Summary and conclusions

Despite the advances in prosthesis design, prosthesis materials and improvements in operative techniques, aseptic loosening of prosthetic components remains the major long-term complication after THA [1;2]. Therefore, when a patient presents with pain following THA, the fixation of prosthetic components may be questioned [3]. In clinical practice, in addition to an extensive history and complete physical examination, radiographic and scintigraphic techniques are often used to diagnose a loose hip prosthesis. The characteristics of imaging techniques, including routine radiography, contrast arthrography, nuclear arthrography and bone scanning, have been studied extensively over the last 2 decades. Although some studies reported that these techniques were beneficial in assessing component failure, there is no consensus with regard to an efficient diagnostic algorithm for the application of these tests. Therefore, this thesis aimed to evaluate the performance of radiography, contrast arthrography, nuclear arthrography and bone scintigraphy and to develop a diagnostic algorithm based on the results obtained. This thesis focussed on patients suspected with an aseptic loosening of THA. In order to comprehensively evaluate the effectiveness of these techniques, a stepwise approach was used. Based on the national survey of all orthopaedic departments in the Netherlands, we found that only a minority of the responding departments had guidelines concerning the application of diagnostic imaging techniques. Subsequently, we performed systematic reviews to summarize the present literature evidence on the performance of different diagnostic techniques that are used for evaluating patients suspected with aseptic loosening of hip prosthesis. Through a clinical study, we evaluated both interobserver variability and diagnostic performance of all the 4 modalities. Moreover, we evaluated the application of PET as a possible future technique for assessing bone metabolism and infections after primary and revision THAs.

Part I: A comparison of radiographic and scintigraphic techniques to assess aseptic loosening of a THA

In Chapter 1, we have described a systematic review on the diagnostic performance and accuracy of radiographic and scintigraphic techniques for evaluating patients suspected with aseptic loosening of the acetabular component. Based on a sensitive search strategy, we selected over 3400 studies from the Pubmed and Embase databases and checked all these studies for relevance. Twenty-eight studies published between January 1975 and October 2004 presented sufficient data for quantitative analysis. During the qualitative analysis, however, several studies showed methodological limitations with regard to study design, data collection and data reporting. Based on a pooled analysis, we found that subtraction arthrography had a significantly higher sensitivity of 89% (95% CI, 84–93) than plain radiography and bone scintigraphy whose sensitivities were 70% (95% CI, 59–79) and 67% (95% CI, 57–76), respectively. Therefore, we
suggest subtraction arthrography as an additional diagnostic technique when plain radiography is inconclusive. Unfortunately, due to insufficient data reporting, a subgroup analysis of the prosthesis fixation techniques could not be performed. Therefore, we hope that in future studies, investigators improve their study designs and reporting methods.

In Chapter 2, we have evaluated the sensitivity, specificity and interobserver variability of plain radiography, subtraction arthrography, nuclear arthrography and bone scintigraphy in patients suspected with aseptic loosening of the acetabular component of THA. From 1994 to 1999, 86 consecutive patients (mean age, 75 years; range, 34–84 years) with painful THAs were evaluated for possible loosening of their acetabular component. Plain radiography exhibited the highest diagnostic accuracy in this evaluation (81%–85%). However, considerable interobserver variability was found in image interpretation, even with experienced radiologists and nuclear medicine physicians. On studying the combinations of these diagnostic techniques, we found that the diagnostic accuracy was significantly increased when plain radiography was combined with bone scintigraphy or subtraction arthrography. Based on these clinical results, we advise that bone scintigraphy should be used as an additional technique along with plain radiography and that image interpretation should be performed by at least 2 experienced physicians.

In Chapter 3, we have described a systematic review that summarizes and compares the diagnostic performance of radiographic and scintigraphic techniques in evaluating patients suspected with aseptic loosening of the femoral component of THA. Thirty-two studies were included using the criteria based on the Cochrane Methods Group on Systematic Review of Screening and Diagnostic Tests. Quantitative analyses revealed that the pooled sensitivity was 82% for plain radiography and 86% for subtraction arthrography and that the pooled specificity was 72% for bone scintigraphy and 85% for subtraction arthrography. No significant difference was observed between the 4 diagnostic modalities. Similar to the studies on acetabular components, these studies showed significant methodological limitations with regard to study design, data collection and data reporting during the qualitative analysis. Unfortunately, only few studies reported the accuracy of imaging techniques specifically for cemented and uncemented components. Therefore, a subgroup analysis based on fixation techniques could not be performed.

In Chapter 4, we have evaluated the diagnostic accuracy and interobserver reliability of the 4 techniques in 78 consecutive patients (mean age, 70 years; range, 29–88 years) who were referred for the evaluation of their symptomatic hip prostheses. Considerable interobserver variability was found among the 4 techniques. Multivariate regression analysis revealed that bone scintigraphy and nuclear arthrography significantly contributed to the diagnosis when combined with plain radiography. Therefore, when plain radiography is inconclusive, bone scintigraphy and nuclear arthrography may be useful additional diagnostic techniques for detecting femoral component loosening.
In Chapter 5, we have described a systematic review that summarizes and compares the diagnostic accuracy of contrast and subtraction arthrographies for assessing aseptic loosening of THAs. Contrast-enhanced arthrography is a frequently applied diagnostic modality for the detection of hip prosthesis loosening. Although subtraction arthrography is considered a more sensitive technique than contrast arthrography, randomized or prospective comparisons of contrast and subtraction arthrographies have not been performed. Therefore, the objective of this meta-analysis was to assess the diagnostic accuracy and to meta-analytically compare the arthrographic techniques currently used in clinical practice. We included original studies written in English and published between January 1975 and October 2004; these studies used contrast-enhanced arthrography with or without subtraction for the diagnosis of loosening of total hip prosthesis. By using the present data, we found that subtraction arthrography is a significantly more sensitive technique for detecting loosening of total hip prosthesis (sensitivity, 89%; 95% CI, 84–93) than contrast arthrography (sensitivity, 70%; 95% CI, 52–84; p = 0.01). Thus, it offers added value over contrast arthrography, particularly when evaluating the femoral component.

Part II: Imaging and quantification of bone metabolism in patients after THA by using PET

In Chapter 6, we have described the results of a study that used PET to visualize and quantify bone remodelling in 10 patients treated with primary or revision THAs. Of these patients, 5 were treated with unilateral cemented primary THA (group A) and 5 patients were treated for revision of one or both the components of total hip prosthesis by using impacted bone grafting to treat bone loss (group B). H$_2$O and 18F- PET scans were performed 1 day prior to the surgery and at 2 and 12 weeks post-surgery. Clinical assessment and radiographs were acquired at the same intervals. Data obtained in this setting were analyzed in order to gain insight into the evaluation of bone graft remodelling. Three months after surgery, bone blood flow was significantly higher around the prosthesis than at the contralateral side. In the group of patients undergoing a revision, bone blood flow around the prosthesis was 2- to 3-fold higher than that at the contralateral side, but the differences did not reach significance. We found a significantly higher preoperative bone metabolism in group B (impacted bone grafting) than in Group A (primary THA; p = 0.024) prior to and immediately after the surgery. However, we found a non-significant difference in bone metabolism between Groups A and B during the third PET scan (p = 0.556). This may suggest that the initial increased bone metabolism is stabilised after bone graft remodelling. Imaging and quantification of bone metabolism with PET may be a promising technique for the evaluation of bone remodelling in a hip revision surgery. However, clinical applications of this technique should be assessed in future studies.

In Chapter 7, we have discussed the use of 18FDG PET scan in a patient with clinical and laboratory signs of infection 2 weeks after the removal of an infected total hip prosthesis; this patient had
shown indistinct signs on bone scan and radiographs. The PET scan confirmed the clinical and laboratory signs and revealed an unidentified focus of infection in the distal area of the femur.

Recent studies have illustrated the diagnostic potentials of $^{18}$FDG PET in the evaluation of the painful hip prosthesis. Cremerius et al described the typical patterns for $^{18}$FDG uptake PET to detect aseptic loosening and prosthetic infection[4]. However, Zhuang et al found non-specifically increased FDG uptake patterns around the prostheses which persisted for years and included patients without complications[5]. Therefore, further studies are required to determine the extent to which $^{18}$FDG PET can improve clinical decision making and patient outcome in comparison with other currently available diagnostic tools. If confirmed, $^{18}$FDG PET may be of considerable benefit in patients suspected with an infection.
Discussion

To effectively assess a symptomatic total hip prosthesis by using diagnostic imaging techniques, validated data on the diagnostic value and combined accuracies of these techniques are imperative. We used a stepwise approach to evaluate these diagnostic techniques.

**Step 1: Identification of the current clinical practice**

Through our national survey, we found that a guideline for the use of diagnostic imaging techniques in patients with a painful THA was available in only 36 of 122 hospitals. For the assessment of painful THAs, 94% of the interviewed orthopaedic surgeons used plain radiography as a baseline technique. When plain radiographs were inconclusive, bone scintigraphy was used as an additional technique by the majority of the orthopaedic surgeons (79%), while subtraction arthrography was used in 14% of the clinics. Subtraction arthrography was used as the third option in 68% of the orthopaedic clinics. Nuclear arthrography was applied in only 13% of the orthopaedic clinics. In conclusion, a minority of the responding departments had guidelines related to the application of diagnostic imaging techniques in patients suspected with total hip prosthesis loosening. X-ray and bone scintigraphy were the most frequently used diagnostic techniques, while nuclear arthrography was only scarcely used as a diagnostic modality.

**Step 2: Systematic review of published evidence**

In Chapters 1, 3 and 5, we systematically reviewed English-language literature published over a period of 25 years on the diagnostic accuracy of plain radiography, subtraction arthrography, nuclear arthrography and bone scintigraphy for evaluating aseptic loosening of the acetabular and femoral components; the literature was retrieved using the Embase and Pubmed databases. A qualitative analysis of the eligible studies identified a number of methodological limitations with regard to internal and external study validity. The limited internal validity of most studies resulted in grade 4 level of evidence, mostly due to the presence of verification bias. In addition, very few studies reported the performance of imaging modalities in evaluating different types of implants and fixation methods (i.e. hydroxapatite-coated implants) to enable subgroup analyses for all groups of interest. Based on the available data, pooled analyses revealed a significantly higher sensitivity of subtraction arthrography than plain radiography and bone scintigraphy for the acetabular component. In contrast to the evaluation of the acetabular component, we found no significant differences in the diagnostic performances of the 4 modalities in assessing the femoral component.

**Step 3: Clinical evaluation**

Through a clinical study, we evaluated 86 consecutive patients with a painful THA who were examined at our orthopaedic department from 1994 to 1999. Imaging evaluation comprised
plain radiography, followed by a 1-day protocol that included bone scintigraphy, subtraction arthrography and nuclear arthrography. For this study, 2 experienced nuclear medicine physicians and 2 experienced radiologists, all of whom were blinded from clinical pre-test data and clinical outcome, retrospectively interpreted the diagnostic images.

With regard to the identification of acetabular component loosening, we observed that plain radiography was the best imaging modality, followed by bone scintigraphy and subtraction arthrography, regardless of whether the component was cemented or uncemented. However, despite its clinical availability as well as its familiarity among all clinicians, we found a surprisingly high interobserver disagreement.

Previous studies have also reported a considerable interobserver variability when evaluating radiographs and bone scans of hip prostheses. [6-8] This variability was demonstrated for both radiologists and nuclear physicians as well as for orthopaedic surgeons. This data indicates that although these imaging modalities may have a good overall performance in the evaluation of THAs, their diagnostic accuracy may be compromised by interobserver variability. Improved clinical training, supported by experienced clinicians and radiologists, in combination with standardized radiological scoring systems may help reduce the interobserver variability and subsequently improve the diagnostic value of these techniques. Although plain radiography is a simple procedure with an adequate accuracy, it is often used in combination with other diagnostic techniques. In our clinical studies, we calculated the diagnostic value of combined imaging techniques. Both subtraction arthrography and bone scintigraphy had a significant predictive value for acetabular cup loosening when used along with radiography. We found no additional value of combining nuclear arthrography for the assessment of the acetabular component.

With regard to the femoral component, we found that plain radiography had a high diagnostic performance for both cemented and uncemented femoral components. However, it had the lowest interobserver agreement among the 4 imaging modalities. As suggested for the interobserver variability in the acetabular component assessment, we believe that improved clinical training, supported by experienced clinicians and radiologists, in combination with standardized radiological scoring systems may help reduce the interobserver variability and subsequently improve the diagnostic value of all 4 modalities for assessing the femoral component. While assessing the combined accuracy of the 4 diagnostic modalities, we found that both bone scintigraphy and nuclear arthrography significantly contributed to the diagnosis when combined with plain radiography. Subtraction arthrography was of no additional value in the assessment of the femoral component.

In conclusion, we, like the other researchers, found plain radiography to be an accurate baseline technique for both acetabular and femoral components. Based on the available data, bone scintigraphy may be of additional value for detecting loosening of both these components. Some remarks should be made however. As illustrated in our clinical studies (Chapters 2 and 4), image interpretation for assessing the THA is difficult. We found significant interobserver variability among all the techniques. Furthermore, in our meta-analyses (Chapters 1, 3 and 5),
we encountered significant limitations in the internal validity of the eligible studies. In addition, there are limitations related to meta-analyses, such as publication bias, which when present may cause an overestimation of test accuracy.

**Step 4: Development and implementation of an evidence-based diagnostic algorithm**

Based on our studies, we propose an algorithm for the investigation of patients suspected with aseptic loosening of a total hip prosthesis. (Figure 1) In clinical practice, a careful history and complete physical examination are the first steps in the assessment of a patient with symptomatic artificial hip joint.

In addition to clinical evaluation, plain radiography is the first imaging modality used when evaluating the status of a prosthesis, and it has been consistently reported to be an accurate technique for assessing cemented and uncemented acetabular and femoral components. The widespread application of this technique is also supported by the data described in both our meta-analyses as well as by the data originating from our own clinical studies.

Bone scintigraphy significantly contributed to diagnostic accuracy when it was combined with plain radiography. This outcome was found in the assessment of both acetabular and femoral components of THA. This is in accordance with the outcome of our national survey in which the majority of the orthopaedic surgeons used this technique in addition to plain radiography. Therefore, we advise bone scintigraphy as the second diagnostic ‘step’ in the algorithm.

Subtraction arthrography significantly contributed to the evaluation of the acetabular component, but it showed no significant effect in the evaluation of the femoral component.

Nuclear arthrography did not exhibit any diagnostic value in the assessment of the acetabular component; however, it showed a significant additional diagnostic effect in the evaluation of

![Figure 1 Flowchart of the radiographic and scintigraphic imaging techniques to assess aseptic loosening of a total hip prosthesis.](image-url)
the femoral component. The limited value of nuclear arthrography in the assessment of the acetabular component could be due to the masking effect of the intra-articularly injected tracer that probably obscures the signs of component loosening. Since limited data on fixation techniques was available, classification based on fixation techniques could not be incorporated in our diagnostic algorithm.

Note: Although the flowcharts begins with painful hip prosthesis, a clinician will sometimes encounter patients with signs of prosthesis loosening on a plain radiograph but without complaints of pain, which is often associated with a loosened hip prosthesis. In these cases, we suggest that the clinician should follow the algorithm demonstrated via the flow chart in order to definitively assess the status of the prosthetic components. This may prevent the delay in the diagnosis of a loosened hip prosthesis, which may in turn reduce acetabular or femoral bone resorption.

Step 5: Assessment of the residual inefficiency of the diagnostic strategy
After the implementation of the diagnostic algorithm developed in Step 4, its clinical efficiency should be studied. A prospective randomised diagnostic study may be required to evaluate the efficiency and cost of a strict diagnostic algorithm in comparison with those of the practices currently followed.

Conclusions and Recommendations
In this thesis, we studied the diagnostic value of imaging techniques that are commonly used in orthopaedic patients with clinically suspected aseptic loosening of a total hip prosthesis.
1. Based on the data discussed in this thesis, the recommended algorithm for the use of diagnostic imaging techniques in patients with clinically suspected aseptic loosening of a total hip prosthesis is presented in Figure 1.
2. In order to enhance the diagnostic value of all the 4 techniques, clinical training should be provided for clinicians and radiologists in order to improve the diagnostic value. Ideally, a multidisciplinary team that includes an orthopaedic surgeon, a nuclear physician and a radiologist should participate in image interpretation.
3. A prospective randomised diagnostic study is mandatory to evaluate the efficiency and cost of a strict diagnostic algorithm in comparison with the practices currently followed.

References


