

# Nuclear Medicine Imaging in the Detection of Complications After Total Knee Arthroplasty (TKA)

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**Abstract:** The differentiation of septic and aseptic total knee arthroplasty (TKA) loosening often generates major difficulties. Nuclear medicine imaging of infection has proven to have a high potential. Therefore, we evaluated the diagnostic accuracy of <sup>99m</sup>Tc-DPD triple-phase bone scintigraphy (TPBS) in combination with <sup>99m</sup>Tc-labelled anti-granulocyte antibody (BW 250/183) for the differentiation of septic and aseptic TKA loosening. Eighty seven patients with 94 TKA were investigated between 2003 and 2007. TPBS was classified as abnormal when an increased blood supply and increased bone uptake around the TKA was visible. BW 250/183 was considered positive for infection, when the activity around the TKA increased from 4 hr to 24 hr by more than 10% as compared with normal bone marrow images after injection of the radio-labelled monoclonal anti-granulocyte antibody. TPBS was true positive for septic and aseptic loosening in all patients, whereas false positive results for septic loosening were found in 9/20 cases (n=45%). False positive results with TPBS were correctly diagnosed by a negative BW 250/183 scan. These results suggest that TPBS is highly sensitive for the diagnosis of TKA loosening, whereas BW 250/183 allows for a specific diagnosis of periprosthetic infection. The combination of both is complementary and increases in diagnostic accuracy significantly (p<0.001).

**Level of Evidence:** Level II, diagnostic study. See the Guidelines for Authors for a complete description of levels of evidence.

**Keywords:** TKA, diagnostic imaging, infections.

Some complications of joint replacement surgery are easily diagnosed, such as fracture or dislocation of arthroplasty. However, differentiating infection from aseptic loosening is difficult because, these entities may appear remarkably similar in clinical and histopathological examination. Clinical signs and symptoms, laboratory tests, radiography, and joint aspiration are either insensitive, nonspecific, or both. Cross-sectional imaging modalities are hampered by artifacts produced by the prosthetic devices themselves. Radionuclide imaging is not affected by the presence of metallic hardware and is, therefore, useful for evaluating the painful prosthesis. Bone scintigraphy has proven to be useful as a screening test, despite an overall accuracy of only 50%–70%, because normal results essentially exclude a prosthetic complication [1-7], i.e. its negative predictive value is higher than 90%. Bone scintigraphy is widely available, easy to perform, and highly sensitive. Most investigators would agree that a study with normal results (i.e., one in which the periprosthetic uptake is indistinguishable from that of the surrounding non-articular bone) provides strong evidence against a prosthetic abnormality [8]. However, the significance of increased periprosthetic uptake is less certain and, in many cases, may not allow to differentiate between septic and aseptic loosening.

The 90% accuracy of <sup>99m</sup>Tc-labelled leukocyte or <sup>99m</sup>Tc-labelled anti-granulocyte antibody (BW 250/183, Scintimun®, Granulocyte) imaging is the highest among available radionuclide studies for imaging infection. Its success is due to the fact, that leukocyte imaging is most sensitive for detection of neutrophil-mediated inflammation (i.e., infection) [1,7]. Imaging infection using radiolabelled leukocytes or radiolabelled monoclonal anti-granulocyte antibodies has shown to be most useful for detecting neutrophil-mediated inflammatory processes. Thus, at least in theory, imaging infection is particularly useful for distinguishing between the inflamed aseptical painful prosthesis, in which neutrophils are generally absent, and on the other hand, the infected prosthesis, in which neutrophils invade and are present [8, 1]. However, a normal result of labelled leukocytes or immunoscintigraphy alone does not give sufficient evidence against a prosthetic abnormality [1, 8, 9].

We asked whether TPBS and BW 250/183 are reliable imaging tools for resolving the problem of TKA loosening. The specific questions asked were whether TPBS and BW 250/183 alone were sufficient for the differentiation of septic and aseptic TKA loosening and whether the combination of both methods gave superior, i.e., complementary results. Furthermore, we asked whether there is a correlation of the imaging results and laboratory findings.

## MATERIALS AND METHODS

The present study is a retrospective evaluation of clinical data available concordant with local ethics committee approvals. The evaluation of patient data was anonymous. For

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this study, 87 patients (mean age  $72 \pm 9$  years), 22 males and 65 females, referred to the nuclear medicine department with painful TKAs were examined. All patients were under care of orthopaedic specialists with an interest in TKA surgery. A total of 120 TPBS were requested (including 8 patients who had repeated investigations either because of inconclusive results from the first study or because of a change in symptomatology over time) and performed on these patients between 2003 and 2007. Twenty patients with suspected septic TKAs were further investigated with the monoclonal antigranulocyte antibody (BW 250/183) three days after TPBS. The average age at surgery was 71.9 years. The mean time period between surgery and the onset of symptoms, which made the TPBS and BW 250/183 necessary, was 11.5 months (range 2 months – 5 years).

### Triple Phase Bone Scintigraphy (TPBS)

Triple phase bone scintigraphies were performed immediately after injection of 600 MBq of  $^{99m}\text{Tc}$ -DPD, after 1 min and after 3 hrs. For all studies the same imaging protocol (Prism 2000, Picker, Cleveland, Ohio; parallel hole, low energy, high resolution (LEHR) collimator using the 140-keV Tc-99m peak; 128x128 matrix; time of acquisition was 60 sec immediately after injection, 3 min during the blood pool phase and 10 min/image for delayed single spot views) was used. All images were interpreted independently by two board certified and experienced nuclear medicine physicians. Due to own published data [11], the quantification of bone scintigraphy was of little value and a comparison with the other knee was often difficult in case of bilateral prosthesis or contralateral degenerative change. For the purposes of this study, the results were summarized into two groups. A normal scintigraphy was one where the uptake was entirely within normal limits, an abnormal study showed evidence of increased uptake in one or both components of the prosthesis. This could be on either one or all three phases of the investigation. For the purposes of this study, investigations showing only mild or questionable increased uptake, were nevertheless considered to be abnormal.

In those scintigraphies which were definitely abnormal, loosening was felt to be most likely, if the blood pool images were normal and the late static images in anterior/posterior or lateral view showed focal or generalized increased uptake. Infection was considered most likely, if blood pool and static images were abnormal. In these cases further investigation was performed with BW 250/183.

### Monoclonal Antigranulocyte Antibody Scintigraphy (BW 250/183)

**Characterisation of the Antibody.** The murine monoclonal antibody (BW 250/183, CIS bio international, France) is an IgG1 isotype, that recognizes the 180-kDa glycoprotein non-specific cross reacting antigen (NCA-95), which is expressed on the surface of granulocytes, myelocytes and promyelocytes [15].

**Labeling Procedure and Application.** One milligram of the lyophilized intact antibody was labelled with freshly eluted 1850 MBq (50 mCi)  $^{99m}\text{Tc}$  pertechnetate according to the Schwartz method [16]. The incubation was performed for 10 min at room temperature. Briefly, after incubation the activity was calculated for the body mass and age of the patient,

resulting in a injected activity of 550-750 MBq per patient. Consequently, the antibody protein amount injected was between 200 and 250  $\mu\text{g}$  of the antibody, labelled with 550-750 MBq  $^{99m}\text{Tc}$ -pertechnetate. The tracer was slowly injected *via* a permanent venous catheter within 2-3 min.

Anterior and posterior whole-body scans as well as single spot view scans of the knees (anterior, posterior and lateral views) were obtained at 4 and 24 hrs p.i. using a double headed gamma camera (Prism 2000, Picker, Cleveland, Ohio) with a parallel hole, high resolution, low energy (LEHR) collimator using the 140-keV Tc-99m peak, a 256x256 matrix and a pre-selected time of 25 min/image for whole-body scans and 10 min/image for single spot views.

**Scintigraphic evaluation.** The scans were read by two independent readers and the evaluation was done quantitatively as described by Klett *et al.* [1, 12]. The activity around the knee prosthesis was compared with the activity of the pelvic bone marrow, using regions of interest (ROI). Bone marrow regions were drawn as large as possible, and the shape and size of the regions around the knee depended on the shape and size of activity in this area. The regions were copied from early to late phase views. According to Klett *et al.* [1], septic arthroplasty was present if the ratios in one of the regions around the TKA increased by more than 10% from the early to the late phase. It has been demonstrated that the threshold of 10% allows a differentiation between septic and aseptic abnormalities of joint prostheses [1, 12, 13].

A scan was regarded as true positive, when an infectious or inflammatory cause for the abnormal uptake was confirmed by biopsy, culture, conventional X-ray, MRI and improvement of the physical disability under specific, e.g., antibiotic, therapy. A scan was scored as false-positive, when an infectious or inflammatory cause of the uptake was not confirmed by other investigations.

A false-negative scan was defined as a scan without abnormal uptake around the TKA, while an infectious or inflammatory cause was subsequently established by one of the other methods. A true negative scan was defined as a normal scan obtained in a patient with suspicious TPBS for infection and no infectious or inflammatory cause could be found during subsequent extensive investigations and during 3-month follow-up. The same study protocol was already used by Klett *et al.* in a similar study [1].

**Histological evaluation.** The Mirra recommendations [14] were applied. Histological specimens were classified as a.) **severe**, if pus, necrotic granular plasma cells, lymphocytic infiltrate or plasma cells and lymphocytes only, b) **moderate**, if plasma cells, lymphoplasma-cellular infiltrates, beginning granulation and scar tissue or c) **mild**, if very little lymphoplasma-cellular infiltrate, mostly sclerosis and scar tissue were present.

Observers evaluating histological samples and TPBS, BW 250/183 were not aware of the related diagnoses in the individual cases.

### Patient Case Records

Patient case records were reviewed and details of other investigations including plain radiography, relevant clinical findings and outcome were obtained. The results of arthroscopy,

open surgery and extended clinical follow-up were available in all patients. The outcome of each patient was categorized into one of the following groups:

1. Normal
2. Loose prosthesis
3. Infected prosthesis

Clinical findings were correlated with the results of TPBS and BW 250/183.

### Statistics

Imaging sensitivity, specificity, positive predictive and negative predictive values and diagnostic accuracies, were calculated according to the standard algorithms. Data were expressed as mean values with standard deviations,  $\bar{x} \pm s.d.$  In-vitro laboratory tests were analyzed for significant differences using the paired Student's t-test.

### RESULTS

**Characteristics of the TPBS Group Alone.** TPBS proved to be highly sensitive for the diagnosis of TKA loosening but only moderately specific for the differentiation of septic or aseptic problems. Data from 87 patients with 94 total TKAs (symptomatic  $n=79$ , asymptomatic  $n=8$ ) were included in the present study. TPBS showed true positive results for infected arthroplasty loosening in 55% and false positive results in 45% of patients. The reason for the false positive results in these patients was predominantly a strong aseptic inflammation of the TKA due to too close narrowing of the patella (retro patellar joint face) (Fig. 1). False positive results were also seen in delayed TPBS images when a slightly increased uptake was noticed in projection to the medial and lateral part of the proximal tibia in patients with micro fractures due to overweight, statical imbalance or overstressing the TKA within the first four to eight weeks after implantation ( $n=6$ ) (Fig. 2). Initial signs and symptoms of aseptic TKA loosening were correctly seen in patients fifteen months after the implantation with increased uptake at the medial and posterior part of the proximal tibia in 18/23 patients (Fig. 3), whereas only 5/23 patients had signs of loosening in the lateral and posterior part of the proximal tibia. Therefore, the sensitivity, specificity, the positive and negative predictive value and accuracy of TPBS for the detection of septic TKA loosening was 100%, 85%, 55%, 100%, and 73%, respectively.

**Characteristics of the BW 250/183 Group Alone.** BW 250/183 proved to be highly specific for the diagnosis of periprosthetic infection but BW 250/183 alone did not allow the diagnosis of aseptic TKA loosening. Ten positive BW 250/183 results were true positive: activity ratios increased by between 19% to 115% (Fig. 4). Three positive BW 250/183 results were false positive; activity ratios increased in these cases by between 12 to 35%. In two patients with aseptic loosening of the TKA, BW 250/183 correctly excluded an infection but did not allow to exclude loosening. Therefore, the sensitivity, specificity, the positive and negative predictive values and accuracy of BW 250/183 scintigraphy were calculated as 91%, 66%, 76%, 85%, 80%, respectively, for septic loosening.

**Characteristics of the Combined TPBS and BW 250/183 Group.** A statistically significant increase in overall diagnostic values over 90% for imaging TKA loosening could be achieved

when the results of the TPBS group and the BW 250/183 group were combined ( $p<0.001$ ). All patients ( $n=9$ ) false positive for infected TKA loosening with TPBS were correctly diagnosed with BW 250/183 as aseptic. On the other side, aseptic loosening of TKA missed with BW 250/183 ( $n=2$ ) was correctly diagnosed with the delayed TPBS images due to higher anatomical resolution. False positive results for BW 250/183 ( $n=3$ ) due to synovitis showed only decent increase in blood flow in projection of the synovial area, thus an infection of the TKA seemed absent with TPBS.

**Laboratory Findings.** There was a strong correlation between WBC, ESR, CRP and the results of BW 250/183 ( $p > 0.0001$ ). WBC tended to be normal in patients with moderate/mild osteomyelitis, ESR and CRP was moderately increased in these patients (Tabl. 1,3). In cases of severe osteomyelitis, WBC, ESR and CRP were significantly higher (Tabl. 1,3). CRP showed significant differences ( $p<0.0001$ ) between the classes of infection. Significant differences ( $p>0.0001$ ) were also seen for ESR and WBC between severe/moderate and severe/mild infections.

### DISCUSSION

The rate of infection following primary implantation is about 1% for hip prostheses and 2% for knee prostheses. The rates of infection following revision surgery is somewhat higher: about 3% for hip replacements and 5% for knee replacements [18]. About one-third of these infections develop within three months, another third develop within one year, and the remainder develop more than one year after surgery. At histopathological analysis, the inflammatory reaction accompanying the infected prosthesis is identical to that present in aseptic loosening, with one important difference: Neutrophils, usually absent in aseptic loosening, are invariably present in large numbers in infection [4, 7]. For this reason an increasing number of surgeons express interest in early and specific differential diagnosis between septic and aseptic TKA loosening. This study attempted to answer these questions by comparing patient outcome, laboratory and scintigraphic results, and the need for revision in patients after having received a TKA. These questions are important because, during the next few decades, the total number of TKAs performed in the United States is expected to increase more than five-fold from approximately 428,000 in 2005 to nearly 2.16 million by 2030 [21-23].

There are different publications supporting that  $^{99m}\text{Tc}$ -MDP bone scan more often gives false positive results under certain circumstances. The authors [24, 25] found that 20% of patients show an increased uptake in the asymptomatic knee one year after surgery and 12.5% at two years after surgery. It was concluded that  $^{99m}\text{Tc}$ -MDP bone scanning could not differentiate loosening from early bone remodelling.

In the present study, the number of false positive results seen with increased blood flow and mildly increased activity in the delayed images was noticed more often, leading to a low positive predictive value and an accuracy of 55% and 76%, respectively, for septic loosening. The reason for the increased blood flow was in 9/20 patients a strong inflammation of the TKA due to narrowing of the retro patellar region and the arthroplasty with consecutively strong irritation and aseptic inflammation. In 6 patients false positive results were also seen

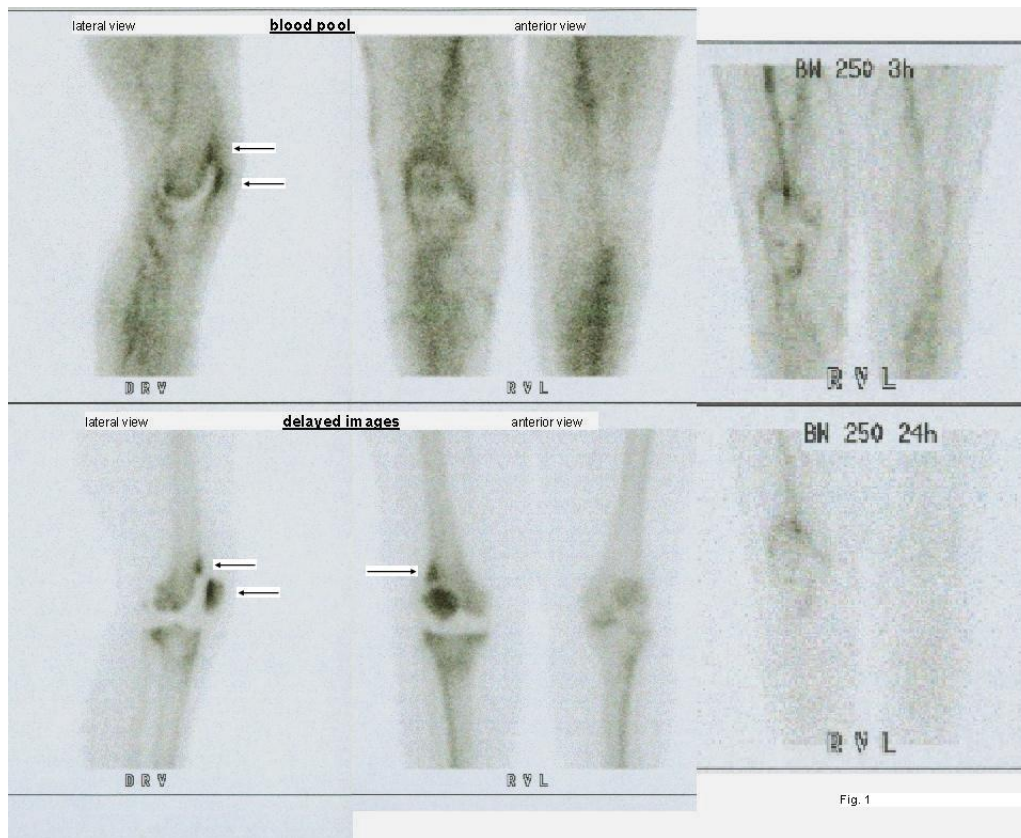


Fig. 1

**Fig. (1).** Sixty six year old female patient with increased blood flow due to postoperative narrowing of the retro patellar space. An infection was correctly excluded, the increased blood flow was decent and localized to the upper part of the patella and supra patellar region. Imaging infection with BW 250/183 showed decreasing activity over time.

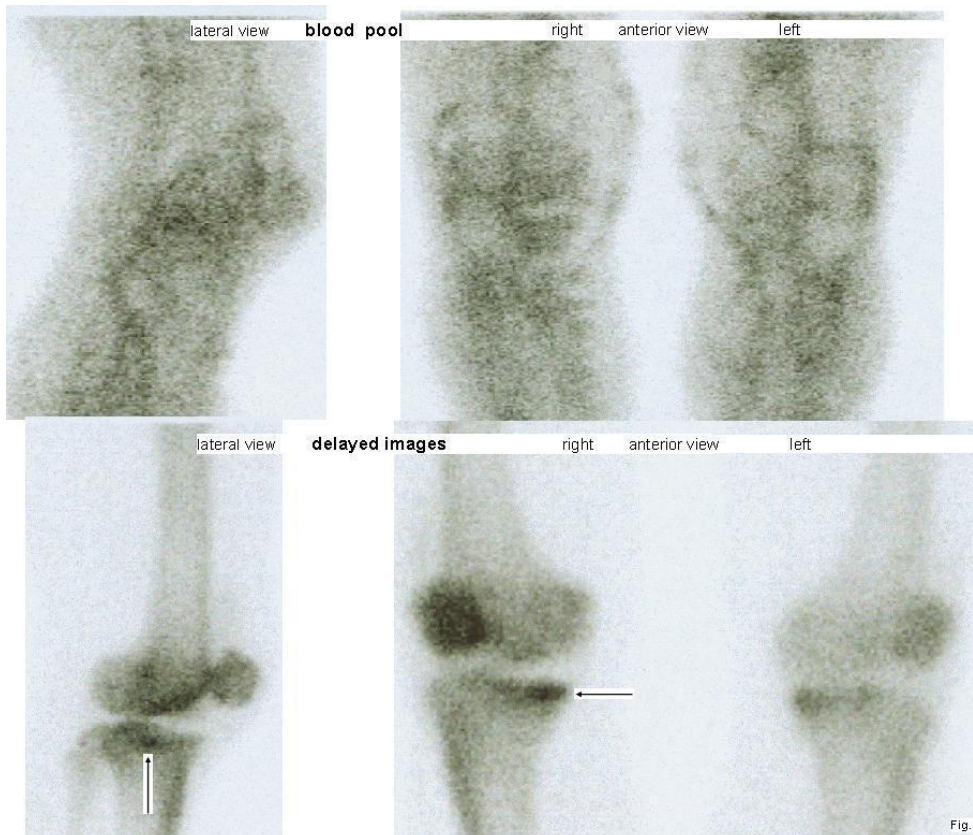
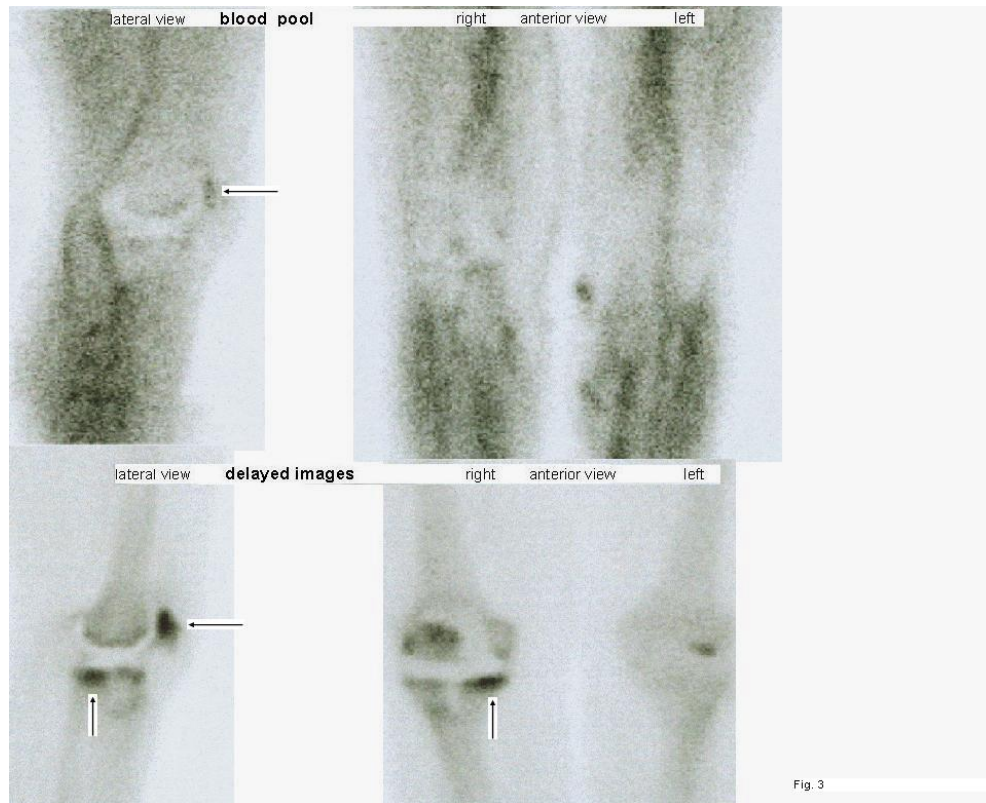
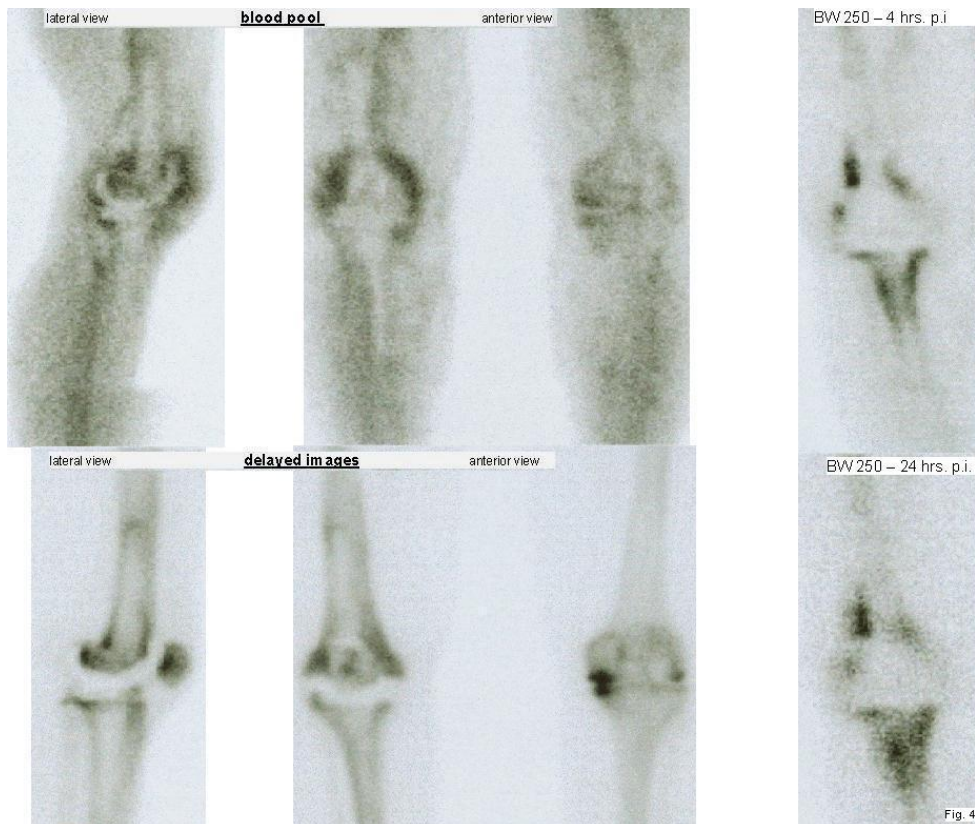


Fig. 2

**Fig. (2).** Increased uptake at the delayed TPBS of the medial and posterior part of the proximal tibia in a 57 year old male patient with micro fractures due to statically misbalance or oversteering the TKA five months after implantation.



**Fig. (3).** A 77 year old female patient with clinical signs and symptoms of aseptic TKA loosening was correctly diagnosed with TPBS showing strong increased uptake uptake at the medial and posterior part of the proximal tibia. Furthermore, the TKA synovitis was primarily due to increased blood flow at the patella and minor due to arthroplasty loosening.



**Fig. (4).** Seventy-eight year old female male patient with septic loosened TKA. Typically TPBS showed increased blood flow and increased uptake in the delayed images around the complete TKA. BW 250/183 had an activity ratio increased by 29%.

**Table 1. Description of All Patients with an Established Diagnosis of Septic Knee Arthroplasty Loosening**

Patient	Age Years	Sex	Fever (Weeks)	CRP (mg/L)	ESR (mm/h)	Leucocyte Count/mm <sup>3</sup>	Isolated Microorganism	Blood flow	Localization	BW 250/183
1	68	m	---	71	68	11300	Staph. Epiderm.	+ / + / +	Arthro.	+ / + / +
2	56	f	3	62	45	9800	Strept. Viridans	+ / + / -	Prox. tibia	+ / + / -
3	54	f	11	44	36	8800	Staph. Epiderm.	+ / + / -	Prox. tibia	+ / + / -
4	62	f	5	101	---	12250	Strept. Viridans	+ / + / +	Arthro.	+ / + / -
5	78	m	---	105	72	13200	E. Coli	+ / + / +	Arthro.	+ / + / +
6	62	f	4	---	52	---	Staph. Epiderm.	+ / + / -	Arthro.	+ / + / +
7	76	m	---	72	---	---	----	+ / - / -	Prox. tibia	+ / - / -
8	75	f	---	82	68	9400	Strept. Viridans	+ / + / +	Retro. Pat.	+ / + / -
9	59	f	---	53	54	8300	Staph. Aureus	+ / + / +	Arthro.	+ / + / +
10	83	m	4	58	---	---	Staph. Epiderm.	+ / + / +	Retro. Pat.	+ / + / -
11	84	f	---	71	66	---	Staph. Aureus	+ / + / +	Prox. tibia	+ / + / -
<b>Mean</b>	68.33	5.40	62.9	74.60	10407.00					
<b>x±s.d.</b>	8.18	1.10	10.1	15.22	1428.21					
<b>Normal Values: CRP ≤8.0mg/L, WBC 4.0-11.0x10<sup>9</sup>/L, ESR &lt;15mm/h</b>										

Abbreviations used are: CRP-C-reactive Protein, ESR- erythrocyte sedimentation rate, WBC- white blood cell count (leukocytes), Strep.: streptococcus, Staph.: staphylococcus, Epiderm.: epidermidis, Aureus: aureus, Blood flow: phase one and two of TPBS, Localization: localization of loosening or infection, Arthro.: Arthroplasty, Prox. tibia: proximal tibia, medial/lateral/posterior or anterior part of the proximal tibia, Retro. Pat.: retropatellar region, + / + / + or - / - / -: intensity of blood flow visually and + / + or - / - increase/decrease in uptake over time for BW 250/183. (Patient 7 had decent increased blood flow, strong uptake in delayed TPBS and was classified false positive with BW 250/183)

**Table 2. Statistical Evaluation of Scintigraphy with TPBS and BW 250/183 Findings in Patients with Suspected Septic Loosening of TKA**

	TPBS	BW 250/183
	Septic Loosening of Knee Arthroplasty	
Sensitivity	100%	91%
Specificity	85%	66%
Positive PV	55%	76%
Negative PV	100%	85%
Accuracy	73%	80%

Bioptical findings, intraoperative results and histology were used as gold standard for final diagnosis.

Abbreviations used are: PV: predictive value.

in delayed TPBS images when little increased uptake was noticed in projection of the medial and lateral part of the proximal tibia in patients with micro fractures due to overweight, statical misbalance or overstressing the TKA.

In all of these patients, a correct diagnosis was possible with BW 250/183 instead. BW 250/183 correctly excluded an infection in all patients with increased blood flow due to inflammation and irritation as well as in all patients with microfractures, overstressed or not completed remodelling of the TKA, which showed mild increased uptakes in the delayed <sup>99m</sup>Tc-DPD bone scan images. The explanation for this is that a significant number of cases of aseptic loosening are the result of an inflammatory-immune reaction. Histopathologic examinations of failed prostheses show a synovia-like pseudomembranous structure that develops at the cement-bone interface.

The cellular composition of the pseudomembrane is varied: Histiocytes are seen most frequently (95% of specimens), followed by giant cells (80%) and lymphocytes and plasma cells (25%). Neutrophils are present in less than 10% of cases [26-32].

Recently, there are several studies with <sup>99m</sup>Tc-HMPAO-labelled leukocytes and <sup>99m</sup>Tc-labelled anti-granulocyte antibodies for imaging infection of hip and knee arthropathies (16, 15). Generally, when <sup>99m</sup>Tc-HMPAO-labelled leukocytes and <sup>99m</sup>Tc-labelled anti-granulocyte antibodies were used without other radionuclides or radiographic images, interpretation of these studies had been based on either the intensity of periprosthetic labelled leukocyte/antigranulocyte antibody activity in comparison with various reference points or a grading system of periprosthetic uptake ( . The reported sensitivity of the procedure using these criteria was generally between 50% and 100%, and its specificity was between 45% and 100% with low percentages of diagnostic accuracy. An increase of diagnostic accuracy could be achieved when using the quantitative evaluation of granulocyte migration as described by Klett [1] *et al.* The employed quantitative interpretation of the time-activity course requires migration of antibody-labelled circulating granulocytes into the inflamed focus. While there is also non-specific extravasation of the free antibody into inflamed areas, accumulation of activity in the inflamed focus is largely caused by this specific mechanism. Our data of the present study give similar results as the data presented by Klett *et al.* [1] with respect to a high sensitivity of 91% and a negative predictive value of 85%. Instead, differences were seen with a specificity of 66%; these results are lower as compared with the data of Klett *et al.* in a similar patient population and comparable with other studies [20-25]. The reason for this are 3 patients with false positive results due to unspecific synovitis.

**Table 3. Description of All Patients with False Positive Increased Blood Flow Due to Narrowing of the Retro patellar Region (n=7) and Aseptic Loosening of TKA (n=2)**

Patient	Age Years	Sex	Fever (Weeks)	CRP (mg/L)	ESR (mm/h)	Leucocyte Count/mm <sup>3</sup>	Localization	Blood Flow	BW 250/183
1	71	m	----	33	9	-----	Retro. Pat.	+/+/+	+/-/-
2	85	m	----	44	7	-----	Retro. Pat.	+/+/+	+/-/-
3	66	f	----	48	----	3500	Retro. Pat.	+/-/+	+/-/-
4	49	f	----	56	22	2800	Arthro.	+/+/-	+/-/-
5	74	f	2	34	31	3600	Retro. Pat.	+/+/+	+/-/-
6	69	f	3	39	18	4200	Arthro.	+/+/-	+/-/-
7	72	f	----	51	----	----	Retro. Pat.	+/+/+	+/-/-
8	81	m	----	39	----	----	Retro. Pat.	+/+/+	+/-/-
9	67	f	3		19	2500	Retro. Pat.		
<b>Mean</b>	70.34	2.6	17.6	3320.00					
<b>x±s.d.</b>	19.65	0.45	9.04	560.40					
<b>Normal Values: CRP ≤8.0mg/L, WBC 4.0-11.0×10<sup>9</sup>/L, ESR &lt;15mm/h</b>									

Abbreviations used are: CRP-C-reactive Protein, ESR- erythrocyte sedimentation rate, WBC- white blood cell count (leukocytes), Retro. Pat.: narrowing of the retro patellar region and the arthroplasty, Arthro.: Arthroplasty, Blood flow: phase one and two of TPBS, +/+/+ or -/-/-: intensity of blood flow visually and +/+ or -/- increase/decrease in uptake over time for BW 250/183.

**Table 4. Overall Statistical Analysis of TPBS and BW 250/183 in Patients with Suspected Septic and Aseptic Loosening of TKA**

TPBS/BW 250/183	Overall Statistics
Sensitivity	94%
Specificity	88%
Positive PV	89%
Negative PV	95%
Accuracy	89%

If considered separately, in the present study, TPBS and BW 250/183 showed considerably high numbers of false positive results of nine and three patients, respectively. Statistically, these false positive results lead to low positive predictive values for TPBS and BW 250/183 with 55% and 76%, respectively, and a comparably low diagnostic accuracy of in between 73 and 80%. A significant increase in positive predictive values and diagnostic accuracy of more than 90% for imaging TKA loosening could be achieved in the present study, when the results of the TPBS group and the BW 250/183 group were combined. All patients (n=9) who were false positive for infected TKA loosening with TPBS were correctly diagnosed as aseptic with BW 250/183. On the other hand, aseptic loosening of TKA missed with BW 250/183 (n=2) was correctly diagnosed with the delayed TPBS images due to higher anatomical resolution. False positive results for BW 250/183 (n=3) due to synovitis showed only decent increase in blood flow in projection to the synovial area, thus an infection of the TKA seemed absent with TPBS. Furthermore, one patient with low grade infection after year long antibiotic therapy missed with BW 250/183 showed almost normal blood flow with TPBS but strong uptake in the delayed TPBS scans, thus a chronic septic TKA loosening was suspected. The combination of both imag-

ing modalities gave comparable results with PET for septic arthropathies and better results as described in the literature for conventional radiography [25], CT or MRI [4] when considered alone. In case of aseptically loosened arthropathies, the combination of TPBS and BW 250/183 is even superior as compared to PET [30-38].

As compared with CT, MRI and PET, the combination of TPBS and BW 250/183 is less expensive and gives reliable and fast results within two to three days. For this reason the combination of TPBS and BW 250/183 has proven to be an important tool for imaging infection which allows specific differentiation between septic and aseptically loosened arthropathies.

## CONCLUSION

TPBS and BW 250/183 alone are useful in the assessment of painful TKA. TPBS is highly sensitive for the diagnosis of arthroplasty loosening, whereas BW 250/183 allows specific diagnosis of periprosthetic infection. Both methods alone have high negative predictive values, but the combination of both is complementary and increases in diagnostic accuracy and positive predictive value for final diagnosis of TKA loosening.

## REFERENCES

- [1] Klett R, Kordelle J, Stahl U, Khalisi A, Puille M, Steiner D, Bauer R. Immunoscintigraphy of septic loosening of knee endoprosthesis: a retrospective evaluation of the antigranulocyte antibody BW 250/183. *EJNM*. 2003; 30: 1463-1466.
- [2] Steinberg DR, Steinberg ME. The early history of arthroplasty in the United States. *Clin Orthop* 2000; 374: 55-89.
- [3] Daniels AU, Tooms RE, Harkess JW. Arthroplasty: introduction and overview. In: Canale ST, eds. *Campbell's operative orthopaedics*. 9th ed. St Louis, Mo: Mosby, 1998; 211-227.
- [4] Harkess JW. Arthroplasty of hip. In: Canale ST, eds. *Campbell's operative orthopaedics*. 9th ed. St Louis, Mo: Mosby, 1998; 296-456.
- [5] Guyton JL. Arthroplasty of ankle and knee. In: Canale ST, eds. *Campbell's operative orthopaedics*. 9th ed. St Louis, Mo: Mosby, 1998; 232-285.

- [6] Deep infections of total joint replacement. Publication no. PA-00-014 Bethesda, Md: National Institutes of Health, December 1999.
- [7] Palestro CJ. Scintigraphic evaluation of infected hip and knee replacements. In: Thrall JH, eds. Current practice of radiology. St Louis, Mo: Mosby, 1993; 367-371.
- [8] Palestro CJ, Torres MA. Radionuclide imaging in orthopedic infections. *Semin Nucl Med* 1997; 27: 334-345.
- [9] Sugawara Y, Braun DK, Kison PV, Russo JE, Zasadny KR, Wahl RL. Rapid detection of human infections with F-18 fluorodeoxyglucose and positron emission tomography: preliminary results. *Eur J Nucl Med* 1998; 25: 1238-1243.
- [10] Zhuang H, Duarte PS, Pourdehnad M, *et al.* The promising role of 18F-FDG PET in detecting infected lower limb prosthesis implants. *J Nucl Med* 2001; 42: 44-48.
- [11] Gratz S, Oestmann JW, Dörner J, *et al.* Pretreated Vertebral Osteomyelitis: Evaluation with Gallium-67-Citrate SPECT *Nucl Med Comm* 2000; 21: 111-120.
- [12] Pelosi E, Baiocco C, Pennone M, *et al.* 99mTc-HMPAO-Leukocyte Scintigraphy in Patients with Symptomatic Total Hip or Knee Arthroplasty: Improved Diagnostic Accuracy by Means of Semiquantitative Evaluation *J Nucl Med* 2004; 45: 438-444.
- [13] Klett F, Steiner D, Puille M, *et al.* Antigranulocyte scintigraphy of septic loosening of hip prosthesis: influence of different analyzing methods. *Nuklearmedizin* 2001; 40: 75-79.
- [14] Mirra JM, Marder MD, Amstutz HC. The pathology of failed total joint arthroplasty. *Clin Orthop* 1982; 170: 175-183.
- [15] Becker W, Dölkemeyer U, Gramatzki M, Schneider M, Scheele J, Wolf F. Use of immunoscintigraphy in the diagnosis of fever of unknown origin. *Eur J Nucl Med* 1993; 20: 1078-1083.
- [16] Schwartz A., Steinsträsser A. A novel approach to Tc-99m-labelled monoclonal antibodies. *J Nucl Med* 1987; 28: 721.
- [17] Gratz S, Göbel D, Behr TM, Herrmann A, Becker W Correlation between the radiation dose, synovial thickness and the efficacy of radiosynoviothecsis *J Rheumatol* 1999; 26: 1242-1249.
- [18] Deep infections of total joint replacement. Publication no. PA-00-014 Bethesda, Md: National Institutes of Health, December 1999.
- [19] Harris WH, Sledge CB. Total hip and total knee replacement (1). *N Engl J Med* 1990; 323: 725-731.
- [20] Harris WH, Sledge CB. Total hip and total knee replacement (2). *N Engl J Med* 1990; 323: 801-807.
- [21] Maloney WJ, Smith RL. Periprosthetic osteolysis in total hip arthroplasty: the role of particulate wear debris. *J Bone Joint Surg Am* 1995; 77: 1448-1461.
- [22] Wooley PH, Nasser S, Fitzgerald RH, Jr. The immune response to implant materials in humans. *Clin Orthop* 1996; 326: 63-70.
- [23] Toumbis CA, Kronick JL, Wooley PH, Nasser S. Total joint arthroplasty and the immune response. *Semin Arthritis Rheum* 1997; 27: 44-47.
- [24] Hanssen AD, Rand JA. Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. *J Bone Joint Surg Am* 1998; 80: 910-922.
- [25] Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. *J Bone Joint Surg Am* 1996; 78: 512-523.
- [26] Della Valle CJ, Bogner E, Desai P, *et al.* Analysis of frozen sections of intraoperative specimens obtained at the time of reoperation after hip or knee resection arthroplasty for the treatment of infection. *J Bone Joint Surg Am* 1999; 81: 684-689.
- [27] Duus BR, Boeckstyns M, Stadeager C The natural course of radionuclide bone scanning in the evaluation of total knee replacement--a 2 year prospective study. *Clin Radiol.* 1990; 41: 341-343.
- [28] Hofmann AA, Wyatt RW, Daniels AU, Armstrong L, Alazraki N, Taylor A Jr. Bone scans after total knee arthroplasty in asymptomatic patients. Cemented versus cementless. *Clin Orthop Relat Res.* 1990; 251: 183-188.
- [29] Kantor SG, Schneider R, Insall JN, Becker MW. Radionuclide imaging of asymptomatic versus symptomatic total knee arthroplasties. *Clin Orthop Relat Res.* 1990; 260: 118-123.
- [30] Gomez-Luzuriaga MA, Galan V, Villar JM. Scintigraphy with Tc, Ga and In in painful total hip prosthesis. *Int Orthop* 1988; 12: 163-167.
- [31] Pring DJ, Henderson RG, Rivett AG, Krausz T, Coombs RRH, Lavender JP. Autologous granulocyte scanning of painful prosthetic joints. *J Bone Joint Surg Br.* 1986; 68: 647-652.
- [32] Schauwecker DS. The scintigraphic diagnosis of osteomyelitis. *AJR.* 1992; 158: 9-18.
- [33] Steinstrasser A, Berberich R, Kuhlmann L, Zabori S, Schwarz A. Binding of the monoclonal antibody BW 250/183 to human granulocytes *Nucl Med* 1992; 31: 57-63.
- [34] Spangehl MJ, Younger AS, Masri BA, Duncan CP. Diagnosis of infection following total hip arthroplasty. *Instr Course Lect* 1998; 47: 285-295.
- [35] Mumme T, Reinartz P, Alfer J, Muller-Rath R, Buell U, Wirtz DC. Diagnostic values of positron emission tomography versus triple-phase bone scan in hip arthroplasty loosening. *Arch Orthop Trauma Surg.* 2005; 125: 322-329.
- [36] Stumpe KD, Romero J, Ziegler O, *et al.* The value of FDG-PET in patients with painful total knee arthroplasty. *Eur J Nucl Med Mol Imaging.* 2006; 33: 1218-1225.
- [37] Toermaenen J, Tervonen O, Koivula A, Junila J, Suramo I. Image technique optimization in MR imaging of a titanium alloy joint prosthesis. *J Magn Reson Imaging* 1996; 6: 805-811.
- [38] Delank ST, Schmidt M, Michael P, Dietlein M, Schicha H, Eysel P. The implications of 18F-FDG PET for the diagnosis of endoprosthetic loosening and infection in hip and knee arthroplasty: Results from a prospective, blinded study. *BMC Musculoskelet Disord* 2006; 7: 20. Published online 2006 March 3. doi: 10.1186/1471-2474-7-20.