Diagnosis of peri-prosthetic infection at the hip using triple-phase bone scintigraphy

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We evaluated triple-phase bone scintigraphy in the differential diagnosis of peri-prosthetic infection in 46 patients with a total hip replacement or bipolar hemiarthroplasty who were due for revision surgery. There were 18 men and 28 women, with a mean age at operation of 64.6 years (28 to 81). We defined peri-prosthetic infection as an increased uptake of radioisotope in all the phases of triple-phase bone scintigraphy and validated these results against the histological and/or microbiology results in every case.

The positive and negative predictive values for the presence of infection were 83% and 93%, respectively. The diagnostic sensitivity was 88% and the specificity was 90%.

This study indicates that triple-phase bone scintigraphy is a useful tool in the detection of peri-prosthetic infection and offers a cost-effective method of screening.

Bacterial infection is a possible cause of loosening of an implant in total hip replacement (THR). The differentiation of infection from aseptic loosening is of great importance because loosening with peri-prosthetic infection is a catastrophic complication. Although the differential diagnosis of the two conditions is essential to the success of further revision surgery, the detection of peri-prosthetic infection remains difficult. Although one-stage revision surgery is indicated for patients with aseptic loosening, two-stage revision surgery, in which implantation after eradication of infection by several surgical steps including removal of the implants, debridement and antibiotics-loaded cement beads, is usually required for the patients with peri-prosthetic infection. Radiographs reveal signs of loosening regardless of the presence of infection. Blood screening investigations may sometimes fail to detect bacterially-induced inflammation. Although MR or enhanced CT scans generally provide useful information, metal implants in patients with a THR interfere with the quality of the images obtained. Examination of tissue cultures can demonstrate bacteria, but undertaking biopsies in every patient with prosthetic loosening is unrealistic. Other diagnostic tools are required to diagnose peri-prosthetic infection.

Triple-phase bone scintigraphy has previously been used for the diagnosis of deep infections and we have used it to detect peri-prosthetic infection since 1999. The aim of this study was to evaluate the clinical effectiveness of this technique in the diagnosis of peri-prosthetic infection in THR.

Patients and Methods
A consecutive series of 46 patients with a THR, scheduled to undergo revision or removal of an implant for indications including recurrent dislocation and aseptic or septic loosening, were examined using triple-phase bone scintigraphy. There were 18 men and 28 women, with a mean age at operation of 64.6 years (28 to 81). The patients were allocated to one of two groups: infection and non-infection. There were 17 patients allocated to the infection group. The criteria for inclusion in this group were a positive peri-prosthetic tissue culture obtained during the revision surgery or open biopsy of the hip, acute inflammation as seen on histological examination by a clinical pathologist (TH) of either frozen sections of peri-prosthetic tissue, or fixed tissues, and visibly purulent synovial fluid in the joint or the area surrounding the prosthesis, according to the criteria of Trampuz et al. The non-infection group comprised 29 patients, in whom none of the diagnostic criteria for infection were present, and who had no more than five neutrophils in any high-powered field on frozen section.

Of the 17 patients in the infection group, there were ten men and seven women, with a mean age at operation of 57 years (38 to 78). MRSA was detected in ten patients, staphylo-
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Coccus epidermis in three, mycobacterium tuberculosis in one and other bacteria in three (enterococcus faecalis, streptococcus, pseudomonas aeruginosa). Nine of the patients had undergone THR and eight had bipolar hemiarthroplasties. These had been performed for fracture of the femoral neck in seven patients, osteonecrosis of the femoral head in four, osteoarthritis (OA) in four and other causes (bone tumour and rheumatoid arthritis (RA)) in two. In nine patients loosening of the acetabular component in a THR or central migration of the bipolar hemiarthroplasty had occurred and in nine, loosening of the femoral component had developed. There were 16 patients who had removal of the implant; secondary reconstruction was performed in five, and 11 were left with an excision arthroplasty. One patient had a biopsy but no revision.

Of the 29 patients in the non-infection group, there were eight men and 21 women, with a mean age at operation of 67.5 years (28 to 81). Previous surgery had been for OA in 19 patients, a fracture of the femoral neck in five and other causes in five (bone tumours in two, RA in one and osteonecrosis of the femoral head in two). Total hip replacement had been performed in 21 patients and bipolar arthroplasty in eight. In this group, there was loosening of the acetabular component in a THR or central migration of a bipolar hemiarthroplasty in 23 patients. The other six did not have loosening of the acetabular component. Acetabular revision was performed in all 23 patients, and 13 patients with loosening of the femoral component had it revised. In five patients exchange of the femoral modular head and polyethylene insert was performed, and one patient was left with an excision arthroplasty.

The bone scintigraphy images were obtained after injecting technetium-99m-labelled (body weight > 70 kg; 740 mBq (1.5 ml); body weight ≤ 70 kg, 555 mBq (1 ml)) diphosphonate and using a SNR-5100R gamma camera (Shimadzu Science Corporation, Kyoto, Japan). There were three phases; the blood flow phase was immediately after infusion of the tracer; the blood pool phase was between 3 and 5 minutes later, and the late phase between 3 and 4 hours after infusion. Using bi-planar digital images, the density of the region of interest in question was measured using the public domain National Institute of Health Images program (US Government), and the density of the region of interest was expressed as a percentage compared with the gradation in the femoral artery for the blood flow phase, the femoral vein for the blood pool phase, and the anterior iliac crest for the late phase. Increased uptake of the isotope in the blood flow and blood pool phases was noted when the density was ≥ 75% of the gradation in the femoral artery and femoral vein, respectively. Increased uptake of the isotope in the late phases was noted when the density was equivalent to, or greater than, 90% of gradation in the anterior iliac crest. The abnormal density could be compared without quantification with the control side. The scintigraphy results were also evaluated by an expert radiologist (KF). In the patients with bilateral hip arthroplasties, the symptomatic side could be compared with the contralateral asymptomatic hip. We defined a triple-phase bone scintigraphy as positive when all three phases demonstrated increased radio-isotope uptake, suggesting peri-prosthetic infection. The scintigraphy was performed at a mean of 8.5 years (1 month to 28 years) after the primary THR, with only four patients examined within six months of the implantation.

The chi-squared test for independence was employed for statistical analysis. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were examined and compared between the infection and non-infection groups using the Mann-Whitney test. A p-value of < 0.05 was considered statistically significant.

Results
Of the 17 patients in the infection group, 15 (88%) were found to be positive according to triple-phase bone scintigraphy (Fig. 1), whereas only three (10%) of the 29 patients in the non-infection group were positive, with no increase in uptake observed during the blood flow phase in the remaining 26 (Fig. 2). These results indicate that triple-phase bone scintigraphy has a sensitivity for detecting infection of 88%, with only two patients from the infection group having no uptake during the blood flow phase, a specificity of 90%, and an accuracy of 89%.

The positive predictive value, i.e. the number of patients found to be infected (n = 15) divided by the number who had positive scintigraphy (n = 18), was 83%. The three patients falsely-positive on scintigraphy had all undergone multiple operations including femoral osteotomy and THR. As 26 of the 28 negative patients were later found to have no infection, the negative predictive value was 93%. One of the two remaining patients who had negative scintigraphy had a peri-prosthetic infection with mycobacterium tuberculosis. The relationship between the incidence of peri-prosthetic infection and positive scintigraphy was statistically significant (chi-squared test, p = 0.003). The patients who had a previously fractured neck of femur had positive and negative predictive values of 86% and 80%, respectively, together with 86% sensitivity, 80% specificity and 83% accuracy. Those without fractures had positive and negative predictive values of 82% and 96%, respectively, and 90% sensitivity, 92% specificity and 91% accuracy. In 36 patients who had undergone operations more than two years earlier in isolation, the positive and negative predictive values were 77.8% and 96.3%, respectively, and the sensitivity was 87.5%, specificity was 92.9% and accuracy was 92%.

In the infection group, the ESR of the 17 patients was increased to a mean of 36.7 mm/hr standard deviation (SD 23.2). This was greater than the mean in the non-infection group of 19.4 mm/hr (SD 17.5) (Mann-Whitney, p = 0.04). It was difficult to differentiate between the two groups on the basis of the ESR as there was much overlapping of individual values between the two groups (Fig. 3). Further
more, there was no significant difference in the level of CRP between the two groups (Fig. 4 infection group (mean 2.43, SD -3.17; non-infection group (mean 0.81, SD -1.25, p = 0.17)). In the infection group, six of the seven patients who had CRP values in the normal range had scintigraphy. In contrast, in the non-infection group, seven patients with an elevated CRP had negative scintigraphy.

All the patients in the infection group had an increased radio-isotope uptake in the blood pool phase. In total, 14 (48%) patients in the non-infection group also had an increased uptake in the pool phase, and all 46 patients had increased uptake in the late phase.

Discussion
Our current knowledge of the management of patients with peri-prosthetic infections has recently been reviewed by Toms et al. It is important to differentiate peri-prosthetic infection from mechanical loosening. Persistent and resting pain give important clues in the diagnosis of peri-prosthetic infection. Although elevation of the ESR and CRP are also signs of infection, some patients in the infection group had normal CRP levels whereas in the non-infection group in some the level was elevated. Although a combination of CRP and interleukin-6 was recently reported to be effective in the screening of peri-prosthetic infection, the positive predictive values of this examination were not high (PPV = 0.72).

Plain radiographs can detect peri-prosthetic osteolysis and radiolucent lines, but this has a low diagnostic value. CT and MR scans are affected by metal implants. Conventional bone scintigraphy may reveal increased isotope uptake not only in infection, but also in the presence of mechanical loosening.

Triple-phase bone scintigraphy has been used to diagnose osteomyelitis. In this setting, the sensitivity was reported as 94% and specificity was 95%, when positive results during the blood flow, blood pool and late phase were interpreted as indicative of infection. Rubello et al reported 100% sensitivity and specificity for triple-phase bone scintigraphy in two patients with prosthetic implants, and Reinartz et al found that the sensitivity and specificity of triple-phase bone scintigraphy was 68% and 76%, respectively, in a series of eight patients with peri-prosthetic infection. However, in these reports, the authors defined infection as showing positive results for the blood pool and late phases only. We followed Schauwecker and took peri-
prosthetic infection to be indicated only when isotope uptake was increased in all three phases.

Our study found that positive results of triple-phase bone scintigraphy were related to peri-prosthetic bacterial infection, with positive and negative predictive values of 83% and 93%, respectively, and 88% sensitivity, 90% specificity and 89% accuracy. However, there were demographic differences between the infection and the non-infection groups. The infection group contained seven of the 12 patients who had a previously fractured neck of the femur, whereas 24 of the 34 patients without a previous fracture were included in the non-infection group. An assessment of the effect of the differences in group make-up on the diagnostic accuracy revealed that the patients who had a fracture had positive and negative predictive values of 86% and 80%, respectively, together with 86% sensitivity, 80%
specificity and 83% accuracy, whereas those without fractures had positive and negative predictive values of 82% and 96%, respectively, and 90% sensitivity, 92% specificity and 91% accuracy. As the results of triple-phase bone scintigraphy have been suggested to remain positive even in the absence of peri-prosthetic infection for two years following surgery the 36 patients who had undergone operations more than two years earlier were studied in isolation. Of these, eight had peri-prosthetic infection and 28 were without infection. In this analysis the positive and negative predictive values were 77.8% and 96.3% respectively, and the sensitivity was 87.5%, specificity was 92.9% and accuracy was 92%.

Positron-emission tomography has been used for the differential diagnosis of a painful THR. Although it has proven useful in diagnosing malignant tumours, it is not thought to be sensitive enough to distinguish between infected and non-infected implants. Furthermore, it is expensive and remains limited to a few institutions, whereas triple-phase bone scintigraphy is widely available and inexpensive.

We found that a negative triple-phase bone scintigraphy result suggests a low probability of peri-prosthetic infection and one-stage revision could be considered. In contrast, when the triple-phase bone scintigraphy is positive, it is prudent to perform histological examination and tissue culture to identify infection. The presence of organisms or infiltration of more than five neutrophils per high-power field in frozen sections was taken as indicative of infection.

We believe that the results of this study have shown triple-phase bone scintigraphy to be useful for the detection of peri-prosthetic infection, as serological examinations such as CRP and ESR, and radiological findings are not always reliable in the detection of peri-prosthetic infection.

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References