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Bearings in hip arthroplasty

Diagnostics and prognosis of adverse reaction to metal debris and long-term risk of revision in young patients

Tyrsted Mikkelsen, Rasmus

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Department of Regional Health Research, Faculty of Health Science,

University of Southern Denmark

Department of Orthopedic Surgery,

Lillebaelt Hospital, Vejle

PhD Thesis

Rasmus Tyrsted Mikkelsen, MD

‘Bearings in hip arthroplasty – Diagnostics and prognosis of adverse reaction to metal debris and long-term risk of revision in young patients’

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Supervisors

Main supervisor

Associate professor Claus Varnum, MD, PhD

Department of Orthopedic Surgery, Lillebaelt Hospital – Vejle

Department of Regional Health Research, Faculty of Health Science, University of Southern Denmark

Co-supervisors

Professor Søren Overgaard, MD, PhD, DMSci

Department of Orthopaedic Surgery and Traumatology, Copenhagen
University Hospital, Bispebjerg, Denmark

University of Copenhagen, Department of Clinical Medicine, Faculty of Health and Medical Sciences, Denmark

Professor Ole Graumann, MD, PhD

Department of Radiology, Odense University Hospital, Odense, Denmark

Department of Clinical Research, University of Southern Denmark

Assessment committee

Søren Rafael Rafaelsen, MD, DMSc, Professor (chair of assessment committee)

Department of Radiology, Lillebaelt Hospital, Vejle and Department of Regional Health Research University of Southern Denmark, Denmark

B. Willem Schreurs, MD, Professor

Department of Orthopedics, Radboud University Medical Center, Radboud Institute for Health Sciences, The Netherlands

Philip Hansen, MD, PhD, Associate professor

Department of Radiology, Bispebjerg and Frederiksberg Hospital and Department of Clinical Medicine Copenhagen University, Denmark

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Correspondance

Rasmus Tyrsted Mikkelsen, MD

Department of Orthopedic Surgery, Lillebaelt Hospital – Vejle

Beridderbakken 4, 7100 Vejle

+45 31231671

Rasmus.tyrsted.mikkelsen@rsyd.dk

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Preface

This thesis is based on the following three studies:

Study I: Sensitivity and specificity for detecting pseudotumors in patients with hip resurfacing arthroplasty, metal-on-metal or metal-on-polyethylene total hip arthroplasty - MRI versus ultrasonography performed by an orthopedic surgery resident

Study II: Long-term follow-up of resurfacing and stemmed metal-on-metal total hip arthroplasty compared to metal-on-polyethylene total hip arthroplasty – metal ion levels, pseudotumors and patient reported outcome

Study III: Does choice of bearings influence the survival of cementless total hip arthroplasty in patients 20 - 55 years? Comparison of 22,664 patients reported to the Nordic Arthroplasty Register Association dataset 1995-2017

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Abbreviations

ALTR = Adverse local tissue reaction

ALVAL = Aseptic lymphocyte-dominant vasculitis-associated lesion

ARMD = Adverse reaction to metal debris

BMI = Body mass index

CI = Confidence interval

CoC = Ceramic-on-ceramic

CoXLP = Ceramic-on-highly-crosslinked-polyethylene

HHS = Harris Hip Score

HR = Hazard ratio

HRA = Hip resurfacing arthroplasty

IQR = Interquartile range

MARS = Magnetic Artifact Reduction Sequence

MoM = Metal-on-metal

MoP = Metal-on-polyethylene

MoXLP = Metal-on-highly-crosslinked-polyethylene

MRI = Magnetic resonance imaging

NARA = Nordic Arthroplasty Register Association

NPV= Negative predictive value

OA = Osteoarthritis

OHS = Oxford Hip Score

OMAR = Metal artifact reduction for orthopedics implants

PPV = Positive predictive value

PROM = Patient reported outcome measure

PT = Pseudotumor

RCT = Randomized clinical trial

THA = Total hip arthroplasty

UCLA = UCLA activity score

UHMWPE = ultrahigh-molecular-weight polyethylene

US = Ultrasonography

XLP = Highly crosslinked polyethylene

Summary – English

Total hip arthroplasty (THA) has improved the life of millions of patients with debilitating conditions of the hip such as osteoarthritis (OA). The positive effect on quality of life and function has led THA to become one of the most frequently performed surgical procedures, a frequency that is projected to rise, especially among young patients. Although the survival of THAs is constantly improved, giving a long enough timeline all THA will eventually wear, break, loosen etc. 25 years after surgery 58-74% of all patients still have their primary THA. However, the survival of THAs is the lowest among young patients compared to all other age groups. Although revision surgery is possible the functional outcome is inferior compared to primary surgery and young patients risk undergoing multiple revisions in their lifetime. This is problematic as young patient likely have the highest demand for functional outcome compared to older patients. To improve the survival of THAs in young patient different bearings have been used. At the turn of the millennium and the following decade, metal-on-metal (MoM) THAs were used, but later showed inferior survival, tendency to metal ion release into the blood and formation of adverse reaction the metal debris (ARMD) in the form of pseudotumors (PTs). The MoM bearings are almost no longer used, and most countries have implemented lifelong follow-up programs in patients with MoM where metal ion levels and radiological findings such as PTs can lead to revision surgery.

Study I

We aimed to investigate the sensitivity and specificity when an orthopedic surgery resident after a short training program performed US scans on patients with THA to detect PTs compared with MARS-MRI as a gold standard. Secondly, we investigated the sensitivity and specificity for US to detect PTs in obese and non-obese patients. We examined 205 patients with 50 pseudotumors on MARS-MRI. We found that the orthopedic resident had a good sensitivity and specificity in both obese and non-obese patients.

Study II

Our aim was to investigate how patient-reported outcome (PRO), metal ion blood levels and ARMD changes over time in hip resurfacing arthroplasties (HRA), MoM and metal-on-polyethylene (MoP) THA at 4 and 13 years. We included 98 hips arthroplasties in 78 patients. The prevalence of PT declined in HRA and MoM THA but increased in MoP THA over time. New PTs were just as common in HRA and MoP THA. Blood levels of cobalt and chromium was higher in HRA and MoM THA compared to MoP THA, but were stable over time. No difference in PROM scores was found

between HRA, MoM and MoP THA at first or second examination. Blood levels of cobalt and chromium or PROM scores were not associated with the presence of PTs. In perspective, surgeons should be cautious with using the presence of long-term pseudotumors as revision causes.

Study III

Our aim was to compare the survival and hazard ratio (HR) of revision of primary stemmed cementless THA with MoM, ceramic-on-ceramic (CoC) and ceramic-on-highly crosslinked polyethylene (CoXLP) to that of metal-on- highly crosslinked polyethylene (MoXLP) bearings in patients aged 20-55 years diagnosed with osteoarthritis or childhood hip disorders. We included 21,594 patients from the Nordic Arthroplasty Register Association dataset. MoXLP had higher survival and lower HR for revision than MoM - mainly for revision causes we cannot specify. MoXLP, CoC and CoXLP had similar survival and HR for revision, but longer follow-up is needed to investigate whether CoC and CoXLP have better, equal or worse performance as both CoC and CoXLP tended to have increased HRs. In perspective, we currently believe that either MoXLP, CoC or CoXLP could be the standard bearings in patients aged 20-55 years.

Summary – Danish/Dansk resumé

Total hoftealloplastik (THA) har forbedret livet for millioner af patienter med invaliderende hofteledssygdomme såsom slidgigt. Den positive effekt på livskvalitet og funktionsniveau har gjort THA til en af hyppigst udførte kirurgiske indgreb i verden. En hyppighed, der forventes at stige, specielt blandt yngre patienter. Selvom holdbarheden af THA konstant forbedres, så vil alle THA før eller siden slides, knække, løsnes osv. 25 år efter operation har 58-74% stadig deres primære THA. Holdbarheden af THA er dog lavest blandt de yngre patienter sammenlignet med alle andre aldersgrupper. Selvom reoperation er mulig, så bliver funktionsniveauet ikke lige så godt som efter første operation, og yngre patienter risikerer at gennemgå flere reoperationer i deres liv. Dette er problematisk, da yngre patienter må formodes at have de største krav til funktionsniveau sammenlignet med ældre patienter. For at forbedre holdbarheden af THA blandt yngre patienter har man forsøgt at bruge forskellige slidoverflader. Ved årtusindskiftet og det efterfølgende årti brugte man metal-mod-metal (MoM). Det vidste sig dog senere, at MoM havde den dårligste holdbarhed, tendens til at frigive metalpartikler ud i blodet og danne uønskede vævsreaktioner pga. metalslidpartikler (ARMD) såsom pseudotumorer (PT). MoM slidoverfladerne bruges stort set ikke længere og de fleste lande har indført livslange opfølgningsprogrammer for patienter med MoM slidoverflader i deres hofte. Finder man uacceptable mængder metalioner i blodet, symptomer og billeddiagnostiske forandringer såsom pseudotumorer, så kan det lede til reoperation.

Studie I

Målet var at undersøge sensitivitet og specificitet, når en ortopædkirurgisk reservelæge efter et kort oplæringsprogram ultralydsscannede patienter med THA for at finde PT, hvilket blev holdt op mod fundene fra MARS-MRI som guldstandard. Yderligere, undersøgte vi ultralydsscanningers sensitivitet og specificitet for at finde PT i overvægtige og ikke-overvægtige patienter. Vi undersøgte 205 patienter med 50 PT på MARS-MRI-scanningerne. Den ortopædkirurgiske reservelæge opnåede en god sensitivitet og specificitet også for de overvægtige og ikke-overvægtige patienter.

Studie II

Målet var at undersøge, hvor patientreporterede oplysninger (PRO), metalion-indholdet i blodet og ARMD ændrer sig over tid i hip resurfacing alloplastik (HRA), MoM og metal-mod-polyethylen (MoP) THA 4 og 13 år efter operation. Vi inkluderede 98 hoftealloplastik i 78 patienter.

Forekomsten af PT faldt i HRA og MoM THA, men steg i MoP THA over tid. De nye PT var lige så hyppige i HRA og MoP THA. Blodindholdet af kobolt og krom var højere i HRA og MoM THA end i MoP THA, men stabilt over tid. Vi fandt ingen forskel i PRO-målene imellem HRA, MoM og MoP THA ved første eller anden undersøgelse. Blodindholdet af kobolt og krom eller PRO-målene var ikke forbundet med forekomsten af PT. Kirurger bør være forsigtige med at bruge forekomsten af PT lang tid efter operation som en årsag til reoperation.

Studie III

Målet var at sammenligne holdbarheden og hazard ratio (HR) for reoperation af primære, stemmede, ucementerede THA med MoM, keramik-mod-keramik (CoC), keramik-mod-highly-crosslinked-polyethylene (CoXLP) slidoverflader holdt op imod metal-mod-highly-crosslinked-polyethylen (MoXLP) slidoverflader i patienter imellem 20-55 år diagnosticeret med slidgigt eller børnehoftesygdomme. Vi inkluderede 21.594 patienter fra the Nordic Arthroplasty Register Association dataset. MoXLP havde en bedre holdbarhed og lavere HR for revision end MoM – hovedageligt pga reoperationsårsager, vi ikke kan specificere. MoXLP, CoC og CoXLP havde sammenlignelig holdbarhed og HR for revision, men vi har brug for studier med længere opfølgning, da CoC og CoXLP viste tendenser til at have dårligere holdbarhed og højere HR for revision. Indtil videre tror vi, at MoXLP, CoC eller CoXLP kan bruges som guldstandard slidoverflade i patienter imellem 20-55 år.

1. Background

1.1 Primary osteoarthritis of the hip

Primary osteoarthritis of the hip (OA), one of the most common forms of osteoarthritis, is a degenerative condition that causes pain, reduced function of the joint and quality of life for the affected person. Destruction of cartilage and alterations in the biomechanics of the joint plays a key role but the etiology might be multifactorial (1,2). On a cellular level a wide range of proinflammatory cytokines and growth factors such as IL-6, MCP-1, VEGF, IP-10, MIG, TGFβ and BMP-2 are present in a joint developing OA leading to stimulation of matrix-degrading enzymes which results in destruction of joint tissues faster than anabolic growth factors can repair the joint tissue such as cartilage and bone (2). OA is a clinical and not solely radiological diagnosis (3) but radiological signs of osteoarthritis contribute to the diagnosis. Radiological signs of osteoarthritis include joint space narrowing, sclerosis of subchondral bone, osteophytes, subchondral cysts, and deformation of bone (2) (Figure 1). The radiological signs along with history, symptoms, and physical examination results in the diagnosis (1,2). The strongest risk factor for development of osteoarthritis is age (4). More females than males develop radiographic and clinical OA (5). Although body mass index (BMI) is a stronger risk factor for clinical osteoarthritis of the knee than of the hip, BMI still plays a role in the development of clinical OA (4). Further, prior injury and cumulated workload are risk factors for development of OA (6,7). As the populations around the world live longer (8), become more obese (9) and have a longer working life the disease burden of OA is expected to increase (10). A great effort is put into slowing disease progression and non-surgical treatment such as physiotherapy, analgesics, injections of corticosteroids and research into cartilage regeneration (2,6). However, currently millions

Figure 1. Radiograph of primary osteoarthritis of the hip

of people worldwide still develop end-stage osteoarthritis with no or inadequate effect of non-surgical treatment (11). When non-surgical treatment fails, clinical and radiological signs of OA along with impaired quality of life are present, orthopedic surgeons in dialog with patients may choose a total hip arthroplasty (THA) as treatment.

1.2 Total hip arthroplasty

THA is one of the most successful and frequently performed surgical procedures ever invented (12,13) and will likely continue to be that for some time (11). A THA involves a femoral and an acetabular component between which the joint movement happens (Figure 2). The first attempt of a hip arthroplasty was performed in the late 19th century where Themistocles Glück replaced the femoral head with ivory in a patient with a hip destroyed by tuberculosis (14). Later in 1923 Marius Smith-Petersen developed the 'mould arthroplasty' consisting of glass. Although glass is biocompatible, the glass shattered (15). It was not until Philip Wiles in 1938 inserted both femoral and acetabular components the first real THA was created. These components were fixated with screws and had a metal-on-metal (MoM) interface consisting of stainless steel (16). MoM THA was used regularly since 1953 by George McKee until the 1970's where the use was stopped because of formation of granulomatous local tissue around the THA seen during revision surgery (17). By this time, Sir John Charnley had invented and shown great results of his low-friction arthroplasty first implanted in 1962. It consisted of a polyethylene liner, a femoral head of stainless steel and a intramedullary femoral stem fixated with acrylic bone cement (18). The low-friction arthroplasty would later show a 25-year survival of 77-81% (19,20). For this Charnley is often considered the father of

Figure 2. Radiograph of uncemented total hip arthroplasty

modern THA (14). Today more than 1.5 million THA are performed each year worldwide (21) and it is one of the largest expenses in healthcare (22). The most common indication for THA is primary OA, but THA is used for a wide range of painful and disabling conditions of the hip such as femoral neck fracture, rheumatoid arthritis, femoral head necrosis, childhood hip disorders and more (23–27). THA reduces pain, improves function of the hip and quality of life of the patient (12,13,28).

1.3 Survival of total hip arthroplasty

Overall, 58-72% patient still have their primary THA 25 years after surgery (23,29). Given a long enough timeline all THA will eventually wear, break, loosen etc. and require revision surgery. However, patients over 75 years of age when receiving their primary THA are more likely to die with the primary THA than to require revision surgery in their lifetime (30). This is not the case for younger patients (31) although “young” might be defined differently in various studies it is usually below 55 to 65 years (32,33). Not only do young patients have a longer life expectancy, but THAs in young patients have the lowest survival compared to all other age groups (23–26,31). Revision surgery can be performed but the clinical outcome after revision surgery is likely poorer than after primary THA (34–38) and the risk of complications higher (23,39,40). Therefore, some argue to delay having THA performed (31,41). However, if THA is put off for too long in young patients, they risk leaving the workforce or have a longer recovery period before return to work after surgery (42,43). This could be the explanation for why more young patients are given THA after the year 2000 and why the incidence is rising (44–46). The younger age of patients, the rising numbers of primary THA along with longer life expectancy results in projections for a sharp increase in volume of THA revision surgery in the next decades (44,45). Improving the survival of THA in young patients is therefore important. Several things affect the survival of the THA. Young patients receiving THA are becoming more obese (46) which could affect the survival of THA negatively although studies show varying results (47–49). Young patients might have an increased level of activity compared to older patients and this might also be associated with lower survival of THA (48). Another factor that influences the survival of THA is choice of materials used in the wear surface of the THA also known as ‘bearings’ (Figure 3).

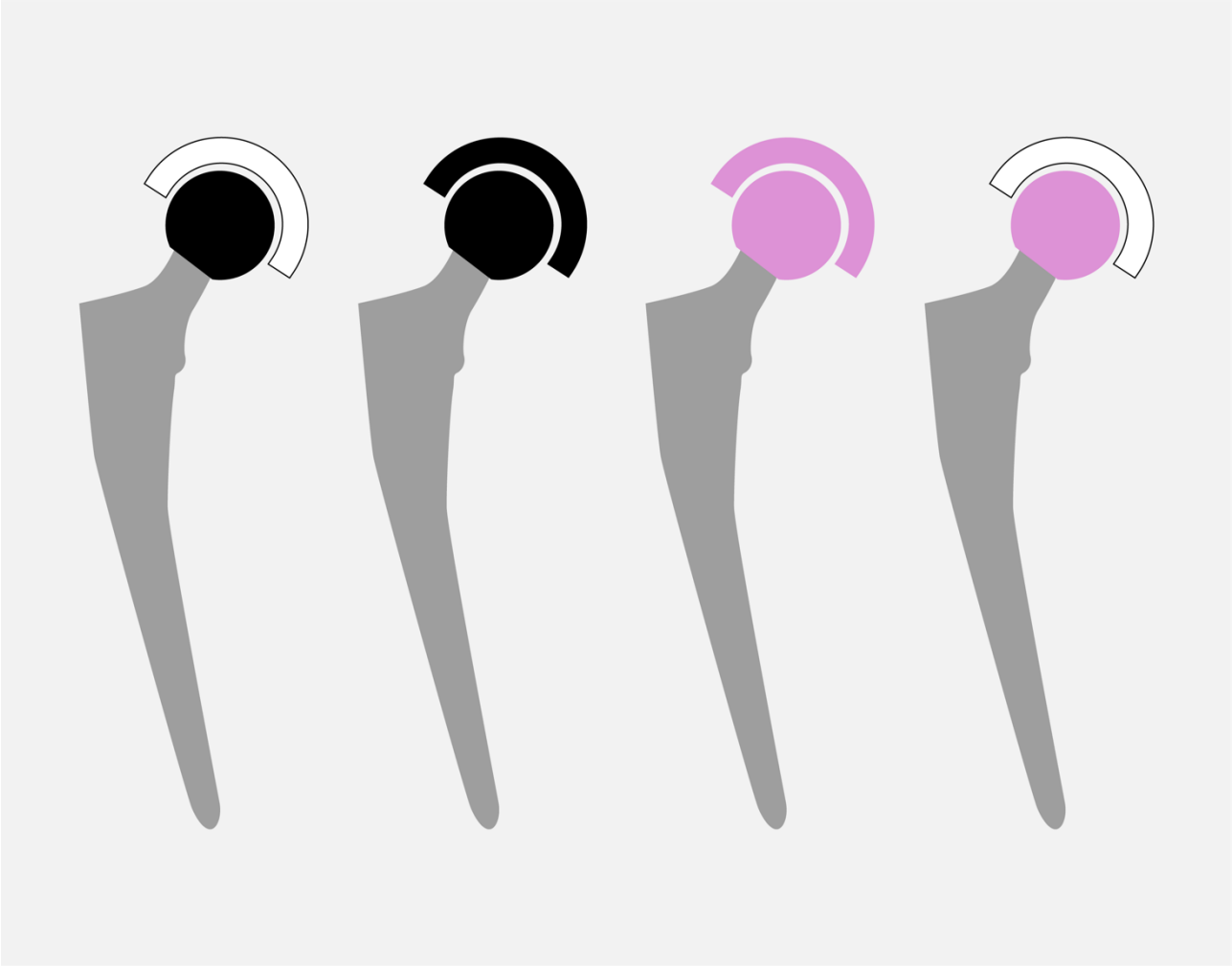

Figure 3. Illustration of bearings.

1.4 Gold standard bearings

Since the introduction of the low-friction THA with a polyethylene liner and a metal femoral head (18) this combination has been and still is the most frequently used bearings worldwide (23–26). Although successful, metal-on-polyethylene (MoP) bearings becomes worn over time. Wear is macro- or microscopic loss particles from the bearing surface and is influenced by patient factors such as age and activity, surgical factors such as component positioning, femoral head size and fixation. It is also influence by component characteristics such as intraarticular debris, lubrication, friction, and fretting. Factors known as the bearings' tribology (50–53). To reduce wear newer generations of polyethylene has been developed. The traditional ultrahigh-molecular-weight polyethylene (UHMWPE) Charnley used was improved multiple times by different processing methods including resin composition, conversion method, temperature, sterilization and gamma radiation (54,55) eventually leading to highly-crosslinked-polyethylene (XLP) by the turn of the millennium (56,57). XLP showed increased wear resistance in biomechanical studies (58,59) and

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later in clinical studies (60–62). In some annual reports of national arthroplasty registers and studies MoXLP THA have superior survival compared to MoP (24,32,63,64) with UHMWPE although not in all (23,65). The femoral head is made of cobalt and chromium alloy. MoXLP is now the most used bearing in most western countries (23–25,27,66).

1.4.1 Wear debris and aseptic loosening

The reason wear of bearing material is given attention is that wear produces debris. Wear debris may cause release of proinflammatory cytokines in the juxtaarticular tissue of the THA. This activates macrophages, that activates the release of interleukins and TNF-α, which leads to increased activity of osteoclasts and less activity of osteoblasts. The result is osteolysis around the components and loss of fixation of the cup and stem of the THA (Figure 4). This is what is known as aseptic loosening (67–71). Aseptic loosening has been and still is the most common cause of revision in THA in some national registers (23,25) although periprosthetic joint infection (PJI) and dislocation are beginning to surpass it in other registers (24,27). This might partly be due to declining incidence of aseptic loosening (23,24). It is still expected that PJI and aseptic loosening will continue to be the 2 most common causes for revision surgery (11,44). Apart from the type of polyethylene, factors such as size of femoral head also effects the rate of aseptic loosening (72). Most studies find increased risk of revision for MoXLP with femoral head sizes smaller than 28 mm (23,24,73) but also increased risk of revision for aseptic loosening with femoral head size larger than 32 mm (24) although it is still debated whether there is a difference between 32 and 36 mm femoral head (72,74–77).

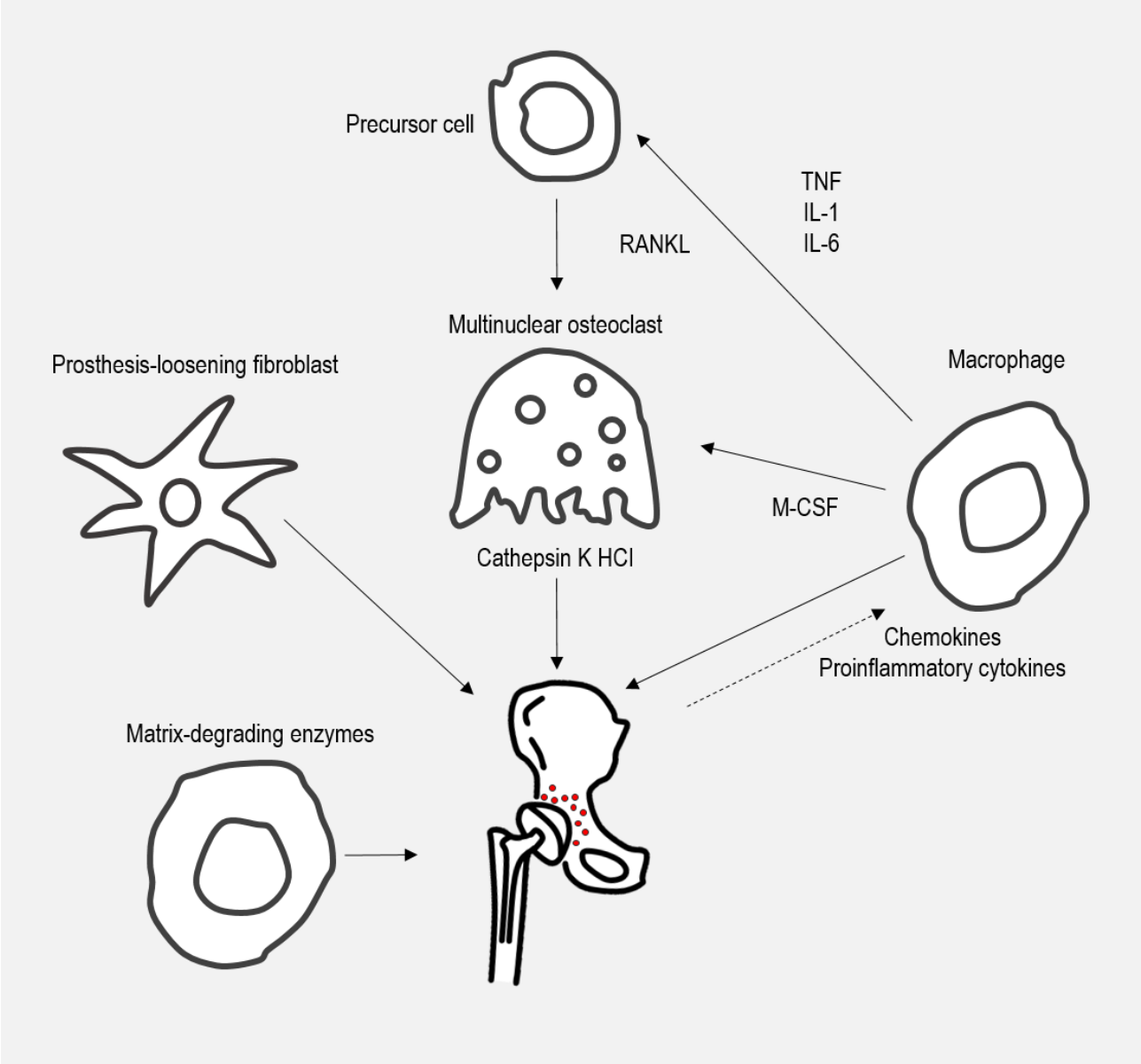

Figure 4. Illustration of the mechanisms behind aseptic loosening.

1.5 Alternative bearings

While different generations of polyethylene have evolved, other materials have been used as alternative bearings in the pursuit to reduce wear and aseptic loosening.

1.5.1 Introduction of alternative bearings

Ceramic-on-ceramic (CoC) bearings have existed since the 1970's (78) and MoM bearings even precedes Charnley's low-friction arthroplasty and was first introduced in the 1930's (16). However, these bearings gained an increased focus at the turn of the millennium as a possible solution to reduction of aseptic loosening (79–81).

During the last three decades MoM have consisted of cobalt chromium molybdenum alloy that had proven to be more wear resistant in biomechanical studies compared to metal-on-conventional-polyethylene (UHMWPE) (81–84) and believed to cause less aseptic loosening (79,81). MoM was popular at a time with several other design changes to the THA. MoM THA typically had larger femoral heads as it was believed to improve motion and decreased risk of dislocation. While larger heads did lower dislocation rates (85) the improved range of motion have not been found in clinical studies (86–88). The design changes used in MoM hip arthroplasties were initiated because of MoM bearings different tribology compared to MoP and MoXLP. MoP and MoXLP rely on boundary lubrication where small femoral heads have lower sliding distance and therefore produce less wear. The tradeoff is a higher risk of dislocation. MoM rely on hydrostatic or fluid film lubrication where large heads are beneficial and also reduce dislocation risk (53). MoM bearings were also the only bearing used in the resurfacing arthroplasty where instead of discarding the head and neck of femur and placing an intramedullar stem, the articular surface was replaced by MoM bearing along with a small peck into the neck of the femur (13) (Figure 5).

Figure 5. Illustration of resurfacing hip arthroplasty.

By the turn of the millennium the 3rd generation of ceramic consisting of alumina was used and produced less wear in biomechanical studies compared to both earlier generations of CoC and MoXLP (75,79,80). In 2004 the 4th generation of ceramic was introduced consisting of alumina matrix composite made from alumina, zirconia, chromium oxide and strontium (75). This composition has a higher wear resistance, crack resistance and toughness than 3rd generation of ceramic (89–91). This improvement reduced one of the complications associated with ceramic bearings: head and liner fracture. This complication is described later in section 1.6.1. Ceramic wear debris might be more biologically compatible and less cytotoxic than polyethylene and metal wear debris (92,93). Further CoC also rely on fluid film lubrication like MoM (53). While 32 mm MoXLP THA is sometimes recommended as 36 mm have higher rates of revision, the 36 mm CoC

bearings does not seem to have the same problem (77) why these head sizes are sometimes recommended (72).

Ceramic-on-highly-crosslinked-polyethylene (CoXLP) is another alternative bearing where the increased wear resistance of ceramic is used while having a lower risk of head and liner fracture compared to CoC bearings (94) although the tribology of CoXLP still rely on boundary lubrication (53). CoXLP is the most often used alternative bearing to MoXLP (66).

While MoM bearings are almost no longer used (95) CoC and CoXLP are increasingly used in young patients (66,75). Some authors even consider ceramic bearings as gold standard in young patients (75).

1.5.2 Survival and risk of revision of alternative bearings

MoM bearings were used especially in young patients as they have the highest lifetime risk of revision and aseptic loosening (79,96). Studies reporting short- and midterm survivorship of THA have since shown inferior survival of hip arthroplasty with MoM bearings up until 8 years after surgery (97–101). The same effect can be seen in the arthroplasty registers (23–25,27). However, little is known about the long-term survival of MoM bearings. Some studies report decreasing number of revisions of MoM hip arthroplasty (102), but large population-based studies with proper methodology into the survival of MoM THA compared to MoXLP beyond 8 years are lacking.

CoC THA have shown similar survival as MoXLP THA in young patients up until 9 years after surgery (103,104). Arthroplasty registers also show similar survival (23,24). Few studies have investigated the survival and risk of revision beyond 10 years (32,105). However, these studies included possible confounders such as cemented cup and stem for young patients (23,106), diagnoses with known inferior survival such femoral neck fracture, rheumatoid arthritis, non-traumatic femoral head necrosis (107,108) and not clearly distinguishing between older metal-on-conventional-polyethylene and MoXLP (24).

CoXLP THA have also shown similar survival as MoXLP THA up until 9 years after surgery (32,105,109–111). Like CoC few large studies into the survival and risk of revision beyond 10 years have been conducted (32,105) with the possible confounders mentioned above. However, the use of CoXLP in young patients is becoming more frequent (66,75).

Metaanalysis of RCTs with short- and midterm follow-up after THA surgery with this CoC, CoXLP and MoXLP bearings have not shown any difference in prosthetic survivorship (33,111,112) but long-term metaanalysis are lacking.

1.6 Concerns

There are some concerns about alternative bearings to MoXLP. Especially MoM bearings have come under scrutiny since they may result in adverse reaction to metal debris in the juxtaarticular tissue and release of cobalt and chromium into the blood. These concerns combined with the low survival have resulted in MoM bearings almost no longer being used (24). Most countries have even implemented follow-up of patients with MoM hip arthroplasties spanning the entire lifespan of the implant (113–116). The concerns are described in detail below.

1.6.1 Squeaking and fracture of head and liner

One of the concerns about MoM and CoC is that they may generate noise in the form of squeaking, popping or clicking. These noises have been associated with pain and decreased patient reported outcomes (PRO) in some studies (117,118). Primarily investigated in CoC THA, these noises can in rare instances be cause for revision (119). Late developed noises from CoC can be caused by head and liner fracture (120). However, long-term studies into revision for noises from CoC THA are needed as these noises might increase over time (121).

A rare but worse possible adverse effect than noises in ceramic bearings is fracture of the head or liner (94,104,122,123). While it can occur in CoXLP it is more frequent in CoC THA (124). Today most ceramic used in CoC THA is 4th generation (24) where fractures of head and liner are more rare compared to 3rd generation ceramic (122,123). The increased risk of head and liner fracture was especially present in CoC THA with 3rd generation ceramic and 28 mm heads (94,103,122,125) which is why 28 mm heads are no longer recommended for CoC THA (72,94,103). The tendency to use 36 or 38 mm heads for CoC THA might be associated with increased risk of fracture of head and liner, but further studies are needed (123).

1.6.2 Elevated blood levels of metal ions

Studies into occupational medicine from the turn of the millennium found that normal blood levels of cobalt and chromium in the unexposed population were 0.06 ug/L (126). However, patients with THA with metal femoral heads or especially MoM bearing are at risk of having elevated blood levels of these metals originating from wear debris (75,114,127). Elevated blood levels of cobalt and chromium can lead to systemic diseases (see chapter 1.6.4). Elevated blood levels of cobalt and chromium is defined in most countries as 7 ug/L although the threshold for clinical concern

might lie between 2-7 ug/L (113–116). Systemic diseases have been reported in patients with MoM hip arthroplasties and blood levels of cobalt at a median of 35 ug/L (14-288) (128), but adverse reaction to metal debris (see chapter 1.6.5) in the juxtaarticular tissue can occur at much lower levels with an increased risk starting at 3 ug/L (129) although the association between the 2 is debated (129–133).

Factors that have been found to be associated with elevated blood levels of cobalt and chromium in MoM hip arthroplasties are increased acetabular component inclination (134), female gender (130,134,135) and high physical activity (135,136). The association of blood levels of cobalt and chromium to femoral heads size is debated (135,137). MoM THA might have higher blood levels of cobalt and chromium compared to HRA (138) and are at greater risk of late rises in blood levels of cobalt and chromium (139). However, most patients with elevated blood levels of cobalt and chromium seem to develop this within the first 4 years after surgery whereafter the levels become stable (132,139–142).

Patients with MoP THA have higher metal ion levels in the blood compared to patients with THA with ceramic bearings (127) but lower than patients with MoM hip arthroplasties (143,144). MoP THA can in rare instances have cobalt and chromium levels above the 7 ug/L threshold (145).

1.6.3 Systemic adverse reactions

Case series from the 1960's have found an association between high blood levels of cobalt an cardiomyopathy (146–148). These patients ingested cobalt through beer where cobalt was used as foam stabilizer. Alcohol might have been a confounder (148) but cobalt cardiomyopathy has also been reported in patients who have handled powdered cobalt in the industry (149). Numerous case report and case series about patients with MoM THA suffering from cardiomyopathy and elevated blood levels of cobalt have been published with a follow-up from surgery to cardiac disease spanning 2 month to 10 years (150–154). However, it is still debated whether the risk of cardiac failure is higher in MoM THA compared to THA with other bearings. One register study suggest there is an increased risk of heart failure in MoM THA patients (155) while other register and cohort studies have found no difference in the risk for cardiac disease (156–158). One register study even found higher risk of cardiac disease in MoP THA compared to CoC THA (159). However, none of the register studies have combined the blood levels of chromium and cobalt with the risk of cardiac diseases.

High exposure to chromium and cobalt have been linked to development of cancer in occupational settings in older studies (160). However, later studies with up to 12 years follow-up have not found increased risk of cancer in MoM THA compared to patients with non-MoM THA (161–165).

Case reports about hypothyroidism and neurological diseases in patients with MoM THA have been published (166–171). Neurological symptoms because of increased cobalt have even been reported in a patient with MoP THA (172). No study has shown increased risk of these diseases in MoM THA. In fact, a register study suggests there is no increased risk for neurotoxicity in MoM THA (173).

A recent metaanalysis of studies into the mortality of patients with MoM THA versus patients with non-MoM THA did find a higher 10-year mortality (174) while older larger register studies on the same subject found no difference (162,175). More long-term population-based register studies are needed to know whether MoM hip arthroplasty patient have a higher or similar mortality as other bearing THA.

1.6.4 Adverse reaction to metal debris/Adverse local tissue reaction

The term adverse reaction to metal debris (ARMD) or adverse local tissue reaction (ALTR) covers aseptic lymphocyte-dominant vasculitis-associated lesions (ALVAL), metallosis, pseudotumors (PT) and osteolysis (176,177). These are the local adverse effects of wear of metal bearings in the surrounding tissue mostly studied in MoM hip arthroplasties. The effects of these conditions are discussed below.

1.6.4.1 Aseptic lymphocyte-dominant vasculitis-associated lesions

When tissue from revision of MoM hip arthroplasties have been histologically examined lesions of aseptic lymphocyte-dominated vasculitis-associated areas around the MoM hip arthroplasties have been found (178). The severity of inflammatory infiltrates, necrosis, tissue organization and metal wear debris can be graded (178,179). The examination of these lesions is important to understand the etiology of failed MoM hip arthroplasties but only available after revision surgery (176). Fortunately, synovial thickness of PT assessed on MRI findings is associated with histological findings of ALVAL (180,181).

1.6.4.2 Pseudotumors

PT are cystic, mixed, or solid periprosthetic masses in continuity of the joint and are non-infective and non-malignant (182) (Figure 6). They originate from an inflammatory reaction to wear debris. PTs have mainly been studied in MoM hip arthroplasties with prevalences varying from 4-59% in different case series (183,184). However, some studies have found PTs to be just as prevalent in MoP and CoP THA (143,144). These changes can be detected on magnetic resonance imaging

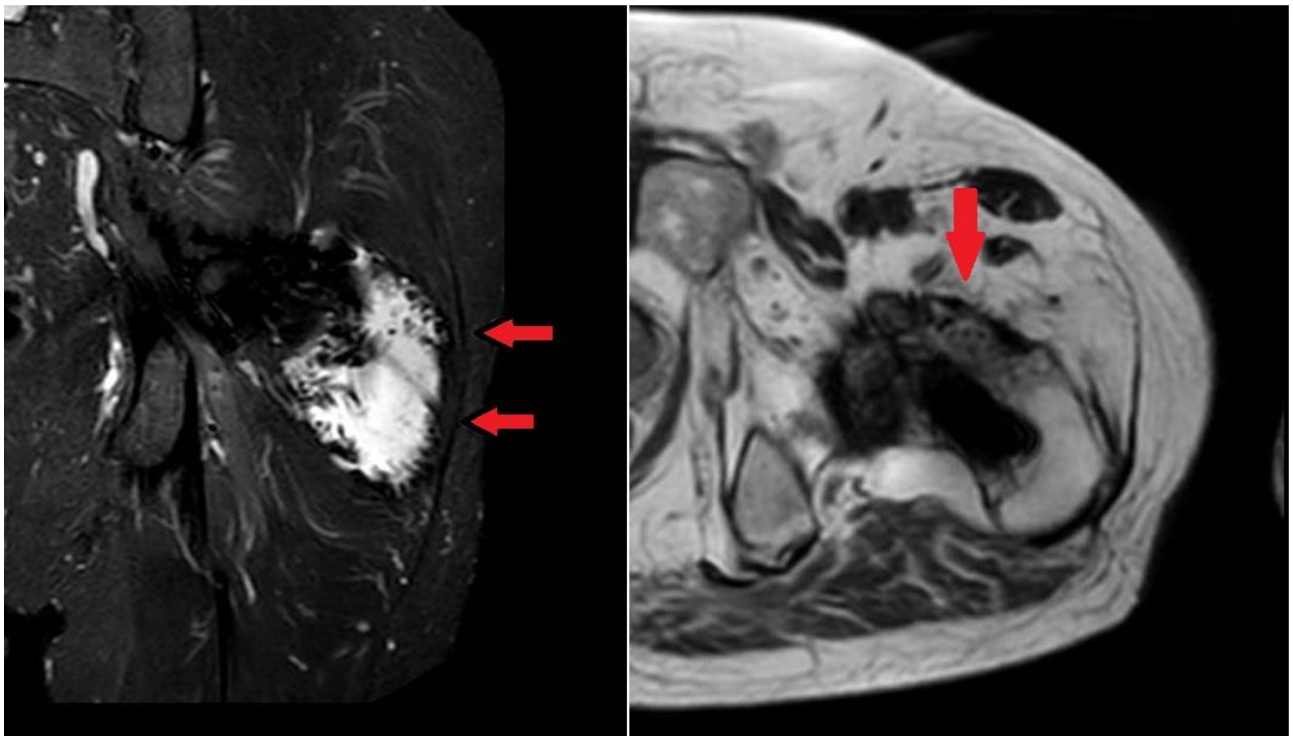

Figure 6. Pseudotumors on OMAR MRI. Left: Type II pseudotumor on STIR. Right: Type III pseudotumor on TW2.

(MRI), ultrasonography (US) or peroperatively during revision surgery (185). It is still debated which diagnostic imaging modality is superior, but they all require experienced musculoskeletal radiologists (185–190). The clinical significance of pseudotumors remain unclear. In some cases PTs can lead to destruction of local tissue with local arterial embolization, hemorrhage, nervepalsy or osteolysis (191–195). However, most PTs are not associated with symptoms in most studies (132,143,144,196) although the largest study on this subject did find an increased risk of symptoms with PT (129). Some studies have found an association between symptoms and size of the PT (131,197). Solid PTs might also result in more symptoms than cystic PTs (130,131,198). Studies with repeat imaging over time show that PTs can regress or disappear, but most are stable (132,133,196,199,200). Solid PTs seem to be stable (133) while cystic PTs are known to regress (201,202). Some authors have even suggested that the cystic PTs might just reflect the surgical approach (203–206). While PTs can form around MoP THA they are rarely a cause for revision (207). On the other hand, PTs around MoM THA together with symptoms and elevated blood levels of cobalt and chromium might lead to revision surgery, although no clear threshold exists (208) and large differences in clinical practice exist internationally (209). Early reports indicated that revision surgery because of PTs could lead to poor clinical outcome (210,211) leading some authors to argue for early revision (114,212,213) while others suggest putting less importance in PT regardless of size and PT classification as clinical outcome after revision surgery might not be associated to these characteristics (214). Since it has become known that some PTs form around

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MoP THA only 1 long-term study about PTs with repeat imaging has included a control group with a low PT prevalence of 4 in 54 patients (215). In a longitudinal study with a midterm follow-up and a MoP control group more HRA developed sign of ARMD than MoP and CoP but used another classification of ARMD and only had 5 years of follow-up. More long-term studies into the natural history of PT with a MoP THA control group are needed.

1.6.4.3 Osteolysis due to metal debris

Like with polyethylene wear the inflammatory response in the juxtarticular tissue created by the metal debris from MoM hip arthroplasties can cause osteolysis and loss of fixation of the implants. Medial calcar erosion seen on ordinary radiographs have been associated with MRI detected ARMD (193). The osteolysis combined with the feared necrosis of soft tissue has led to some authors recommending early revision (114,212,213). However, 1 case report have shown that even quite large areas of osteolysis can go into remission over time in a patient who have refused revision surgery (216).

The risks of complications related to choice of bearing are compared below (Table 1):

	MoXLP	MoM	CoC	CoXLP
Aseptic loosening	↔	↑?	↓	↔
Dislocation	↔	↓*	↓?	↔
PJI	↑?	?	↓?	↓?
Periprosthetic fracture	↔	↑*	↔	↔
ARMD	↑	↑	↓	↓
Component failure	↓	↓	↑	↑

Table 1. Greater (↑) or lesser (↓) risk of complications for MoXLP, MoM, CoC or CoXLP.

1.7 Follow-up programs for metal-on-metal hip arthroplasty

Since the inferior survival and adverse effect of MoM hip arthroplasties became well-known, the use of MoM bearings has almost ceased, and some implants recalled from the marked (24,95,114). However, as these implants were especially used for young patients (79) thousands of

patients still have their MoM hip arthroplasty. As described above the prognosis of the survival and adverse effects for the remaining patients with MoM hip arthroplasties are uncertain. This has led most countries to implement follow-up programs for all patients with MoM hip arthroplasty for the entire lifespan of the implants (113–116). These follow-up programs include patient interviews, blood test for cobalt and chromium levels, diagnostic imaging for ARMD, and physical examination. However, as little is known about the prognosis and diagnostics several challenges exist. These follow-up programs are also expensive and require trained personnel such as musculoskeletal radiologist.

1.8 Motivation

With projections of increased number of young patients receiving THA, longer life expectancy and higher requirement for physical activity together with poor clinical outcome after revision surgery, finding the bearing with the best prognosis for this segment of patients is very important. However, only few large population-based studies have examined the survival and risk of revision in young patients beyond 10 years after surgery. These studies did not exclude hip fracture, inflammatory arthritis, femoral head osteonecrosis or ‘unspecified diagnoses’ or distinguish between the older metal-on-conventional-polyethylene and MoXLP which could be significant confounders. It is also very important to know the natural history of ARMD as these form part of the decision to perform revision surgery with possible poorer clinical outcome as a result. Finally, US has been suggested as an alternative to MRI to detect PT, but all studies in this field have used experienced musculoskeletal radiologists which are not available at every hospital. If other trained clinicians could accurately perform US of the hips, US could be performed to assess the need for MRI. However, no study has investigated how a non-radiologist performs when detecting PTs with US. All these gaps in knowledge warrant further investigation.

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2. Aims

The aims of the thesis were:

Study I:

To investigate the sensitivity and specificity to detect PTs when an orthopedic surgery resident after a short training program performed US scans on patients with THA compared with MARS-MRI as a gold standard. Secondly, we investigated the sensitivity and specificity for US to detect PTs in obese and non-obese patients.

Study II:

To investigate how ARMD, metal ion blood levels and PRO changes over time in HRA, MoM and MoP THA at 4 and 13 years.

Study III:

To compare the survival and hazard ratio (HR) of revision of primary stemmed cementless THA with MoM, CoC and CoXLP to that of MoXLP bearings in patients aged 20-55 years diagnosed with osteoarthritis or childhood hip disorders.

3. Methods

3.1 Literature search

The literature search was not part of a systematic review. The literature search was conducted throughout the study period. The medical subject headings (MeSH) term ‘Total hip arthroplasty OR total hip replacement’ was combined with the relevant MeSH terms or keyword in each study or subject of the thesis.

Examples of keywords used are ‘pseudotumor’, ‘ultrasonography OR ultrasound’, ‘magnetic resonance imaging OR MRI’, ‘adverse reaction to metal debris OR adverse local tissue reaction’, ‘sensitivity’, ‘specificity’, ‘cobalt’, ‘chromium’, ‘metal-on-metal’, ‘metal-on-polyethylene’, ‘metal-on-highly-crosslinked-polyethylene’, ‘ceramic-on-ceramic’, ‘ceramic-on-highly-crosslinked-polyethylene’, ‘survival’ and ‘revision’. However, there are no complete record of all literature searches used in this PhD project.

In addition to the literature searches described above the annual reports of hip arthroplasty registers and reference lists of other articles on the subject were reviewed. Studies less than approximately 10 years old were preferred except when the historical significance of older articles was recognized.

3.2 Data sources

In Denmark, Norway, Sweden, and Finland every citizen is given a unique and personal identification number that is registered in the national population system of each country. This identification number is used in all local and national healthcare registers. These 4 countries have a combined population of approximately 27 million citizens and similar largely tax supported public healthcare systems (217). This offers the possibility to collect large amounts of medical data with a high completeness and quality. In Study I and II a cohort was based on information from the Danish Hip Arthroplasty Register (DHR) and in Study III a cohort was based on information from the Nordic Arthroplasty Register Association (NARA) dataset.

3.2.1 The Danish Hip Arthroplasty Register (Study I and II)

The DHR was established in 1995 with the aim of improving the quality of THA surgery by monitoring all primary and revision surgery procedures performed in Denmark (218). Registration of procedures are compulsory in both public hospitals and private clinics (219). In 2021, the DHR contains a registration completeness of 97% for primary surgery and 92% for revision surgery

compared to information in the Danish National Patient Register (23). The orthopedic departments of each hospital are funded from the Danish government according to their reporting to the Danish National Patient Register which is therefore considered gold standard.
Data registered in the DHR includes patient characteristics, date of surgery, implant characteristics and more.

3.2.2 The Nordic Arthroplasty Register Association dataset (Study III)

To obtain the largest available study population data from the NARA dataset was used. The dataset was formed in 2007 where data from the national hip arthroplasty registers in Denmark, Norway and Sweden were included in a common minimal dataset (220). In 2010 data from the national hip arthroplasty in Finland was included as well (221).
The NARA dataset contains information from nearly all hip arthroplasty surgery performed in these 4 countries, which amounts to 572,552 hip arthroplasties implanted between 2005-2018. That is the version of the dataset used in Study III.
The variables of the 4 national hip arthroplasty registers are not completely similar and could therefore not be merged in its entirety. The NARA dataset therefore consist of 36 variables with agreed upon definitions. Before merging the selected data, it was anonymized (220).
Registration completeness varies from 90-98% for primary surgery and 85-94% for revision surgery compared with the national patient registers in each country. Data is frequently validated within the national registers ensuring a high data quality (222) (Figure 7).

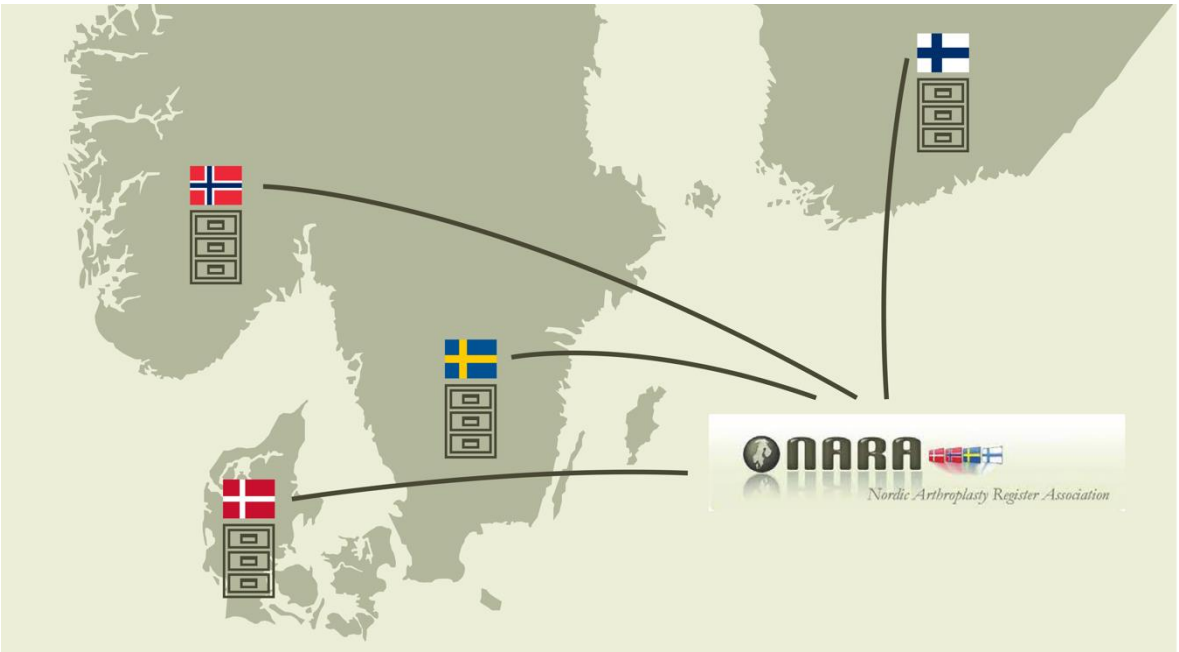


Figure 7. The Nordic Arthroplasty Register Association.

3.3 Design and study population

When comparing outcomes of different interventions, the randomized controlled trial (RCT) is considered the gold standard. The advantage of this design is that the randomizing process ensure exchangeability meaning that all measured and unmeasured confounders are balanced between the intervention and control group. The term confounder is discussed in section 3.10. High quality RCTs are therefore able to conclude on causality while observational study designs can only conclude on associations. However, for rare outcomes or outcomes that occur many years after the intervention the RCT might not be feasible in terms of economy, management, and ethics (223).

3.3.1 Study I

To answer the aim of Study I a diagnostic study was performed where the ability of US to detect PT in the hands of a non-radiologist was compared to MRI. Ideally, a sample size that takes the disease prevalence into account would then be calculated as described by Buderer (224). This would require expected sensitivity, expected specificity, expected prevalence of disease, significance level, precision and expected dropout rate. A non-radiologist such as an orthopedic resident would then be trained to perform US to detect PT on the number of patients with the expected prevalence of the disease from the power calculations.

However, previously at my institution a cross-sectional cohort was defined with the aim of detecting differences in prevalence of PT in HRA, MoM and MoP THA were conducted. An orthopedic resident was trained with a standardized training program to detect PT with US. All patients also had their THA/HRA scanned with metal artifact reduction sequence (MARS) MRI and the images were interpreted by an experienced musculoskeletal radiologist. The data could be used as the diagnostic test (US) and the gold standard (MARS-MRI).

In total, 205 hip arthroplasties were scanned with both US and MARS-MRI. This is the largest sample size compared to other studies into the sensitivity and specificity of US to detect PT with MRI as gold standard (187–190). Sample size calculations should not be performed post hoc (225) but if the same sensitivity and specificity as other studies was used (85% and 90%) with a disease prevalence of 25%, a significance level of 0.05 and a precision of 10% then 196 patients would be needed for this study.

It was therefore decided to use those data. The cohort was used in Study I and Study II.

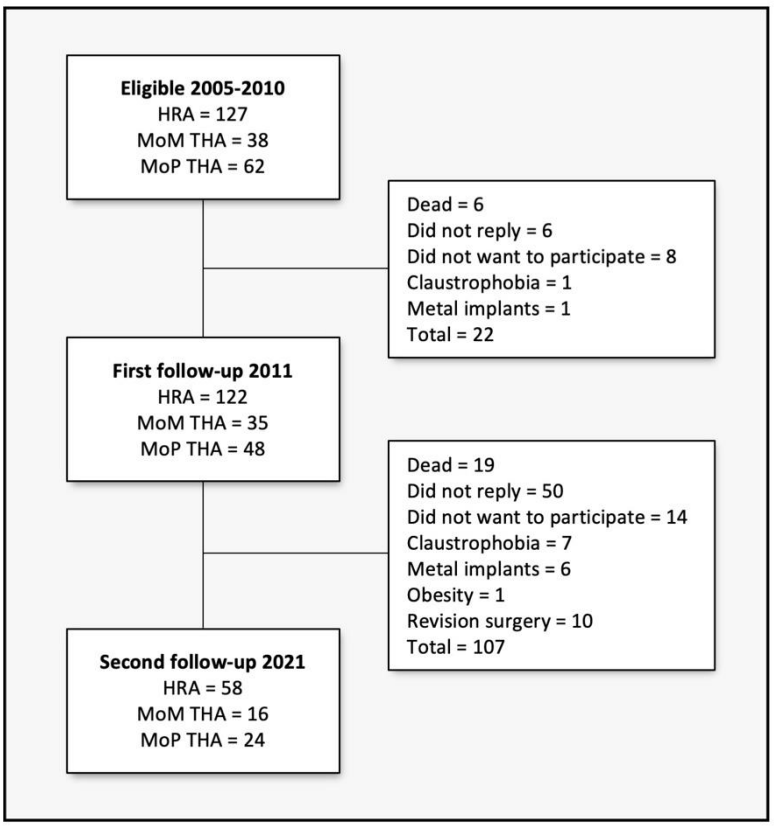
3.3.2 Study II

In Study II the aim was to compare diagnostic imaging, blood levels of metal ions and PROM between 3 interventions at 2 points in time. A large long-term RCT would ideally be used for this comparison to reduce or eliminate the effect of confounders. However, as mentioned earlier in this thesis MoM bearings are almost no longer used as they have shown inferior survival compared to all other bearings. A RCT started in recent years would therefore not be feasible nor ethical. As it is more than 10 years since the usage of MoM bearings stopped, the study also required MoM and MoP THA that had already been examined few years after surgery in a standardized manor.

Fortunately, a cohort of HRA, MoM and MoP THA patients were previously formed at my institution and examined as part of a cross-sectional cohort study into the prevalence of PT between different hip arthroplasties and data was never published. I set out to use data and collect new data from this cohort in a prospective cohort study.

The cohort size was based on an 80% power calculation where PT prevalence was expected to be 9% in HRA and 0.3% in MoP THA. These calculations showed a need for 141 patients with MoM arthroplasty (HRA and MoM THA) and 47 patients in the MoP group. There was no original intend to re-examine the cohort and drop out or exclusion of patients at later examinations were therefore not originally considered. However, as no longitudinal long-term study into this subject has been conducted including a control group, the study was still considered merited.

The patients enrolled in the study form 2 centers: Odense University Hospital and Næstved Hospital. In 2011, the patients were identified from the Danish Hip Arthroplasty Register. All patients with HRA (ASR Hip resurfacing system, Depuy/Johnson&Johnson, Raynham, Massachusetts, US) and MoM THA (M2a Magnum, Biomet, Warsaw, Indiana, US) who underwent surgery between 2005-2010 were invited. The MoP THA (Mallory head/Bimetric, Biomet, Warsaw, Indiana, US) patients were matched with the first 48 from HRA patients enrolled. The control group was matched on gender, age and date of surgery +/- 2 months.



Figre 8. Flowchart of inclusion and exclusion of patients in Study II.

In total, 169 patients with 122 HRA, 35 MoM and 48 MoP THA were included in the cohort in 2011. 36 patients had bilateral hip arthroplasty. A total of 205 hip arthroplasties were included. Bilateral hip arthroplasty in this study was allowed as PT formation in the local tissue of each hip was considered independent of each other.

The patients in the cohort were invited to participate in the study again in 2021 where 78 patients with 58 HRA, 16 MoM and 24 MoP THA totaling 98 hip arthroplasties accepted the invitation and were included. 20 patients had bilateral hip arthroplasty (Figure 8).

3.3.3 Study III

The assess the effect choice of bearing has in young patients a large long-term RCT would be ideal. However, it would also be extremely expensive, difficult and time consuming. It was therefore decided to use the prospectively collected data in the NARA dataset in the cohort study as this presented the best way to gain a large sample size with a long follow-up. Data from registers can be used to emulate RCT in a study design called target trial but it requires sufficient information about baseline confounders to mimic the RCT random assignment (226). As MoM and CoC were introduced for the active patients the choice of bearing might not be randomly assigned to patient with different activity level, comorbidities, and physically demanding occupations. It was therefore decided to conduct a prospective cohort study.

Young patients was defined as patients between 20-55 years of age. Stemmed (not resurfacing) and cementless (uncemented stem and cup) THA were included as this design and fixation are known to have superior survival in this age group (23). Patients with the diagnosis OA and

childhood hip disorders were included. OA is the most common diagnosis for THA. Hip dysplasia, slipped capital femoral epiphysis or Perthes disease are all combined into childhood hip disorders. Previous studies with this definition of childhood hip disorders have shown similar survival of THA as for OA (227,228), while other diagnoses such as femoral neck fracture, non-traumatic necrosis of the femoral head and rheumatoid arthritis have inferior THA survival compared to OA and were therefore not included (24,107,108). The start of the study period was sat at January 1, 2005 as the 4th generation of ceramic was introduced in 2004 according to the manufacturer (CeramTec, Plochingen, Germany) and the usage of MoXLP instead of MoP became popular around the same time. However, ceramic material is not captured in the NARA dataset. The dataset used in Study III included patients who underwent surgery up until December 31, 2018. Patients were included until December 31, 2017 thereby allowing a minimum of 1-year follow-up.

THAs with dual mobility cups were excluded even though similar survival has been found compared to ordinary cups in older patients (229). However, the survival of dual mobility cups in this age group could be different. Stem and cup designs used less than 50 times in each country were considered a learning curve and excluded. THAs with missing data on cup, stem, fixation, diagnosis, or size of femoral head were excluded. THAs with missing revision cause were still included in the analyses of HR of revision for any cause. THAs with femoral heads smaller than 28 mm were excluded as less than 50 cases were found. Only the first surgery was included in patients with bilateral THA to make observations independent. After these exclusions 21,594 patients remained (Figure 9).

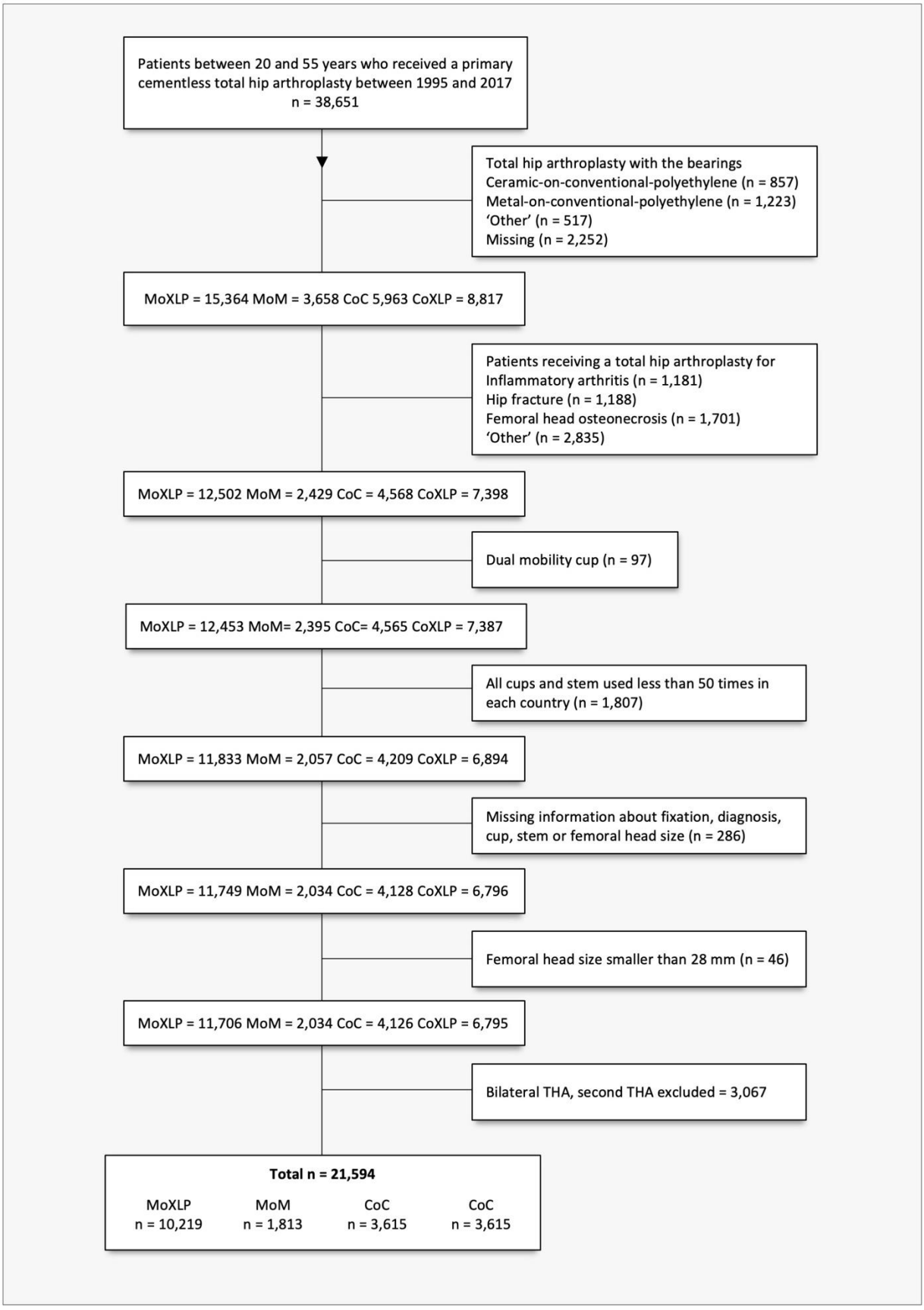


Figure 9. Flowchart of inclusion and exclusion of patients in Study III.

3.4 Adverse reaction to metal debris – classifications

ARMD is a wide range of inflammation and destruction of local bone and soft tissue (section 1.6.5). We chose to focus on PT as the long-term clinical significance remains unclear, but the presence of PT is still taken into account when considering revision surgery. Different PT classifications exist to describe PT characteristics such as Hauptfleisch (198), Anderson (230), Matthies (231), Boomsma (194) and Hart (183). Of these Hauptfleisch and Anderson classification seems to be the most widely used in the literature. All PT classifications were developed from short-term MoM case series with no control group of standard bearing THA. Different classifications have shown similar interobserver reliability (232), but Hauptfleisch was preferred as the definition of PT seemed easy to understand and the PT classification had taken patient symptoms into account under development of the classification. Moreover, the Hauptfleisch PT classification is the reference in our national follow-up program (113). The Hauptfleisch PT classification consist of the following 3 categories (Table 2):

Hauptfleisch pseudotumor classification	Pseudotumor characteristics
Type I	Thin-walled cystic mass (cyst wall <3 mm)
Type II	Thick-walled cystic mass (cyst wall >3mm, but less than the diameter of the cystic component)
Type III	A predominantly solid mass

Table 2. The Hauptfleisch classification.

3.5 Ultrasonography

For the US a 7L4s linear 5-10MHz transducer (Mindray M7 high powered color doppler laptop, Mahwah, New Jersey, US) was used. PT was defined as any solid, cystic or mixed mass, in continuity of the hip joint or arthroplasty. On the US scans this was interpreted by the PT hypo- or hyperechogenicity. One orthopedic surgery resident conducted the US examinations. He had been trained according to the European Federation of Societies for Ultrasound in Medicine and Biology Guidelines ‘Minimum Training Requirements for Rheumatologists Performing Musculoskeletal

Ultrasound' (233). This training program includes 300 US scans of joints, supervised by an experienced radiologist. The orthopedic surgery resident was solely trained in hips.

The US examination consisted of 8 projections as recommended by Hansen et al. (234). The projections used were 1. Anterior, longitudinal/oblique 2. Anterior transversal 3. Medial, longitudinal/oblique 4. Medial, transversal. Projections 1-4 were performed with the patient in a supine position. 5. Lateral, longitudinal/oblique 6. Lateral, transversal. Projections 5-6 were performed with the patient in a lateral position. 7. Posterior, longitudinal 8. Posterior, transversal. Projection 7-8 were performed with the patient in a prone position (Figure 10).

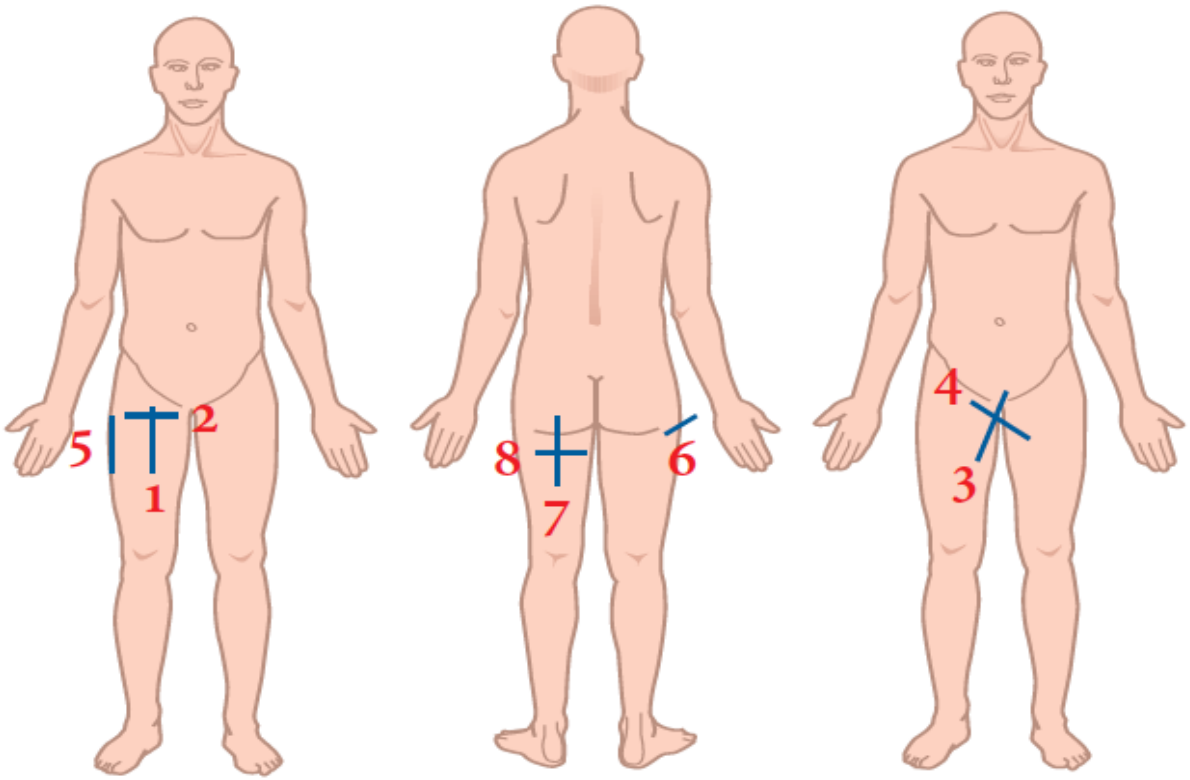


Figure 10. Projections used in the US examinations.

The abdominal convex transducer (3.5-5 MHz) was used for obese patients to create an overview. Then the examination continued with a linear transducer.

3.6 MRI

In Study II MRI in 2011 and 2021- was used. Obviously, the technology evolved in the meantime. Therefore, the MRI scanners and the protocols were different at those 2 points in time. Both protocols were designed to reduce the biggest obstacle with MRI and orthopedic implants: metal

artifacts. Metal artifacts obscure the view of all tissue next to the orthopedic implants by distortion of the magnetic field.

The first MRIs were performed in an open 1 Tesla MRI scanner (Philips Panorama, Best, Nederland) with the following technical MARS-MRI sequences: transversal and coronal T1, coronal T2 and a coronal STIR. For reduction of artifacts resulting from the metal prothesis the bandwidth was increased, and matrix size altered.

Technology evolves and therefore the second MRIs were performed in a closed 1.5 Tesla MRI scanner (Philips, Best, Nederland) with the following technical orthopedic metal artifact reduction software (OMAR) MRI sequences: coronal OMAR STIR, coronal T1, axial T2 OMAR XD and axial T1. The T1W series were performed for the specific hip while the STIR and T2 were performed for the pelvis. The protocol involves view angle tilting (VAT) and slice encoding metal artifact correction (SEMAC) that further reduces metal artifacts.

PT was defined as any mass, solid or cystic mass, in continuity of the joint according to the Hauptfleisch PT classification system (198) (section 3.4) with no minimum size. Cystic masses only situated at bursae and no additional fluid in the joint was interpreted as bursitis. Picture Archiving and Communications System (PACS) (General Electric Healthcare Centricity, Illinois, Ca, USA) was used for all MRI analyses. The MRIs were reviewed twice 1 month apart by 1 experienced musculoskeletal radiologist. The radiologist was blinded of her previous assessments. The volume of PT at second examination was calculated by multiplying the greatest dimension in 3 planes as in other studies in the fiel (235,236).

3.7 Metal ion levels

Blood levels of cobalt and chromium were measured in full blood in all patients at second examination while none of the MoP THA patient had cobalt and chromium examined at first examination. The blood samples were taken according to the protocol described by Penny et al. (237) and handled as described by MacDonald et al. (238) The blood samples were frozen and analyzed as a batch. The thresholds for elevated cobalt and chromium were defined as 7 ug/L as this the cut off in most follow-up programs (113–116).

3.8 PROM

PROs are statements about the patients' health, quality of life and functional status directly reported by the patients without interpretation by a clinician. PROM are tools to measure PRO typically in the form of questionnaires the patients fill out (239).

Harris Hip score (HHS) which was used in Study III is strictly not a PROM since items are fulfilled by the physician and not the patient. It was developed to assess the results of hip surgery and consist of 10 items (240,241). The scale ranges from 0 (low) to 100 (high). Studies have shown unacceptable ceiling effect of HHS (242), however HHS is used in some studies that our results might be compared to (133,144,215) and therefore included in Study II.

UCLA activity score consist of a single question regarding the physical activity of patients undergoing total hip or knee arthroplasty. The scale ranges from 1 (low – cannot leave residence) to 10 (high - regularly participates in contact sport) and has been validated in Danish (243).

Information about HHS and UCLA activity score was available from the first examination of the patients in Study II. It was decided to also include the Oxford Hip Score (OHS) for the second examination. OHS gave a more detailed view into the patients' life although only at the second examination. The OHS consist of 12 questions regarding function and pain in patient undergoing total hip arthroplasty. The scale ranges from 0 (low) to 48 (high) and has been validated in Danish (244).

3.9 Statistics

Data was analyzed in STATA version 16.1 (STATACorp, TX, USA).

Study I

Patient characteristics were given as medians and range due to skewness. Normal distribution was tested with Q-Q plots and Shapiro-Wilks test. Results of the MRI scans were used as the gold standard, when calculating sensitivity, specificity, positive predictive value and negative predictive value of ultrasonography, and 95% confidence intervals (CI) were calculated. Sensitivity and specificity were calculated for all patients and stratified as obese and non-obese.

Study II

Fischer's exact test was used to compare proportions as it is more suitable for small sample sizes than chi squared. Normal distribution was tested with Q-Q plots and Shapiro-Wilks test. Most continuous variables were not normally distributed, and results were given as medians and range. Wilcoxon rank sum test was used to compare medians of continuous variables in 2 groups and Kruskal-Wallis test for 3 groups. If Kruskal-Wallis showed a p-value below 0.05, Dunn's test corrected with Bonferroni adjustment was used to show HRA and MoM THA compared to MoP THA.

The 4 patients with MoP THA with either a HRA or MoM THA on the contralateral side were excluded in the analyses of cobalt and chromium, as their blood levels of these metals might be elevated because of the MoM arthroplasty. In the analyses of the participants excluded for second examination age and potential follow-up are given at June 30th 2021. Ninety-five percent confidence intervals (CI) were given and a p-value below 0.05 was considered significant.

Study III

Different methods could have been used to assess which bearing was least likely to require revision surgery. As mentioned earlier a RCT or target trial would be ideal, but it was considered most realistic to conduct a population-based prospective cohort study using data from national arthroplasty registers.

I chose to use Kaplan-Meier survival function and Cox regression as these are 2 well known statistical approaches used in other studies we refer to. I chose not the use death as competing risk in these young patients as we expected death to be rare in the study period.

I calculated survival function and hazard ratio (HR) of revision for any reason and specific causes. In the dataset revision causes are categorized as aseptic loosening, prosthetic joint infection, periprosthetic fracture, dislocation, pain only and 'other'. 'Other' being reasons not covered by the beforementioned categories. Revision was defined as any surgical intervention with partial or complete exchange or removal of the THA components. Patients were censored at the time of revision surgery, death or end of study.

For demographic characteristics we used descriptive statistics. Age and follow-up were given in medians with interquartile range (IQR) due to non-normal distribution assessed with Q-Q plots and Shapiro-Wilks test. We used Kaplan-Meier estimator for survival function. Cox regression was used to calculate HR for revision.

MoXLP was the most frequently used bearing, therefore considered the standard bearing and used as reference in all analyses. I tested the assumption of proportional hazards by log-log plots and Schoenfeld residuals. To meet the assumption of proportional hazards we split the analyses into 3 periods: 0-2, 2-7 years and 7-13 years.

Adjustments were made for possible confounders (23,24): gender, age, diagnosis, year of primary surgery and femoral head size in the Cox regression for revision due to any cause. In our Cox regression we allowed no more than 1 degree of freedom of the covariates for every 10 events to prevent the model from being overfitted (245). I could therefore only perform revision cause specific Cox regression for revision caused by ‘others’ as too few events occurred in each period due to the remaining revision causes. Cox regression for revision caused by ‘others’ was adjusted for sex, diagnosis, year of primary surgery and size of femoral head.

Sensitivity analyses were performed to study effect modification for gender (adjusted for diagnosis and year of primary surgery) and for OA (adjusted for gender, age, year of primary surgery and femoral head size). I also performed a sensitivity analysis with the 5 most common combinations of brand specific cup and stem with CoC articulation with all 28 mm head CoC THA excluded (adjusted for gender and diagnosis). The latter analysis was performed as ‘other’ was the most common revision cause for CoC which could cover head and liner fracture, a revision cause that is not specified in the NARA dataset. All MoXLP THAs served as reference. I excluded 28 mm head CoC THA as this head size constitutes the major difference in risk of fracture between 3rd and 4th generation ceramic (122). I did not perform this analysis for CoXLP as similar revision causes between MoXLP and CoXLP were found.

To assess the possible impact of information bias (see section 3.10.2) due to missing information different statistical methods can be used such as versions of imputation. I chose to perform worst-case scenarios to assess the most extreme way the results could be affected. Those patients with missing information about their bearings were included in either the MoXLP, MoM, CoC or CoXLP groups in 4 analyses and the effect on HR for revision were assessed.
95% confidence intervals (CI) were given and a p-value below 0.05 was considered statistically significant.

3.10 Bias and confounding

Several factors can influence the validity of the results in scientific studies. These factors can be separated into bias and confounding. Both can lead to false conclusions, but the mechanisms of bias and confounding are different. Different types of bias are caused by systematic errors in the study design or conduct that distorts the results away from what is seen in the real world. Bias can be differential and non-differential. Differential bias happens when the bias is associated to both the exposure and the outcome while non-differential bias is only associated to either exposure or outcome but not both. Differential bias will affect the estimates of the study while non-differential bias will not. Confounding on the other hand occurs when factors are associated with both the studied exposure and outcome, and if the factors are unequally distributed between the groups studied.

3.10.1 Selection bias

A common bias in scientific studies is selection bias. It occurs when the association between exposure and outcome differs in those eligible versus those included, when inclusion in study is associated with the outcome.

Study I

In diagnostic studies typical versions of selection bias includes partial verification bias and spectrum bias. Patients in the HRA and MoM THA group were consecutively invited and few excluded in the diagnostic study. No index test was required to be included. Partial verification bias and spectrum bias was therefore not considered a problem in the HRA and MoM THA group. However, MoP THA was included in the diagnostic study and compared to the findings of other studies where only MoM THA had US scans performed. This could lower the disease prevalence, but disease prevalence turned out the be similar in the MoP group making the impact of spectrum bias less likely.

Study II

One of the reasons to perform this study was because previous studies contained selection bias as they did not include the standard MoP THA as a reference in the making of PT classifications.

However, roughly half of the cohort was excluded between the 2 examinations. This could result in selection bias. Patient characteristics, PT prevalence and PROM scores were similar between those included in both examinations and those only included in the first indicating selection bias from drop-out to be less pronounced. 50 patients did not respond, and 14 patients did not want to

participate. The second examinations were conducted during the Covid-19 pandemic, which could have affected the invited patients' willingness to participate. Patients with more comorbidities might have been more prone to self-isolate and less able to respond to the digitally based invitation. The result might be selection bias out of the cohort.

The study design of Study II also includes survivor bias another form of selection bias out of the cohort. I excluded all patients who underwent revision surgery. Therefore, all short- or mid-term failures were excluded before the first and second examinations. I thereby study those patients with the best outcome of the surgery. However, the intend of this study is not to investigate whether HRA or MoM THA bearings should be used but rather to obtain knowledge about what is radiologically normal and pathological in those still included in the MoM follow-up programs in the future.

Study III

Selection bias in population-based register studies occur if one group or certain study participants within this group are more likely to be lost to follow-up. In Study III the NARA dataset was used and it has a registration completeness of 90-98% for primary surgery and 85-94% for revision surgery. I therefore possibly miss 1:10 revisions which is our main outcome and the differences in survival and risk of revision for 3 of the bearings are small. If 1 bearing group is more likely to have incomplete registration of revision surgery, then selection bias could affect our results.

3.10.2 Information bias

Another form if bias is information bias often called measurement bias and occurs with systematic errors in measuring, collecting, remembering, recording, and storing data. Missing data is a type of information bias.

Study I

Information bias in a diagnostic study could occur if the examiner of the index test knew the results of the reference test (246). However, MARS-MRI scans (the reference test) were performed after US (the index test) and the radiologist interpreting the MARS-MRI images were blinded regarding the results of US. All data was collected prospectively, and all MARS-MRI scans were reviewed twice by the radiologist. It was therefore consided that the possible impact of information bias was low.

Study II

All data was collected prospectively which eliminates recall bias. All MRI scans were evaluated twice by an experienced radiologist, the first MRI scans were even evaluated again in 2021 which should reduce misclassification bias. However, the MRI scanners did improve between the first and second examination. We found new but small PTs in the second examination. I cannot know whether these were new or the improved MRI technology in the second examination made it possible to see PTs that had been there the whole time. Some missing information about blood levels of metal ion and PROM scores in the first examination could lead to information bias. Some patients also needed assistance to fill out the electronic questionnaires prior to the second examination. This makes the results less reliable than they ideally could be.

Study III

I could not adjust for generation of ceramic which is a known risk factor for femoral head fracture, especially for 28 mm heads (122). Even though the 4th generation of ceramic was introduced in 2004, it is unknown when it became dominant in this dataset. Generation of ceramic is an unmeasured confounder in this study. However, the sensitivity analysis with the 5 most common stem and cup combinations in CoC THA without 28 mm heads did not change the results.

2,252 patients were excluded because of missing information about type of bearing. This could result in possible information bias if 1 bearing group was more likely to have missing bearings. Only the worst-case scenario with all missing bearings being MoXLP or CoXLP changed the results markedly. However, 53% of the missing bearings were operated between 2005-2009 which is before MoXLP and CoXLP were widely used. The possible impact of the information bias is therefore considered low.

3.10.3 Confounding

A confounder is a factor with 3 characteristics (Figure 11):

1. It is associated with the exposure.
2. It is an independent risk factor for the outcome.
3. It is not an intermediary step in the causal pathway.

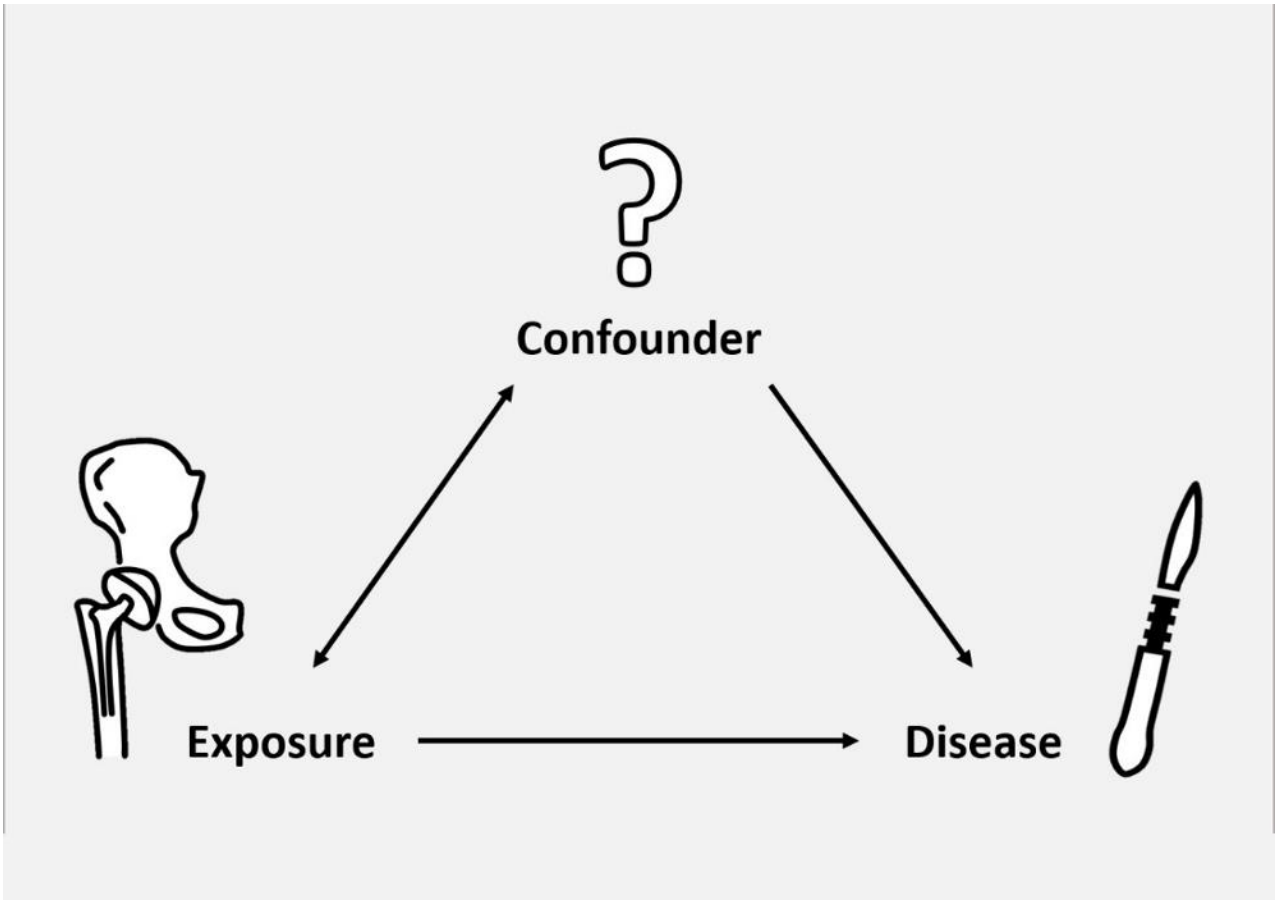


Figure 11. The confounder triangle.

In randomized controlled trials confounders are in theory equally distributed between the intervention and control group and the effect on the estimates is thereby eliminated. However, it is often the case that not all confounding can be controlled in the study design and will often have to adjust for in the statistical analyses using different regression models. Confounding can occur in all observational studies. As described under ‘Statistics’ we tried to eliminate the effect of certain confounder in our study design in Study III be excluding patients with known on suspected confounders such femoral neck fracture, rheumatoid arthritis, femoral head osteonecrosis (24,107,108), dual mobility cups, resurfacing design, fixation (23,24), femoral head size below 28 mm and brand specific cups and stem used less than 50 times in each country. However, it was still needed to adjust the Cox regression for gender, age, diagnosis, year of primary surgery and femoral head size as they could affect the outcome (23,24).

Male patients generally have a higher risk of revision compared to females patients (23,24), although female patients have a higher risk of developing ARMD (247) and surgeons were

precautious concerning teratogenicity from metal ion release in female patients in the fertile age. Therefore, fewer women received MoM THA. Gender could thereby meet the criteria of a confounder.

Study III only included young patients and we know the implants in younger patients have the lowest survival and highest risk of revision compared to implants in older patients. However, I still adjusted for age, as 20-year-old patients might have a higher risk of revision compared to 50-year-old patients (23,24) and the younger the patient the more likely they might have been to receive MoM or CoC. Age could thereby meet the criteria of a confounder.

I adjusted for year of primary surgery as treatment with hip arthroplasties are constantly improved and newer THA have a superior survival and risk of revision compared to older THA (23,24). Some choices of bearings are more prevalent in certain years compared to others like when everyone thought MoM was the next big thing. Year of primary surgery could thereby meet the criteria of a confounder.

I adjusted for size of femoral head because as we mentioned in section 1.5.1 different head sizes have different survival, complications and risk of revision which are different for MoXLP, MoM, CoC and CoXLP (72). Therefore, different head sizes might be selected for these bearing. Size of femoral head could thereby meet the criteria of a confounder.

In a previous study of THA for OA and childhood hip disorders had similar risk of revision (227). However, they included all age groups. They did adjust for age but with much larger intervals than applies for our study. The anatomy in OA and childhood hip disorders is different which could lead to differences in choice of size and type of implant. This could lead to differences in size of femoral head and thereby bearings. Diagnosis could thereby meet the criteria of a confounder.

However, there are limitations to how many variables it is appropriate to adjust for in a regression model. As a rule of thumb 1 degree of freedom for every 10 events is a widely agreed upon limit to avoid the models from being overfitted (245). That is also the reason why it was chosen not to perform regression analyses in Study II as too few events occurred because of the small sample size.

Even though adjustments for possible confounders were made in the Cox regression in Study III some possible unmeasured confounders might still remain. As MoM and CoC THA were originally

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introduced for the active and young patients (75) these patients could have a higher activity levels, more physically demanding jobs, and fewer comorbidities than the MoXLP patients. Higher activity levels and physically demanding jobs could lead to more wear, aseptic loosening, ARMD and fracture of head and liner. While fewer comorbidities could lower the threshold for revision surgery as fewer per- and postoperative complications is expected in those patients. However, these are factors that are not included in the available data, and we currently do not have a way of obtaining them.

4. Main results

4.1 Study I

In this study 205 hips were included of which 122 had HRA, 35 MoM and 48 MoP THA. The median follow-up was 5 years (range 2-7 years). MRI found a prevalence of 50 PT out of 205 hips (24%). 142 non-obese and 60 obese patients were included in this study.

The sensitivity was 0.92 (CI 0.81 – 0.98), the specificity was 0.94 (CI 0.89 – 0.97), positive predictive value was 0.84 (CI 0.73 – 0.91) and the negative predictive value was 0.97 (CI 0.93 – 0.99) for US to detect PTs when MRI findings were used as gold standard.

The sensitivity and specificity for non-obese and the obese patients were also calculated. These analyses showed sensitivity and specificity of 0.89 (CI 0.74-0.97) and 0.92 (CI 0.85-0.97) for non-obese and 0.93 (CI 0.66-1.0) and 0.98 (CI 0.89-1.0) for obese.

4.2 Study II

98 hips in 78 patients in both 2011 and 2021 were included. 58 had HRA, 16 had MoM THA and 24 had MoP THA. Median follow-up for all patients were 4.4 (range 0.39-6.6) and 13 years (10-16) in 2011 and 2021, respectively.

The total prevalence of PT was 28 in 2011 and 18 in 2021. The prevalence of PT declined in HRA and MoM THA but increased in MoP THA between the 2 examinations. 16 PTs were no longer visible, 12 remained and 6 new PTs were diagnosed between 2011 and 2021 (Table 2). Overall, there was no difference in 2011 or 2021 in PT prevalence ($p=0.125$ and $p=0.272$) or PT classification ($p=0.346$ and $p=0.872$) between the 3 groups. No pseudotumor grew, 5 regressed and 7 were unchanged in size. The 6 new PTs found in 2021. Two of which were in HRA and 4 were in MoP THA and none in MoM (Table 3).

Cobalt and chromium were elevated above 7 ug/L in 9 and 12 patients in 2021. All these patients had HRA. All but one patient with normal blood cobalt level at first examination had normal blood cobalt at second examination. All patients with normal blood chromium levels at first examination had normal chromium levels at second examination. The blood levels of chromium and cobalt were statistically higher in both HRA and MoM THA compared to MoP ($p<0.001$ and $p<0.001$).

There was no difference in HHS (p=0.272 and p=0.229) between the groups in 2011 and 2021. UCLA activity score was slightly higher in HRA compared to MoM and MoP THA in 2011, but there was no difference in 2021 (p=0.047 and p=0.359). The median OHS in 2021 was similar in HRA to MoM and MoP THA (p=0.060).

Patients with and without PTs in 2021 had no difference in blood levels of cobalt (p=0.450) or chromium (p=0.459), HHS (p=0.475), UCLA (p=0.844) or OHS (p=0.363).

	HRA n = 58	MoM THA n = 16	MoP THA n = 24	P-value
Pseudotumor 2011	19	6	3	0.125
Hauptfleisch classification 2011				
I	9	5	1	
II	7	0	2	0.346
III	3	1	0	
Pseudotumors 2021	9	2	7	0.272
Hauptfleisch classification 2021				
I	5	2	4	
II	1	0	2	0.872
III	3	0	1	
Pseudotumors no longer visible 2021	12	4	0	0.039
Pseudotumors new diagnosis 2021	2	0	4	0.141
Pseudotumor volume 2021 (cm^3)	48 (2-126)	28 (24-32)	16 (2-60)	0.554

Table 3. Pseudotumor prevalence and characteristics in patients included in 2011 and 2021. HRA: Hip resurfacing arthroplasty. MoM: Metal-on-metal. MoP: Metal-on-polyethylene. OHS: Oxford Hip Score. THA: Total hip arthroplasty.

4.3 Study III

I included 21,594 patients between 20 and 55 years of age with cementless unilateral THA for OA and childhood hip disorders. 10,219 patients had MoXLP, 1,813 MoM, 3,615 CoC and 5,947

CoXLP bearings. Median follow-up was 5 years for MoXLP, 10 years for MoM, 6 years for CoC and 4 years for CoXLP.

13 years after surgery the survival was 95% (94-95%) for MoXLP, 82% (80-84%) for MoM, 93% (92-95%) for CoC and 93% (CI 92-94%) for CoXLP bearings.

In the study period 1,012 revisions were performed. The most common revision cause was ‘other’, meaning unspecified reasons followed by prosthetic joint infection.

MoM had similar adjusted HR of revision for any cause as MoXLP during the first period (0-2 years) but had significantly higher HR during the two later periods (adjusted HR for revision of any cause 2-7 years: 3.9 (3.0-4.9), 7-13 years: 3.6 (2.3-5.7)). CoC and CoXLP had similar adjusted HR for any cause compared to MoXLP in all 3 periods. However, the 7-13 years adjusted HR of revision for any cause was almost significantly higher for both CoC and CoXLP compared to MoXLP (Table 4).

Bearing	Number at risk at start of period	Number of revisions in period	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95%CI)
0-2 years				
MoXLP	10,219	230	1 (ref.)	1 (ref.)
MoM	1,813	45	1.1 (0.8-1.5)	1.3 (0.8-2.4)
CoC	3,615	79	1.0 (0.7-1.2)	1.0 (0.8-1.3)
CoXLP	5,947	166	1.3 (1.0-1.5)	1.2 (1.0-1.5)
2-7 years				
MoXLP	8,538	120	1 (ref.)	1 (ref.)
MoM	1,756	141	3.9 (3.0-4.9)	3.6 (2.3-5.7)
CoC	3,284	42	0.8 (0.6-1.1)	0.8 (0.6-1.1)
CoXLP	4,640	69	1.1 (0.8-1.5)	1.2 (0.9-1.6)

7-13 years				
MoXLP	2,726	12	1 (ref.)	1 (ref.)
MoM	1,536	79	8.0 (4.3-14)	4.1 (1.7-10)
CoC	1,294	16	2.7 (1.3-5.7)	2.1 (1.0-4.5)
CoXLP	1,412	13	2.0 (0.9-4.3)	2.1 (1.0-4.6)

Table 4. Unadjusted and adjusted hazard ratios for revision due to any cause from the Cox model by bearing. The hazard ratios have been adjusted for sex, age, diagnosis, year of primary surgery and femoral head size.

Sensitivity analyses

The 5 most common combinations of cup and stem in CoC THA without 28 mm heads (55% of all CoC) were Pinnacle/Corail (n=1,039), R3/Synergy (n=351), Igloo/Filler (n=234), Continuum/M/L Taper (n=262) and Exceed/Bi-metric collarless (n=105). The sensitivity analysis with these 5 combinations revealed a higher adjusted 7-13 years HR 4.4 (1.6-12) compared to HR for CoC THA for the complete study population and period 2.1 (1.0-4.5).

5. Discussion

5.1 Comparison with other studies

In the section below the results of the studies included in this thesis will be compared to the results of other studies.

5.1.1 Sensitivity and specificity of US compared to MRI

Previous studies into the sensitivity and specificity of US to detect PT compared to MRI has shown sensitivity ranging from 69-74% and specificity ranging from 83-92% when US is performed by an experienced radiologist (1–3). In Study I the orthopedic resident achieved a sensitivity of 92% (CI 95% 81-98) and a specificity of 94% (CI 95% 89-97). The results are summarized in Table 5.

Study	Design	Cohort size	Implants	Outcome	
Nishii et al. 2014	Diagnostic study	131	Metal-on-metal and metal-on-polyethylene	Sensitivity Specificity Positive predictive value Negative predictive value	74% 92%
Siddiqui et al. 2014	Diagnostic study	19	Metal-on-metal	Sensitivity Specificity Positive predictive value Negative predictive value	69% (39-91) 83% (36-97)
Muraoka et al. 2015	Diagnostic study	83	Metal-on-metal	Sensitivity Specificity Positive predictive value Negative predictive value	72% (54-85) 88% (82-92) 65% (48-77) 91% (86-95)
Mikkelsen et al. 2023	Diagnostic study	205	Metal-on-metal and metal-on-polyethylene	Sensitivity Specificity Positive predictive value Negative predictive value	92% (81-98) 94% (89-97) 84% (73-91) 97% (93-99)

Table 5. Sensitivity and specificity of US to detect PT compared to MRI in various studies. Numbers in parenthesis are 95% confidence intervals.

The studies are all small. Since confidence intervals are overlapping it cannot be concluded that the sensitivity and specificity were higher in Study I compared to the other studies, but the orthopedic resident did not have an inferior performance.

Several factors could influence to results. As described in section 3.10.1 a possible bias in diagnostic studies is spectrum bias and we did include MoP THA. Theoretically this could lower the disease incidence and affect the sensitivity and specificity. However, the PT prevalence in Study I is similar to some of the studies mentioned above (1,2) but lower than in the smallest study (3). It therefore seems unlikely Study I contain spectrum bias compared to the studies referenced.
The cohort consisted of more males than females compared to the other studies. Body fat is distributed differently between the genders with more fat typically placed around the hips in females (4). This could affect the distance from the probe to the hip and thereby the diagnostic accuracy. The PTs in the patients in Study I might therefore have been easier to detect. A similar factor could be body mass index (BMI). In study I similar sensitivity and specificity in obese and non-obese patients was found, but the median BMI in both groups were close to the cut off value of 30 kg/m^2 that separated obese from non-obese. The groups might therefore have been too similar. No other studies have reported the BMI of their cohorts.

The MRI protocols were similar in all studies although outdated by modern standards. However the US protocol used in Study I included a medial projection of the hip which only Muraoka et al. also used (1). This could have revealed more PTs in Study I compared to other studies (2,3), since 3 medial PTs were detected.

Some studies have calculated the sensitivity and specificity of US to detect PT compared to intraoperative findings (5–8). As those studies used intraoperative findings during revision surgery as gold standard the results will not be compared in detail, but they achieved similar sensitivity and specificity as in Study I.

5.1.2 Pseudotumors in hip arthroplasties

Previous cross-sectional studies have shown that MoM, MoP and CoP THA have similar prevalence of PTs on MRI (9,10). In our study most PTs in HRA and MoM THA were no longer visible at follow-up while PTs in MoP THA were still visible. Some new, small PTs were even seen at second examination. This is similar to some longitudinal case series with no MoP control group where PTs in HRA and MoM THA regressed or were unchanged (11–15). In Study II, most PTs in HRA and MoM THA were cystic PTs. Cystic PTs have regressed in previous studies (16,17). This

could explain why more of the HRA and MoM THA PTs in Study II are no longer visible at follow-up. This is in contrast to the long-term longitudinal case series by Moon et al where most PTs were solid (12). The natural history of PTs in HRA, MoM and MoP THA in Study III may therefore not apply for solid PTs.

Some previous MoM case series found new PTs a few years after the first examination (14,15,18). In Study II the first scan was performed at a median of 4 years after surgery which correspond to the last scan in most studies. However, most new PTs in Study II were diagnosed in MoP THA which underlines the importance of a control group in these studies.

A recent midterm longitudinal cohort study of PTs in HRA, MoM, MoP and CoP used synovial thickness as indicator for ARMD and found increased risk of developing ARMD in HRA (19). However, the follow-up in that study corresponds to the first examination in Study III which makes it difficult to compare the longitudinal evolution of PT as it might be different short- and long-term.

PTs in Study II were smaller than what was described as ‘symptomatic’ PTs in other studies (20–22). This could explain why there were no association between PTs and PROM scores in Study II. Other studies have not found an association between PT and PROM either (10,13,15,20). These studies did not have a minimum size of what is defined as a PT or measure the volume of PT.

5.1.3 Survival and risk of revision of different bearings

It is well known that MoM THA have inferior survival and higher risk of revision compared MoP up to 8 years after surgery (23–27) but the Kaplan-Meier curves of the annual report of national joint registries could indicate that the rate of revisions of MoM THA decreases more than 10 years after surgery (28–30). However, long-term studies into the survival and risk of revision are lacking which is why I included MoM in Study III. It showed that the HR of revision does not seem to decrease after 7 years compared to MoP THA. The results are in line with previous studies but are of relevance for the lifelong follow-up programs of all patients who still have a MoM THA.

Previous register studies have shown similar survival and risk of revision of CoC compared to MoP/MoXLP up to 9 years after surgery (31,32). The annual reports of national joint registries also show similar survivorship (28–30). Meta-analysis of short- and midterm RCT has also shown similar survival and risk of revision (33,34). I also found similar survival and HR for revision up to 7 years after surgery. Only a few studies have investigated the survival and risk of revision beyond 9 years (35–37) where they found similar or slightly lower risk of revision for CoC. However, they

included some known confounders such as different fixation techniques (28,30,38), no clear differentiation between MoP and MoXLP (28,30), all age groups together (28,30), including patients from before the 4th generation of ceramics were available (39–41) and patients with rheumatoid arthritis, non-traumatic femoral head necrosis and femoral neck fracture (28,30,42,43). This could explain the differences in our results. I found a near but non-significantly higher HR for revision for CoC compared to MoXLP 7-13 years after surgery. I purposely did not include patients from before 2005 as we could not adjust for generation of ceramic as that variable is not captured in the NARA dataset. However, patients might still have had the 3rd generation of CoC. I performed a sensitivity analyses with only the 5 most commonly used cup and stem combination without 28 mm heads as the 28 mm heads have the highest risk of head and liner fracture in older generations of ceramic (44). The result was a higher HR for revision for CoC in the sensitivity analyses.

Previous studies into the survival and risk of revision for CoP/CoXLP compared to MoP/MoXLP have shown similar or even slightly better survival up to 10 years after surgery (37,45). Annual reports from national joint registries have also shown similar survival for CoXLP as for MoXLP (28–30). Like CoC few large studies into the survival and risk of revision beyond 10 years have been conducted (35–37). These studies show superior survival and risk of revision for CoXLP compared to MoP/MoXLP. However, as mentioned above these studies include possible confounders that I tried to eliminate or reduce in Study III. I found a near but non-significantly higher HR for revision for CoXLP compared with MoXLP 7-13 years after surgery. Study III has the longest median follow-up compared to the other studies but studies with longer follow-up are still needed.

5.2 Diagnostics

There are several ways to diagnose PTs. US could be a helpful tool to screen for the presence of abnormalities around the hip such as PTs. If orthopedic surgeons were trained in performing US it could be a faster, cheaper, and more available way to assess the need for MRI compared to just referring the patients the MRI. Some studies using peroperative findings as gold standard even advocate performing both US and MRI as the sensitivity and specificity improves (5,7,8). I did not make that comparison as our aim was to prioritize the use of musculoskeletal radiologist. However, MRI should still be considered the gold standard as it offers the best overview of deeper soft tissue and bone. It is also easier to store and review MRI scans later compared to US. US on the other hand offers a great alternative to patients with contraindications for MRI such as claustrophobia, obesity (possibly difficult) and metal implants such as pacemakers.

MRI technology obviously evolves and the MARS-MRI protocol used in Study I and first examination in Study II is now obsolete. An OMAR protocol including view angle tilting (VAT) and slice encoding metal artifact correction (SEMAC) was used in Study II as it was the standard protocol at my institution at the second examination. These newer techniques further reduces the metal artifacts from the implants and can among other things better visualize the inferomedial recess (19,46,47) making MRI even more reliable as a gold standard. In Study I US found some medial PTs not visible on 1 Tesla MARS-MRI. However, it is possible that these PTs were visible on newer MRI scanners with newer protocols.

A major weakness of diagnosing the PTs using the most used PT classifications are that they are old and were developed on MoM case series without a control group of standard MoP/MoXLP bearings as a reference for what is normal (48–50). MoP/MoXLP can also develop ARMD through trunnionosis (51), but it is rarely a cause for revision (52). Therefore, studies into asymptomatic MoP/MoXLP might contain important information regarding PT classification. Some of the cystic PTs might just reflect the surgical approach. Dehiscence of the external rotators of the hips after posterior approach can create cystic masses similar to what is classified as a Hauptfleisch Type I PT (53,54). These masses also regressed over time similar to what was experienced in Study II although earlier than in Study II (19). Studies have generally not found an association between clinical outcome and what is defined as PTs (9,10,13,15). PT characteristics does not seem to be associated with the clinical outcome after revision surgery either (55). However, some PTs result in catastrophic consequences for the patients due to local osteolysis, bleeding, thrombosis and destruction of soft tissue (56–60). We might therefore simply not have the right way to classify what is pathological resulting in symptoms for the patient and what is acceptable yet.

Some studies have investigated how MRI findings are associated to histological findings of ALVAL after revision surgery. They found that synovial thickness was the best measure (47) while cystic changes with thin walls are not associated with ALVAL (61). However, these findings were not associated to clinical outcome either (19).

Now that most MoM hip arthroplasties in follow-up programs are more than 10 years old another issue is needed to consider: Do PTs in old hip arthroplasties have the same clinical significance as in new hip arthroplasties. Study II suggest most PT are visible a few years after surgery, typically regress or remain unchanged in size and are asymptomatic. However, more studies into long-term clinical significance of PTs are needed.

Given the weak association between what is defined as a PT, symptoms and clinical outcome after revision surgery, clinicians should be cautious with using PT as a revision cause, although it might still be merited in some cases.

5.3 Choice of bearings

Several factors should be considered when choosing the best bearing for young patients and all bearings have pros and cons.

MoM bearings is widely regarded as the least favorable bearing, although some resurfacing designs are still used (29). While the tribology seemed favorable and the risk of dislocation is lower in HRA and large head MoM THA (62,63) they risk developing ARMD and have a lower survival and higher risk of revision compared to all other bearings (23–27). In Study II some of the ARMD seen on diagnostic imaging regress over time, do not affect the PROs and might not be pathological which is similar to other studies (10–15,53). However, the results of Study III indicate that this lower survival and higher risk of revision continues more than 13 years after surgery. Follow-up is therefore still merited.

CoC bearings have the best tribology of all bearings and newer generations of ceramic have been introduced which have lowered the risk of head and liner fracture (39,63). CoC bearings might also be associated with lower risk of PJI which is probably the worst postoperative complication related to THA (64–66). However, some of these studies might be underpowered and confounding by indication might lead to patients with fewer comorbidities to receive CoC bearings. Such patients might already be at lower risk of infection. CoC bearings might create squeaking and other noises that can negatively affect the patients' life (67) but rarely a cause for revision (68). While noises can occur in all THA they are more frequent in CoC THA (67). Head and liner fracture is a feared complication but have been become rare after the introduction of the 4th generation of ceramics (39). The survival of CoC bearings is similar to MoP/MoXLP up to 9 years after surgery (31,32). In study III we found a tendency towards higher risk of revision beyond 7 years. A tendency that remained when excluding less used implants and 28 mm heads.

CoXLP bearings have lower wear rates but similar lubrication and friction compared to MoXLP (63). It benefits from the biologically compatible wear debris of ceramics and possibly lower infection risk compared to MoXLP (69–71). It also has lower risk of head fracture than CoC bearings (41). Studies have shown similar or better survival compared to MoXLP up to 9 years

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after surgery (35–37,45,72). However, like with CoC a tendency was found in Study III towards higher risk of revision beyond 7 years after surgery.

MoXLP bearings is still considered ‘standard’ in many countries. It relies on boundary lubrication and have the highest friction of the bearings discussed in this PhD (63). Wear debris might still cause aseptic loosening although less than the older metal-on-conventional-polyethylene (73–75). Studies show similar or slightly lower survival and higher risk of revision compared to ceramic bearings (31,35–37,45,72). However, in Study III MoXLP showed tendencies towards having superior long-term survival and risk of revision. As mentioned above further studies are needed to reduce the possible impact of unmeasured confounding.

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6. Conclusion

6.1 Study I

We found that an orthopedic surgery resident after a short training program could diagnose PT around hip arthroplasty using US with acceptable sensitivity and specificity compared to MRI scans. US performed similarly in obese and non-obese patients. In perspective, orthopedic surgeons can be trained to reliably screen patients for the need of an MRI when detecting PT.

6.2 Study II

The prevalence of PT declined in HRA and MoM THA but increased in MoP THA over time. New PTs were just as common in HRA and MoP THA. Blood levels of cobalt and chromium was higher in HRA and MoM THA compared to MoP THA, but were stable over time. No difference in PROM scores was found between HRA, MoM and MoP THA at first or second examination. Blood levels of cobalt and chromium or PROM scores were not associated with the presence of PTs. In perspective, surgeons should be cautious with using the presence of long-term PT as revision causes.

6.3 Study III

MoXLP had higher survival and lower HR for revision than MoM - mainly for revision causes we cannot specify. MoXLP, CoC and CoXLP had similar survival and HR for revision, but longer follow-up is needed to investigate whether CoC and CoXLP have better, equal or worse survival and risk of revision compared to MoXLP. In perspective, we currently believe that either MoXLP, CoC or CoXLP could be the standard bearings in patients aged 20-55 years.

7. Perspectives and future research

Finding the best choice of bearing and implant for young patients with debilitating OA of the hip will continue to be relevant until revision surgery is no longer needed. However, MoM bearings stands as a cautionary tale about how important it is to introduce medical implants systematically, under strict surveillance and only change 1 detail of the design at a time. When new medical implants show inferior performance, it is also important to keep doing research as short-term results and assumptions might not apply long-term. Continued surveillance of MoM hip arthroplasties is still merited as they continue to have inferior survival and increased risk of revision.

More non-radiologist personnel could be involved in diagnostic imaging of PTs mainly to screen for the need for more advanced diagnostic imaging conducted and interpreted by experts. However, more diagnostic studies need to be conducted to confirm that this workflow is safe. Such studies could involve reexamination with US by an experienced radiologist.

Current methods to categorize ARMD/ATLR/PT are not sufficiently associated with PRO or the need for revision surgery. Future diagnostic and cohort studies should focus on findings that link and include control group with standard bearings to distinguish between normal and pathological. If long-term pathological PT are rarer than first assumed, then a lot of studies into the field of diagnostic imaging about PT might be underpowered. Future studies could include pooled data from different studies.

The recent trend towards increased use of CoC and CoXLP bearings for young patients stresses the need for long-term population-based register studies with longer follow-up as they might have inferior survival and increased risk of revision. However as register studies might lack information about unmeasured confounders such as activity level, occupation, and comorbidities there is also a need for metaanalyses of long-term RCTs.

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9. Original papers

9.1 Study I

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Original Article

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Sensitivity and specificity for detecting pseudotumors in patients with hip resurfacing arthroplasty, metal-on-metal or metal-on-polyethylene total hip arthroplasty—MRI versus ultrasonography performed by an orthopedic surgery resident

Rasmus T Mikkelsen[1,2,3], Martin Schou[4], Trine Torfing[5], Ole Graumann[5,6], Søren Overgaard[3,6,7,8] and Claus Varnum[1,2]

Abstract

Background: Metal artifact reduction sequence magnetic resonance imaging (MRI) scan is a common method to detect adverse reaction to metal debris in total hip arthroplasty (THA). It might be quicker and cheaper if ultrasonography (US) could screen for the need for an MRI. However, both require trained personnel.

Purpose: We aimed to investigate the sensitivity and specificity of US for detecting pseudotumors (PT) when performed by an orthopedic surgery resident compared to MRI. We also investigated the sensitivity and specificity of US to detect PTs in obese and non-obese patients.

Material and methods: We examined 205 patients with hip resurfacing arthroplasty, metal-on-metal or metal-on-polyethylene THA with both MRI and US. US was performed by an orthopedic surgery resident who was trained according to a standardized training program in musculoskeletal US. Results from MRI were used as gold standard.

Results: US had a sensitivity of 0.92 (95% CI 0.81–0.98) and specificity of 0.94 (95% CI 0.89–0.97) for detecting PT. It had a positive predictive value of 0.84 (95% CI 0.73–0.91) and a negative predictive value of 0.97 (95% CI 0.93–0.99). US performed similarly in obese and non-obese patients.

Conclusions: US had a high sensitivity and specificity for detecting PT when performed by an orthopedic surgery resident. Trained orthopedic surgeons could screen for the need of an MRI scan when searching PTs.

[1]Department of Orthopedic Surgery, Lillebaelt Hospital, Vejle, Denmark
[2]Department of Regional Health Research, Faculty of Health Science, University of Southern Denmark, Odense, Denmark
[3]Department of Orthopedic Surgery and Traumatology, Odense University Hospital, Odense, Denmark
[4]Department of Emergency Medicine, Holbaek Hospital, Holbaek, Denmark
[5]Department of Radiology, Odense University Hospital, Odense, Denmark
[6]Department of Clinical Research, University of Southern Denmark, Odense, Denmark
[7]Department of Orthopaedic Surgery and Traumatology, Copenhagen University Hospital, Bispebjerg, Denmark
[8]University of Copenhagen, Department of Clinical Medicine, Faculty of Health and Medical Sciences, Kobenhavn, Denmark

Corresponding author:
Rasmus T Mikkelsen, Lillebaelt Hospital, Department of Orthopedic Surgery, Beriderbakken 4 7100, Vejle, Denmark.
Email: rasmus.tyrsted.mikkelsen@rsyd.dk

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Keywords
Total hip arthroplasty, metal-on-metal, ultrasonography, magnetic resonance imaging, adverse reaction to metal debris, pseudotumor

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Introduction

Total hip arthroplasty (THA) with metal-on-metal (MoM) bearings are almost no longer used as they have high complication and revision rates.[1,2] These THA produce metal ion release[3] which may cause adverse reaction to metal debris (ARMD) also called adverse local tissue reaction such as pseudotumors (PT).[4–6] PTs also form around metal-on-polyethylene (MoP) THA probably due to trunnion wear.[7–9] Some PTs might adversely affect the patients' health[10–12] while others are asymptomatic.[11] The majority of PTs seem to stabilize or regress[13–15] and risk of complications after revision for ARMD and PTs is high.[16] However, some countries have introduced lifelong follow-up programs for MoM hip arthroplasties.[3] Therefore, repeated diagnostic imaging might be needed before the surgeon decides to perform surgery.

The gold standard for detecting PTs is a metal artifact reduction sequence (MARS) MRI scan. However, MRI is expensive, time consuming, and in some places the availability of MRI is low.[17] Furthermore, some patients might have absolute or relative contraindications to have an MRI scan performed. Therefore, several studies have suggested the faster and cheaper US as an alternative or supplement to MRI[17–20] with sensitivity and specificity ranging from 0.69 to 0.90 and 0.83 to 0.92 when performed by experienced musculoskeletal radiologists. Some even using repeat US to observe PTs.[21] However, experienced musculoskeletal radiologist with special interest in US is not available at every hospital. If other trained clinicians could accurately perform US of the hips, US could be performed to assess the need for MRI, thereby prioritizing the time and skills of musculoskeletal radiologists. However, no study has to our knowledge investigated how a non-radiologist performs when detecting PTs with US. Further, obese patients have a greater distance from the hip to the US probe,[22] but obesity's effect on sensitivity and specificity for PTs have not been studied. Therefore, we aimed to investigate the sensitivity and specificity when an orthopedic surgery resident after a short training program performed US scans on patients with THA to detect PTs compared with MARS-MRI as a gold standard. Second, we investigated the sensitivity and specificity for US to detect PTs in obese and non-obese patients.

Material and methods

We conducted a cross-sectional cohort study where US and MARS-MRI were compared including patients operated at 2 hospitals. The cohort consisted of patients with hip resurfacing arthroplasty (HRA) (ASR, Depuy) and MoM THA (M2a-Magnum, Biomet). In 2011, all patients with these 2 types of hip arthroplasty and operated at the 2 centers during 2005–2010 were invited. Further, we had a matched control group of patients with MoP THA from those 2 centers from the same period, matched with the first 50 from HRA patients at 1 of the centers. The control group was matched on sex, age, and year of surgery. The cohort was part of another study into the prevalence of MARS-MRI detected PT between HRA, MoM, and MoP THA. In total, 205 patients with 121 HRA, 34 MoM, and 50 MoP THA were included in the cohort (Figure 1).

MRI scan

The MRI scans were performed in an open 1 T MRI scanner (Philips Panorama, Best, Nederland) with the following technical MARS-MRI sequences: transversal and coronal T1, coronal T2 and a coronal STIR. For reduction of artifacts resulting from the metal prothesis, the bandwidth was increased and matrix size altered. PT was defined as any mass, solid, cystic, or mixed, in continuity of the joint (Figure 2) according to the Hauptfleisch PT classification.[23] The Hauptfleisch PT classification consists of 3 categories: Type I: Thin-walled cystic mass (cyst wall <3 mm), Type II: Thick-walled cystic mass (cyst wall >3 mm, but less than the diameter of the cystic component) and Type III: A predominantly solid mass. Picture Archiving and Communications System (PACS) (General Electric Healthcare Centricity, Illinois, Ca, USA) was used for all MRI analyses. MRI images were reviewed by a senior consultant in radiology who is specialized in musculoskeletal MRI with more than 25 years of experience. The radiologist also re-evaluated all MRI images a minimum of 2 months after the first review and was blinded to the first review.

US

The US scans were performed with a 7L4s linear 5–10 MHz transducer (Mindray M7 high powered color doppler laptop, Mahwah, New Jersey, The United States). PT was defined as

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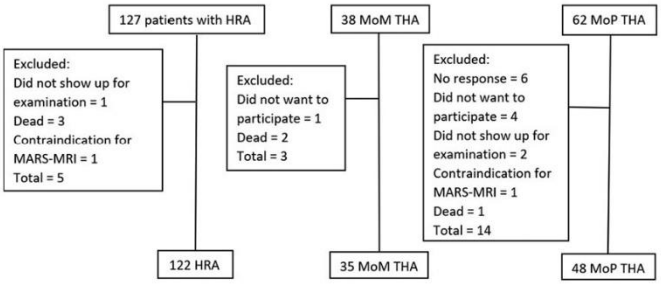

Figure 1. Flowchart of inclusion and exclusion of patients. HRA: Hip resurfacing arthroplasty. MoM: Metal-on-metal. THA: Total hip arthroplasty. MoP: Metal-on-polyethylene.

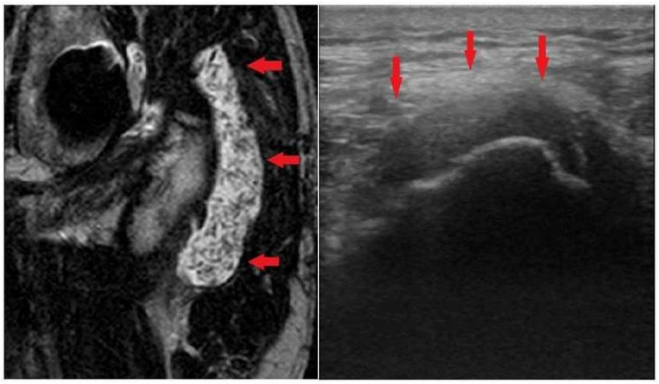

Figure 2. Hauptfleisch Type II PT as seen on MRI and US (red arrows). The patient has a MoP THA. On the left is a MARS-MRI STIR sequence image in coronal plan showing left-sided Type II PT. On the right is a lateral transversal US showing a cystic Type II PT with little solid mass.

any cystic or solid mass, solid, cystic or mixed, in continuity of the existing hip joint (Figure 2). If cystic or solid masses were situated both in contact with the implant and in the adjacent tissue, they were assumed to be connected.

The US scans were performed by a single orthopedic surgery resident. The resident was trained according to the European Federation of Societies for Ultrasound in Medicine and Biology Guidelines 'Minimum Training Requirements for Rheumatologists Performing Musculoskeletal Ultrasound',[24] which in brief includes 300 US scans of joints, in this case only hips, supervised by an experienced radiologist. The results of the supervised US scans were not included in the results of this study. Each US examination consisted of 30 min of examination in 8 projections as recommended by Hansen et al.[22] The projections used were 1. Anterior, longitudinal/oblique 2. Anterior transversal 3. Medial, longitudinal/oblique 4. Medial, transversal. Projection 1–4 were done with the patient in a supine position. 5. Lateral, longitudinal/oblique 6. Lateral, transversal. Projection 5–6 were done with the patient in a lateral position. 7. Posterior, longitudinal 8. Posterior, transversal. Projection 7–8 were done with the patient in a prone position. For obese patients, the abdominal convex transducer (3.5–5 MHz) was used to create an overview, after that the above-mentioned transducer and method was used. Not all US images were stored, but the orthopedic resident filled out a chart of his findings during the examinations. We consider these charts the raw data.

Obesity

Body mass index (BMI) was obtained for all patients as the distance from the probe to the hip and surrounding tissue might affect the quality of the US scan. It was calculated by dividing the patients' weight by their height squared as is the

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international standard.[25] We categorized patients as obese when BMI ≥30.

Statistics

Patient characteristics were given as medians and range. Results of the MRI scans were used as the gold standard, when calculating sensitivity, specificity, positive predictive value and negative predictive value of ultrasonography, and 95% confidence intervals (CI) were calculated. Sensitivity and specificity were calculated for all patients, for obese and non-obese, and for each type of arthroplasty. Data was analyzed in STATA statistical analysis software 16.1.

Ethics

Approval for the study was obtained from the National Committee on Health Research Ethics (reference number SJ-203, application number 27.938). Written and verbal informed consent was given in compliance with the Declaration of Helsinki.

Results

There were twice as many males as females in the cohort. The age ranged from the 34–83 years. The median follow-up was slightly longer in the HRA group than in the other 2 groups. There were 142 non-obese and 60 obese patients in this study, and BMI was not obtained in 3 cases (Table 1).

MRI found a prevalence of 50 PT out of 205 hips (24%). The most common Hauptfleisch type of PT was Type I[28] followed by Type II.[19] There were only 3 Type III (Table 2). There was consensus in all evaluation and re-evaluations of the MRI scans done by the radiologist a minimum of 2 months apart resulting in a kappa value of 1.0 (95% CI 1.0–1.0).

The sensitivity was 0.92 (CI 0.81–0.98), the specificity was 0.94 (CI 0.89–0.97), positive predictive value was 0.84 (CI 0.73–0.91), and the negative predictive value was 0.97 (CI 0.93–0.99) for US to detect PTs compared with findings from MRI as the gold standard (Table 3).

We additionally calculated the sensitivity and specificity for non-obese and the obese and found a sensitivity and specificity of 0.89 (CI 0.74–0.97) and 0.92 (CI 0.85–0.97) for non-obese and 0.93 (CI 0.66–1.0) and 0.98 (CI 0.89–1.0) for obese. A subanalysis showed that the sensitivity in the HRA group was 0.94 (CI 0.79–0.99), 0.83 (CI 0.36–0.99) in the MoM group, and 0.80 (CI 0.44–0.97) in the MoP group, respectively. The specificity in the HRA group was 0.96 (CI 0.89–0.99), 0.90 (CI 0.70–0.99) in the MoM group, and 0.95 (CI 0.83–0.99) in the MoP group, respectively.

US did not find 4 out of the 50 PT found on the MRI, but US did find 9 PT, that were not found on the MARS-MRI. In 3 of the 4 false negative, the patients' BMI ≥30 and the PT was situated medial to the implant Figure 3. Three patients had HRA and 1 had a MoP THA. The PTs were described on MRI as minimal in size. In 7 of the 9 false positive, the PT were typically situated close to the implants and measured marginally more than 10 mm. All cases of false negative and false positive were Hauptfleisch Type I.

Discussion

We conducted a cross-sectional cohort study comparing the ability of US to detect PT in patients with 3 types of hip

Table 1. Patient characteristics. Female/male is given in numbers. Age, follow-up, and BMI are given as medians and range.

	HRA n = 121	MoM n = 34	MoP n = 50	Overall n = 205
Female/Male	41/80	13/21	15/35	69/136
Age in years	58 (22–79)	61 (34–83)	58 (37–77)	58 (34–83)
Follow-up in years	5 (2–6)	4 (2–7)	4 (2–7)	5 (2–7)
BMI	27 (18–40)	28 (23–36)	28 (21–46)	27 (18–46)

BMI: Body mass index. HRA: Hip resurfacing arthroplasty. MoM: Metal-on-metal. MoP: Metal-on-polyethylene.

Table 2. PT distribution between type of hip arthroplasty and Hauptfleisch PT classification as found on MRI.

Hauptfleisch classification	HRA n = 121	MoM n = 34	MoP n = 50	Overall n = 205
Type I	15	7	6	28
Type II	14	1	4	19
Type III	2	1	0	3
Total	31	9	10	50

HRA: Hip resurfacing arthroplasty. MoM: Metal-on-metal. MoP: Metal-on-polyethylene.

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Table 3. Sensitivity, specificity, positive predictive value and negative predictive value with 95% confidence intervals (CI).

	MRI pseudotumor positive	MRI pseudotumor negative	
Ultrasonography pseudotumor positive	46	9	Positive predictive value 46/55 = 0.84 (CI 0.73–0.91)
Ultrasonography pseudotumor negative	4	146	Negative predictive value 146/150 = 0.97 (CI 0.93–0.99)
—	Sensitivity 46/50 = 0.92 (CI 0.81–0.98)	Specificity 146/155 = 0.94 (CI 0.89–0.97)	—

MRI: metal artifact reduction sequence magnetic resonance imaging.

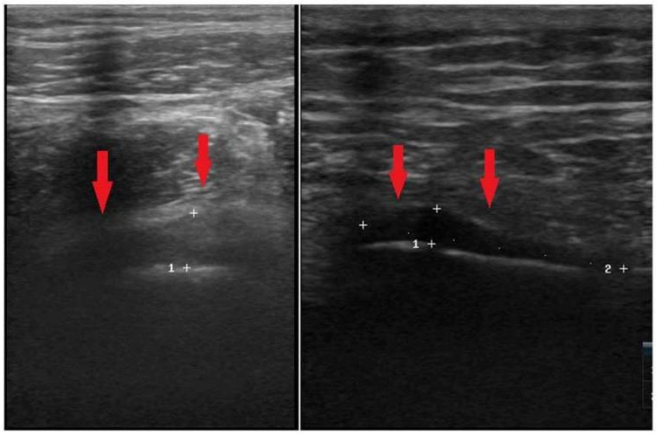

Figure 3. Small medial PTs of less than 10 mm anterior of the femoral neck/implant only visible on US and not MRI.

arthroplasties, where the US scans were performed by a trained resident in orthopedic surgery. MRI findings were performed and considered the gold standard. We found overall sensitivity and specificity above 90% and similar sensitivity and specificity for obese and non-obese. This is to our knowledge the only study investigating a non-radiologist's sensitivity and specificity to detect PTs with US.

The sensitivity and specificity found in our study were similar to that of other studies where the US scans were performed by radiologists.[18–20] We had a similar follow-up to that of 2 of those 3 studies,[18,19] and a shorter follow-up to that of another study.[20] The prevalence of MRI detected PT in our study was similar to that of Nishii et al. and Muraoka et al.[18,20], but much lower than in the study by Siddiqui et al.[19]. Our protocol for MRI was similar to that of other studies, but our US scans also focused on a medial projection of the hip, which Nishii et al. and Siddiqui et al. did not, but Muraoka et al. did. The extra projection might have a better view and therefore better reveal PT.

Contrary to other studies in this field, most of our patients were male. This could have an effect as body fat distribution tend to be deposited on the hips in women and on the stomach in men.[26] Therefore, we might have had a shorter distance from the probe to the implant. This distance might also be affected by the patients' BMI. In our study, the sensitivity and specificity were similar in the non-obese and obese groups. The trained orthopedic surgeon could reliably detect PTs in both groups. However, this study might be underpowered to detect any difference between the non-obese and obese group, and the BMI of most patients were just below or just above the non-obese/obese cutoff point. BMI was not included in other studies in this field[18–20] so we cannot compare our results.

We found slight differences in the sensitivity and specificity for US to detect PTs in different types of arthroplasties. However, this study might be underpowered, and larger studies are needed to investigate the sensitivity and specificity for US to detect PTs between the different designs of hip implants.

There were some false positive and false negative findings of US. The false negative findings were small PTs situated medially to the hip in obese patients. US might have some limitations in these situations. The false positive PTs

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were marginally larger than 10 mm close to the implants and could have been overlooked on the MRI due to metal artifacts. This is similar to another study where US and MRI findings were compared to intraoperative findings of revised hip resurfacing arthroplasties.[27] However, we consider US and MRI agreement sufficient in our study for US to be used as a screening tool to assess the need for an MRI.

It is difficult to differentiate between postoperative seroma, bursitis, synovitis and pseudotumor. This point has also been made in previous studies in MRI.[28] Ultrasonography has the same limitations. The Hauptfleisch classification defines a PT as any mass solid or cystic in continuity ***with*** the joint which leaves the possibility for false positive in both MRI and US. In this study, postoperative seroma seems less likely as the median follow-up was 5 years.

A limitation of this study is that the US scans were not cross-checked by an experienced musculoskeletal radiologist. However, the point of our study is *not* that US or orthopedic surgery residents should replace musculoskeletal radiologists, but rather to find a more efficient way to screen patients according to their need for more precise diagnostic imaging by preferably musculoskeletal radiologists. The musculoskeletal radiologist could then focus on describing the PTs in greater detail and precision. Our results show that most of our patients with PT would have been referred to MRI because of a positive US. Those patients that would not have been referred to MRI had small Type I PTs that typically are asymptomatic and stabilize or regress.[11,14,29,30]

Another limitation of this study is that repeated scans to assess intraobserver variability were not performed. As PT might have changed over time, we cannot redo the US scans to examine intraobserver variability. However, given the high sensitivity and specificity, we still consider the results reliable.

The use of power-Doppler might have improved the US scans by visualizing inflammation. However, we kept the US scans as simple as possible to demonstrate the utility of US in the hands of inexperienced personnel.

In conclusion, we found that an orthopedic surgery resident after a short training program could diagnose PT around hip arthroplasty using US with acceptable sensitivity and specificity compared to MRI scans. US performed similarly in obese and non-obese patients. In perspective, orthopedic surgeons can be trained to reliably screen patients for the need of an MRI when detecting pseudotumors. (See Figure 3)

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ORCID iDs

Rasmus T. Mikkelsen https://orcid.org/0000-0001-6086-4263
Ole Graumann https://orcid.org/0000-0002-9663-8361

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9.2 Study II

9.3 Study III

University of Southern Denmark
Campusvej 55
DK-5230 Odense

Phone: +45 6550 1000
sdu@sdu.dk