cup at the right side and FDG accumulation in the joint capsule and around the prosthesis neck at the left side, corresponding to Reinartz classification 4c and 3a, respectively. It was concluded that there was loosening of the acetabular cup and stem at the right side and small particle disease without loosening at the left side. However, infection at the right side could not be ruled out because of the presence of periprosthetic soft tissue uptake (b). A WBC scan (C) was performed with consent of the patient, showing no signs of infection.

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