Radionuclide imaging of the painful hip arthroplasty

POSITRON-EMISSION TOMOGRAPHY VERSUS TRIPLE-PHASE BONE SCANNING

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Two major complications of hip replacement are loosening and infection. Reliable differentiation between these pathological processes is difficult since both may be accompanied by similar symptoms. Our aim was to assess the diagnostic ability of triple-phase bone scanning (TPBS) and positron-emission tomography (PET) to detect and differentiate these complications in patients with a hip arthroplasty. Both TPBS and PET were performed in 63 patients (92 prostheses). The radiotracer for PET imaging was ^{18}F -fluorodeoxyglucose (FDG). Image interpretation was performed according to qualitative and quantitative criteria although the final diagnosis was based upon either surgical findings or clinical follow-up.

The sensitivity, specificity and accuracy of PET was 0.94, 0.95 and 0.95 respectively, compared with 0.68, 0.76 and 0.74 for TPBS. We found that an image interpretation based exclusively upon quantitative criteria was inappropriate because of its low selectivity. The histological examination indicated that increased periprosthetic uptake of FDG in patients with aseptic loosening was caused by wear-induced polyethylene particles and the subsequent growth of aggressive granulomatous tissue.

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Although total hip arthroplasty (THA) is one of the most frequently performed operations and is largely successful, complications do occur in many patients. Up to 8% of all arthroplasties are revisions, of which nearly 70% are for loosening.¹⁻⁵ After loosening, infection of a prosthesis is the next most common complication.^{5,6} It may be difficult to distinguish between these two complications since both can be accompanied by similar symptoms.⁷ A solution to this diagnostic problem is clearly important since infection and loosening each require a fundamentally different therapeutic approach. One well-established diagnostic procedure which is used to differentiate between causes of a painful THA is triple-phase bone scanning (TPBS).⁸⁻¹² Recently, positron-emission tomography (PET) with ^{18}F -fluorodeoxyglucose (FDG) has also been reported to be useful for diagnosing complications after THA.¹³⁻¹⁷ PET is a high-resolution imaging technique which identifies the energy consumption of different tissues three-dimensionally. However, there are no consistent assessment criteria in the literature. Some authors recommend interpretation based upon specific patterns of result,¹³⁻¹⁵ whereas others consider that the level of uptake of FDG is an important diagnostic criterion.¹⁷

Our aim therefore was to investigate whether PET or TPBS was more useful for the diagnosis of complications after THA. Particular emphasis was placed on the ability of both methods to differentiate between loosening and infection. To this end, the scans were interpreted according to specific patterns of result which were developed after consideration of existing data and our own observations. The significance of the level of uptake of FDG was also assessed. Finally, the cause for any increased uptake of FDG was investigated histologically since no definitive conclusion has been offered to explain the periprosthetic accumulation of FDG in patients with aseptic loosening in THA.

Patients and Methods

Our series comprised of 63 consecutive patients (32 men, 31 women) with a mean age of 68 ± 9.8 years (43 to 88) who were examined between January 2001 and March 2003. The study was approved by the local ethical board and all patients gave their informed consent before their inclusion. In 29 patients (46.0%), both hips had been replaced, giving a total of 92 arthroplasties in the study (48 right, 44 left). Of these, 60 (65.2%) were cemented and 32 (34.8%) were cementless. All the patients

Table I. Patterns of PET^{*} findings and their clinical correlates in patients with a THA

Pattern	Description	Clinical correlation
1	No increased uptake of FDG [†] in the prosthesis-tissue interface	No loosening
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	
3b	Increased uptake of FDG in the area of the femoral neck and in parts of the prosthesis-bone interface of the proximal stem	
3c	Pattern 3a and 3b	Loosening
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	
4c	Pattern 4a and 4b	
5	Uptake of FDG in the periprosthetic soft tissue	Infection

* PET, positron-emission tomography

†FDG, ¹⁸F-fluorodeoxyglucose

were investigated because of increasing pain in the region of at least one arthroplasty, with 64 hips (69.6%) being symptomatic and 28 (30.4%) asymptomatic. Since non-specific uptake of tracer can occur in the periprosthetic region immediately after arthroplasty,¹⁸ only those patients whose operation had taken place at least six months before their PET scan were included. The mean time interval between operation and PET examination was 9.8 ± 6.8 years in patients with symptomatic arthroplasties (cemented, mean 10.2 ± 7.3 (1 to 31); cementless, mean 8.1 ± 4.2 (1 to 12)), and 8.3 ± 4.1 years in those who were asymptomatic (cemented, mean 8.7 ± 3.8 , (2 to 18); cementless, mean 4.7 ± 3.8 , (2 to 12)).

Thirty-six arthroplasties (39.1%) were revised. For these, the final diagnosis was based upon intra-operative findings as well as histological examination and microbiological cultures. The remaining 56 (60.9%) which were not revised were followed up clinically between nine and 18 months. During this follow-up, clinical assessments, plain radiography, and laboratory tests were performed. Arthroplasties which did not require revision or treatment with antibiotics during the follow-up period were considered to be uninfected and stable. In order to minimise bias, the orthopaedic surgeons were blinded to the results of both PET and TPBS. The type of treatment was chosen solely on the basis of radiological examinations, laboratory tests and clinical assessment.

PET. All patients were examined 58 ± 8 minutes after intravenous administration of 283 ± 38 MBq of FDG using a dedicated full-ring PET scanner (Siemens ECAT Exact 922/47; Siemens-CTI, Knoxville, Tennessee). Imaging was performed bilaterally from the upper pelvis to the distal femora. Before examination, all patients fasted for at least ten hours, which was verified by determination of the blood glucose level. The acquisition time was 12 minutes per bed position with a transmission time of four minutes each. Attenuation-corrected images were reconstructed by using an iterative ordered subsets-expectation maximisation

algorithm (OSEM). Transverse, coronal, and sagittal slices 7 mm thick were used for the qualitative interpretation of images. This was undertaken by two experienced and board-certified nuclear medicine physicians (PR, UB) who were blinded to the results of other examinations and clinical data. A consensus was reached by discussing each case.

Qualitative interpretation of the PET scans took into account the five different patterns of result which are described in Table I. These patterns were determined in a pre-study training cohort of 20 patients who had undergone revision after their scan. During that training period, the PET findings (Fig. 1) were directly compared with the results of surgical intervention. The development of the patterns used in our study is partly based on our own observations during that training period and partly on data from the literature.^{13-15,17} No patient from the pre-study training cohort was included in the present study.

Standardised uptake value. The standardised uptake value is defined as the regional concentration of tissue radioactivity, normalised for injected dose and body-weight.¹⁹ It is a semiquantitative parameter which does not require any arterial blood sampling and allows the estimation of the relative glucose consumption within a defined region of interest. In our study, the mean standardised uptake value was calculated for the lesion which had the highest uptake of FDG for each arthroplasty. The appropriate lesion was determined visually using a monochrome colour scale. A correction for partial volume effects was applied in order to achieve a higher level of accuracy, especially for small lesions.

TPBS. In addition to PET, all patients underwent TPBS. The time between PET and TPBS was a maximum of three weeks, although in 44 patients (69.8%) both examinations were performed within 24 hours. Acquisitions were performed after intravenous administration of 733 ± 44 MBq of ^{99m}Tc-labelled hydroxymethylene diphosphonate (HDP) using a double-head gamma camera equipped with low-energy/high-resolution parallel hole collimators (Siemens

Fig. 1

Typical patterns (see Table I) for PET (coronal slices, anterior view) showing: a) left hip, pattern 1, no loosening; b) both hips, pattern 2, no loosening; c) right hip, pattern 3a, no loosening; d) left hip, pattern 4a, loosening of the cup; e) right hip, pattern 4b, loosening of the stem; left hip, pattern 3a, no loosening; and f) both hips, pattern 5, infection and loosening of the right acetabular component.

ECAM; Siemens, Erlangen, Germany). A dynamic scan of the arterial flow was acquired immediately after administration of HDP (20 frames, nine seconds each). In addition, two static blood pool images, with an acquisition time of three minutes each, were obtained during the third and sixth minutes of the examination. Whole-body scans were acquired 176 ± 17 minutes after injection. Interpretation of the scans was undertaken according to the criteria described by Wilson.²⁰ Loosening of the stem was assumed in patients with significant, pathological uptake of HDP in the area of the tip in combination with, at least, a second substantial lesion in the region of the lesser trochanter. Loosening of the cup was diagnosed in those with continuous, pathological uptake of HDP at the cup-bone interface. Finally, infection was assumed in patients in whom both the bone scan and the blood pool images showed substantial pathological uptake at the prosthetic interfaces. Typical TPBS findings are shown in Figure 2.

Fig. 2

Typical patterns of TPBS (left column, anterior view of blood pool acquisition six minutes after injection; right column, anterior view of bone scan) showing: a) left hip arthroplasty without pathological findings; b) loosening of the left hip arthroplasty (negative blood pool, increased uptake on the bone scan); and c) infection of the right hip arthroplasty with a distinctly positive blood pool and bone scan.

Statistical analysis. Statistical analysis was performed using Excel 97 (Microsoft, Redmond, Washington) and SPSS for Windows, release 10.0 (SPSS Inc, Chicago, Illinois). Results were expressed as the mean $\pm$ SD. Significance was tested using the non-parametric Mann-Whitney test for unpaired samples. A p value of less than 0.05 was considered to be significant.

Results

In 26 of the 92 arthroplasties (28.3%), revision confirmed loosening of at least one component (cup, 10; stem, 4; and cup and stem 12). The loose components were revised. Eight arthroplasties (8.7%) were infected and an excision arthroplasty was performed. In two patients (2.2%), surgical intervention revealed a stable, uninfected prosthesis, but with a severe abrasion of the polyethylene liner. In these cases only the worn liner was replaced. For the remaining 56 arthroplasties (60.9%), neither infection nor loosening was diagnosed during the follow-up period.

An initial analysis of the data was performed in order to determine the ability of PET and TPBS to diagnose pathological processes within THAs, but without differentiating between loosening and infection. These results are shown in

Table II. Analysis of the ability of PET and TPBS to detect pathological processes within hip arthroplasties but without differentiating between loosening and infection

	PET [*]	TPBS [†]
True positive	32	27
True negative	56	51
False positive	2	7
False negative	2	7
Total	92	92
Sensitivity	0.94	0.79
Specificity	0.97	0.88
Negative predictive value	0.97	0.88
Positive predictive value	0.94	0.79
Accuracy	0.96	0.85

* PET, positron-emission tomography

† TPBS, triple-phase bone scanning

Table III. Analysis of the ability of PET and TPBS to differentiate between loosening and infection. An incorrect diagnosis of infection rather than loosening was considered as a false positive while a diagnosis of loosening rather than infection was regarded as a false negative

	PET [*]	TPBS [†]
True positive	31	17
True negative	56	51
False positive	3	16
False negative	2	8
Total	92	92
Sensitivity	0.94	0.68
Specificity	0.95	0.76
Negative predictive value	0.97	0.86
Positive predictive value	0.91	0.52
Accuracy	0.95	0.74

* PET, positron-emission tomography

† TPBS, triple-phase bone scanning

Table IV. Mean standardised uptake values (SUV_{mean}) ± SD found for non-pathological, loosened, and infected arthroplasties. The p values of a between-group comparison are also given (Mann-Whitney test). Significant differences (p < 0.05) are marked with an asterisk

	No loosening or infection (n = 58)	Loosening (n = 26)	Infection (n = 8)
SUV _{mean} [†]	3.3 ± 1.6	5.0 ± 3.0	5.9 ± 2.7
		p < 0.01*	p = 0.35
			p < 0.01*

† SUV, standard uptake value

Table II. In a second analysis, the ability of both methods to distinguish between loosening and infection was assessed. To this end, an incorrect diagnosis of infection instead of loosening was considered to be a false-positive result while a diagnosis of loosening instead of infection was regarded as false-negative. The results of this analysis are shown in Table III. While all the eight cases of infection were diagnosed correctly by PET, TPBS detected seven. An incorrect diagnosis of infection was made by TPBS in 13 cases and by PET in one. For TPBS, the dynamic scan of the arterial flow was negative in all but two cases.

Fig. 3

Comparison of standardised uptake values in non-pathological (n = 58), loosened (n = 26), and infected (n = 8) arthroplasties.

In the subgroup of 28 asymptomatic arthroplasties, 25 (89.3%) had PET patterns 1 to 3 (no loosening or infection). In the remaining three cases (10.7%), pattern 4 (loosening) was found. While loosening could be excluded in two of these cases by additional follow-up examinations (false-positive), revision in the third case confirmed loosening of the cup (true-positive).

In the subgroup of 64 symptomatic arthroplasties, 33 (51.6%) had PET patterns 1 to 3 (no loosening or infection), 22 (34.4%) pattern 4 (loosening), and nine (14.1%) pattern 5 (infection). Of these cases, one was false-positive and two false-negative.

The mean standardised uptake values measured in the subgroups of loosened, infected, and non-pathological arthroplasties are shown in Table IV. There was no significant difference between the standardised uptake values of loosened arthroplasties and those which were infected (p = 0.35). By contrast, highly significant differences were found between non-pathological and both infected and loosened arthroplasties (p < 0.01). Figure 3 shows a comparison of the standardised uptake value measurements in the different subgroups.

Histological examination revealed that in all cases of aseptic loosening, extensive parts of the arthroplasty, and particularly the prosthesis-bone interface, were covered with large quantities of granulomatous tissue. Within this tissue, there was an excessive number of polyethylene particles (micron and submicron) as well as macrophages and multinuclear giant cells (Fig. 4). The diameter of the polyethylene particles was between 0.3 and 500 µm. Tissue specimens of patients with an acute infection also showed signs of wear of polyethylene and the corresponding immunological reactions. Such samples were rich in leucocytes and parenchymal cell debris.

Fig. 4

Surgical and histopathological findings from a patient with aseptic loosening of the acetabular cup. Figure 4a – The yellowish tissue in the area of the femoral neck (arrow), which was found throughout the acetabular interface, proved to be wear-induced granulomatous tissue containing many macrophages and multinuclear giant cells. Figure 4b – Photomicrograph showing multiple polyethylene particles as dark objects (haematoxylin and eosin, x75). Figure 4c – Photomicrograph showing polyethylene particles (asterisk) surrounded by macrophages and multinuclear giant cells (haematoxylin and eosin, polarisation, x150).

Discussion

TPBS is a widely accepted and frequently performed imaging technique for diagnosing pathological processes of the musculoskeletal system.^{5,8-12,21,22} Unlike TPBS, for many years PET has been mainly used in the fields of oncology, cardiology, and neurology. Recently, an increasing number of reports have also confirmed its effectiveness in diagnosing inflammatory processes.^{13-17,23-26} Our aim was to compare the ability of PET and TPBS to detect and differentiate the two major complications of hip arthroplasty, loosening and infection. Our first analysis showed that both methods were very effective when no differentiation between infection and loosening was made (Table II). While PET is the more sensitive, specific, and accurate method, TPBS is still satisfactory as a planar imaging technique. These findings change, however, when the differentiation between loosening and infection is considered. While PET showed only a minimal decrease in accuracy from 0.96 to 0.95, TPBS demonstrated a substantial drop from 0.85 to 0.74 (Table III). These observations agree with the findings of both Pfahler, Schidlo and Refior²⁷ and Itasaka et al,¹¹ who reported accuracy values for TPBS of 0.74 and 0.79, respectively. Remarkably, the dynamic scan of the arterial flow acquired in the course of the TPBS did not contribute substantially to the diagnosis since it was negative in all but two cases. A more accurate result may be achieved by combining TPBS with white blood cell scintigraphy. According to Johnson et al,¹² sensitivity, specificity, and accuracy can be increased to 0.88, 0.95, and 0.93, respectively, by this diagnostic approach. However, the combination of these examinations shows several shortcomings in comparison with PET. Besides the higher costs, the lower spatial resolution and the higher exposure to radiation, the longer time that is required to complete the examinations lowers the efficiency of the procedure. Furthermore, the technique of separating, labelling, and re-injection of white blood cells is complex and open to processing errors.

The patterns of PET findings which are used for qualitative interpretation of images (Table I) proved to be highly reliable, especially for the differentiation between infection

and loosening. In addition to our own observations, the development of these specific patterns is based upon the findings of Zhuang et al,¹³ Manthey et al,¹⁴ and Chacko et al.¹⁵ In contrast with these patterns of results, the level of uptake of FDG cannot be recommended as the sole criterion for interpreting PET scans. Although highly significant differences in the standardised uptake value were found between pathological and non-pathological arthroplasties ($p < 0.01$), it proved to be a criterion with poor selectivity. This fact is clearly seen in Figure 3. While a tendency towards higher standardised uptake values can be observed in loosened and infected prostheses, no clear cut-off value is found in comparison with non-pathological arthroplasties. Because there is also no significant difference between the standardised uptake values of loosened and infected arthroplasties ($p = 0.35$, Table IV), this parameter should only be used for additional information.

To date, no conclusive explanation has been given in the literature for the periprosthetic accumulation of FDG in patients with aseptic loosening, although the reason for its increased uptake in inflammatory tissue has been explained by several studies.^{15,24,25,28} With infection, a massive exudation of leucocytes and other immunologically active cells is observed because of increased vascular permeability and mediator-induced chemotaxis. These activated leucocytes and macrophages have an increased energy requirement which is reflected by an increased uptake of FDG. Because periprosthetic tissue is also affected by this immunological reaction, a diffuse accumulation of FDG is found not only at the prosthesis-bone interface but also in the surrounding soft tissue. The creation of PET pattern 5 was based upon this observation. However, this does not explain the increased periprosthetic uptake of FDG in patients with aseptic loosening of an arthroplasty. During our study, strong histological evidence was found which indicated that polyethylene particles and, to a less extent, metal wear particles were responsible for this phenomenon. The interfaces of all loosened prosthetic components were covered with large amounts of granulomatous tissue which contained excessive numbers of such particles. These were

released by the mechanical wearing which occurs between the prosthetic head and the polyethylene acetabular liner.

Several authors describe a complex immunological reaction induced by this polyethylene and metal debris.²⁹⁻³³ In the course of a foreign-body reaction, many macrophages and multinuclear giant cells migrate into the affected tissue (Fig. 4). Osteoclasts and macrophages are activated by mediators and lead to osteolysis and eventual aseptic loosening of the arthroplasty. During this process, the wear-induced, aggressive granulomatous tissue grows further into the prosthesis-bone interface. Because of its high content of activated immunological cells, with their substantially increased energy consumption, this granulomatous tissue shows an increased uptake of FDG on the PET scan. This hypothesis is further supported by the fact that most PET scans of THAs show an increased uptake of FDG in the area of the femoral neck, even when there are no signs of loosening or infection. This increased uptake can be explained by a wear-induced immunological reaction to polyethylene and metal particles which have accumulated in this region because of gravity and intra-articular pressure.

We thus conclude that, although TPBS satisfactorily detects pathological processes in THAs, it has serious limitations in the differentiation of aseptic loosening from infection. In comparison with TPBS, PET shows much greater potential for diagnosing complications after THA. It is a highly accurate diagnostic procedure which is able to differentiate reliably between the two complications. PET imaging in cases of aseptic loosening suggested that increased periprosthetic uptake of FDG is caused by wear-induced polyethylene particles and the subsequent growth of aggressive granulomatous tissue. In contrast with an image interpretation based upon specific patterns of results, the level of uptake of FDG was inconclusive. While the calculation of standardised uptake values may be helpful in some special cases, it cannot be recommended as the sole criterion for interpretation because of its low selectivity.

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