AARHUS UNIVERSITY

Metal-on-Metal Hip Arthroplasty

Investigations of activity and surgical approach in relation to pseudotumors

PhD dissertation

Mette Holm Hjorth

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Aarhus University
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Preface

This PhD thesis is based on scientific work carried out at the Orthopedic Research Unit, Aarhus University Hospital, Denmark, during my enrolment as a PhD student at the Faculty of Health at Aarhus University from 2013 to 2018.

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II. Hjorth MH, Mechlenburg I, Soballe K, Jakobsen SS, Roemer L, Stilling M. Physical activity is associated with the level of chromium but not with changes in pseudotumor size in patients with metal-on-metal total hip arthroplasty and resurfacing hip arthroplasty. *Journal of Arthroplasty, 2018 April 23*

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Abbreviations

95% CI = 95% Confidence Interval
AAOS = American Academy of Orthopedic Surgeons
ALTR = Adverse local tissue reaction
ALVAL = Aseptic lymphocyte-dominated vasculitis-associated lesion
AntLat = AnteroLateral
AOANJRR = Australian Orthopedic Association National Joint Replacement Registry
AP = Anterior-Posterior
ARMD = Adverse Reaction to Metal Debris
ASR = Articular Surface Replacement, Deputy Orthopedics, Warsaw, IN, USA
BHR = Birmingham Hip Resurfacing, Smith & Nephew, Memphis, TN, USA
BMD = Bone Mineral Density
BMI = Body Mass Index
CAD = Computer-Aided Design
CI = Confidence Interval
CN = Condition Number
CoC = Ceramic-on-Ceramic
CoCr = Cobalt-chromium
CoP = Ceramic-on-Polyethylene
CR = Coefficient of Repeatability
CRP = C-Reactive Protein
CT = Computed Tomography
DHR = Danish Hip Arthroplasty Register
DOS = Danish Orthopedic Society
DXA = Dual-Energy X-Ray Absorptiometry
EBRA = Einzel Bild Roentgen Analysis
eGFR = estimated Glomerular Filtration Rate
EMG = ElectroMyoGraphy
FDA = United States Food and Drug Administration
HA = HydroxyApatite
HAGOS = The Copenhagen Hip and Groin Outcome Score
HHS = Harris Hip Score
HXLP = Highly Cross-Linked Polyethylene
ICP-MS = Inductively-coupled Plasma Mass Spectrometry
Lat = Lateral
MARS = Metal Artifact Reduction Sequence
MARVIC = Multi-Acquisition variable-Resonance Image Combination
Med = Medial
MHRA = Medical and Healthcare products Regulatory Agency, UK
MoC = Metal-on-Ceramic
MoM = Metal-on-Metal
MoP = Metal-on-Polyethylene
MRI = Magnetic Resonance Imaging
NICE = National Institute for health and Care Excellence, UK
NJR = National Joint Registry
nmol/l = Nano-moles per liter
NSAID = Non-Steroidal AntiInflammatory Drugs
OHS = Oxford Hip Score
PA = Physical Activity
PE = Polyethylene
Post = Posterior

ppb = Parts per billion
PROM = Patient-Reported Outcome Measure
RCT = Randomized Clinical Trial
RBE = Rigid Body Error
ROI = Region of Interest
ROM = Range Of Motion
RHA = Resurfacing Hip Arthroplasty
RSA = Radiostereometric Analysis
SD = Standard Deviation
SEMAC = Slice Encoding for Metal Artifact Correction
6MWT = 6-Minute Walk test
STIR = Short Tau Inversion Recovery
T1W = T1 Weighted image
T2W = T2 Weighted image
TE = Time to Echo
THA = Total Hip Arthroplasty
3D = Three-Dimensional
Ti = Titanium
TT = Total Translations
TR = Total Rotations
TUG = Timed Up-and-Go test
UCLA = University of California and Los Angeles
UHMWPE = Ultra High Molecular Weight Polyethylene
US = Ultrasound
µg/l = Micrograms per liter
VAS = Visual Analog Scale

Definitions

Accelerometer	A device that measures changes in gravitational acceleration in three planes of a moving or vibrating body.
Accuracy	The degree of agreement between an experimental result and the true value.
Aseptic loosening	Loosening of an implant without signs of infection. Also referred to as mechanical loosening.
Bone mineral density	A measurement of the amount of calcium and other minerals per square centimeter of bone.
Implant	A medical device made from one or more biomaterials that is intentionally placed within the body, either totally or partially buried beneath an epithelial surface [48].
Migration	Movements of an implant relative to the bone it has been insert in. Generally taking place during a period of months or years.
Osteolysis	A process of progressive destruction of bone tissue surrounding an implant. Characterized on serial radiographs as progressive radiolucent lines and/or cavitation at the implant-bone or cement-bone interface [280].
Precision	The degree to which repeated measurements under unchanged conditions show the same results. A measurement of the reproducibility of results rather than their correctness.
Radiolucent lines	Linear osteolysic regions in the bone surrounding implants.
Revision	A revision surgery; a second surgery where the entire implant or parts of an implant is removed or exchanged.
Stress shielding	A reduction in bone density (osteopenia) as a consequence of removal of the normal stress from the bone by an implant [330].
Wear	Undesired removal of material from implants and other biomaterials.

1. English summary

The orthopedic community had big expectations to the third generation of metal-on-metal (MoM) total hip arthroplasty (THA) and resurfacing hip arthroplasty (RHA), which was considered a low-wear and dislocation-safe treatment option for young and physically active patients. Unfortunately, during 2006-2008, a growing number of reports revealed that metal wear debris generated from the bearing surfaces was associated with unexpected and undesirable side effects such as high systemic levels of cobalt and chromium metal-ions and adverse cystic, mixed, or solid soft-tissue reactions in relation to the hip joint termed "pseudotumors". In addition, National Joint Replacement Registries reported higher revision rates of MoM THA and RHA than for metal-on-polyethylene (MoP) THA, which led to official safety alerts and market withdrawal of some MoM hip arthroplasty designs. At the same time, different screening programs were launched.

The main aim of this thesis was to assess the pseudotumor prevalence and investigate the effect of physical activity (PA) on metal-ion measurements and pseudotumor dynamics in a relativity large study population of patients with MoM THA, MoM RHA, and MoP THA. Additionally, we wanted to evaluate differences between the anterolateral (AntLat) and the posterior (Post) surgical approach in patients with MoM RHA.

In the first study, a cross-sectional study with mean 7 years of follow-up, pseudotumor prevalence and type were assessed by metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) scans in 111 patients (148 hips) with either MoM THA, MoM RHA, or MoP THA. The pseudotumor prevalence in the three bearing types was statistically similar; however, the prevalence of mixed or solid pseudotumors was statistically significantly higher in patients with MoP THA than in patients with MoM THA and MoM RHA. Furthermore, hips with mixed or solid pseudotumors had poorer clinical outcome scores and higher metal-ion levels of cobalt than hips without a pseudotumor or with a cystic pseudotumor.

The second study investigated the correlation between patients' daily PA level, metal-ion measurements, and pseudotumor dynamics, as well as changes in pseudotumor type/size over time. The PA of 111 patients (148 hips) with MoM THA, MoM RHA, or MoP THA was monitored during a 2-week period at baseline and at 3, 6, 9, and 12 months. After each 2-week activity period, MRI scans with MARS sequences, and metal-ion measurements were obtained, and questionnaires were completed. MoM THA/RHA patients' daily PA was correlated with metal-ion measurements of chromium, but not with changes in pseudotumor size. Ten of 26 (38%) pseudotumors in MoM THA/RHA and 8 of 29 (28%) pseudotumors in MoP THA changed classification according to the Anderson Grading. No pseudotumors changed in appearance or anatomical location.

The third study, which was conducted in patients with MoM RHA, evaluated if the anterolateral (AntLat) surgical approach, which preserves the blood supply to the femoral head, provided superior outcomes of implant stability and periprosthetic Bone Mineral Density (BMD) than the post-surgical (Post) approach. Three months after surgery, cups inserted by the AntLat approach had more pronounced migration than cups inserted by the Post approach; but at 1 and 2 years, the migration patterns were similar, and all cups were well fixed, indicating good

secondary fixation. BMD measurements at 1 year were lower in the AntLat group than in the Post group, but measurements were comparable at 2 years.

The fourth study examined the location, grade, and prevalence of pseudotumors and muscle atrophy in patients allocated to MoM RHA by the AntLat or the Post approach approximately 5 years after primary surgery. Pseudotumors were located antero-laterally to the hip joint in patients operated by the AntLat approach, and postero-laterally to the hip joint in patients operated by the Post approach. The pseudotumor prevalence was similar in the two groups. Higher grades of muscle atrophy of the caudal part of the gluteus medius and minimus were seen in patients operated by the AntLat approach, and higher grades of muscle atrophy of the small external rotators were seen in patients operated by the Post approach.

The findings of this thesis provides novel insights concerning the prevalence of pseudotumor in MoM THA, MoM RHA, and MoP THA, and concerning the effect of patients' daily PA on metal-ion measurements and pseudotumor dynamics with the three bearing types. Furthermore, it compares the effect of using the AntLat versus the Post surgical approach for insertion of MoM RHA on implant stability, periprosthetic BMD, the anatomical location of pseudotumors, and grades of muscle atrophy.

2. Danish summary

I ortopædkirurgiske kredse var der høje forventninger til den tredje generation af metal-mod-metal (MoM) total hofteproteser (THA) og resurfacing hofteproteser (RHA). Ved disse protesetyper forventede man en større slidstyrke og mindre risiko for hofteluksation, hvorfor proteserne hovedsagligt var tiltænkt unge og aktive patienter. I løbet af 2006-2008 blev det dog klart, at metalslidpartiklerne fra protesedelene var forbundet med uventede og uønskede bivirkninger, så som høje niveauer af metalioner i blodet og udvikling af cystiske eller solide bløddelsreaktioner i relation til hofteleddet, betegnet "pseudotumorer". Nationale Hoftealloplastik Registre afslørede desuden, at revisionsraterne for MoM THA og MoM RHA var højere end for de traditionelle metal-mod-plast (MoP) THA, hvilket medførte en række officielle sikkerhedstiltag herunder tilbagekaldelse af nogle protesetyper/designs og udarbejdelse af forskellige udredningsprogrammer.

Det primære formål med denne ph.d.-afhandling var at estimere pseudotumorprævalensen og undersøge effekten af fysisk aktivitet på koncentrationen af metal-ioner i blodet og størrelsen af pseudotumorer i en patientgruppe opereret med MoM THA, MoM RHA eller MoP THA. Endvidere undersøgte vi to forskellige kirurgiske teknikkers betydning for proteseforankring, protesenær knogletæthed, anatomiske lokalisation af pseudotumorer og muskelatrofi efter operation med MoM RHA.

I det første studie estimerede vi pseudotumorprævalens og -type hos 111 patienter (148 hofter) med MoM THA, MoM RHA eller MoP THA ved hjælp af Metal Artefakt Reducerende Sekvens (MARS) magnetisk resonansskanninger (MRI). Pseudotumorprævalensen var sammenlignelig i de tre protesetyper. Dog var der signifikant flere blandings- eller solide pseudotumorer i patientgruppen med MoP THA end i gruppen med MoM THA og MoM RHA. Derudover havde patienter med blandings- eller solide pseudotumorer lavere kliniske værdier og højere kobolt-ion koncentration i blodet end patienter uden en pseudotumor eller med en cystisk pseudotumor.

Det andet studie undersøgte effekten af fysisk aktivitet på koncentrationen af metal-ioner i blodet og størrelsen af pseudotumorer samt eventuelle ændringer i pseudotumorstørrelse/type over tid. I alt blev 111 patienter (148 hofter) med MoM THA, MoM RHA eller MoP THA fulgt i 1 år. Patienternes aktivitetsniveau blev monitoreret i en 14-dages periode ved baseline og efter 3, 6, 9 og 12 måneder. Efter hver aktivitetsmonitorering blev patienterne MR-skannet med MARS sekvenser, fik taget blodprøver og udfyldte spørgeskemaer. MoM THA/RHA-patienternes aktivitetsniveau var korreleret med koncentrationen af krom-ioner i blodet, men ikke med ændringer i pseudotumorstørrelse. Ti ud af 26 (38%) pseudotumorer ved MoM THA/RHA og 8 ud af 29 (28%) pseudotumorer ved MoP THA ændrede sig ifølge Andersons Pseudotumor Klassifikationssystem.

Det tredje studie undersøgte, om operation med forreste adgang (hvor blodforsyningen til lårbenshovedet bevares) førte til bedre knogleforankring af protesekomponenterne og bedre knogletæthed end operation med bagerste adgang. Tre måneder efter operationen fandt vi større mikrobevægelser af den kunstige hofteledskål hos patienter opereret med forreste adgang end hos patienter opereret med bagerste adgang. Men ved 1- og 2-årsundersøgelserne var der ingen

forskel, og alle protesekomponenterne var velforankrede, hvilket indikerer en god knogleindvækst i proteseoverfladerne. Knogletætheden var lavere i patienter opereret med forreste adgang efter 1 år, men efter 2 år var knogletætheden ens i de to grupper.

I det fjerde studie blev lokalisering, grad og prævalens af pseudotumorer og muskelatrofi undersøgt i en patientgruppe, som var opereret med den forreste eller den bagerste kirurgiske adgang ca. 5 år tidligere. Pseudotumorer var lokaliseret foran hofteleddet hos patienter opereret med den forreste adgang og bag ved hofteleddet hos patienter opereret med den bagerste adgang. Pseudotumorprævalensen var sammenlignelig i de to grupper. Patienter opereret med den forreste adgang havde mere udtalt muskelatrofi af gluteus medius og minimus end patienter opereret med den bagerste adgang, som havde mere udtalt muskelatrofi af de dybe rotatormuskler.

Denne ph.d.-afhandling bidrager med ny viden om pseudotumorprævalensen i MoM THA, MoM RHA og MoP THA, og den giver ny viden om betydningen af fysisk aktivitet på koncentrationen af metal-ioner i blodet og størrelsen af pseudotumorer ved de tre protesetyper. Ydermere beskriver afhandlingen to forskellige kirurgiske teknikkers betydning for proteseforankring, protesenær knogletæthed, anatomiske lokalisation af pseudotumorer og muskelatrofi efter operation med MoM RHA.

3. Introduction

The conventional metal-on-polyethylene (MoP) total hip arthroplasty (THA) may be a satisfactory treatment option in older patients with osteoarthritis (OA) of the hip [37]. However, in younger patients with high physical activity (PA) levels, MoP THA is not a lasting solution due to wear of the polyethylene (PE) liner. PE wear particles have been associated with osteolysis, aseptic implant loosening, and an increased risk of future revision surgery with less satisfactory clinical outcomes [76, 249, 332]. This issue is clearly documented in recent results from the Danish Hip Arthroplasty Register (DHR), which reports that patients older than 74 years have a 51% lower risk of revision than patients younger than 50 years [335]. Much orthopedic research has therefore been devoted to developing alternative "hard-on-hard" bearing surfaces such as metal-on-metal (MoM) and ceramic-on-ceramic (CoC) surfaces. Compared with the traditional "hard-on-soft" bearing surfaces (MoP THA and ceramic-on-polyethylene (CoP) THA), these "hard-on-hard" surfaces were expected to prolong implant lifetime because the implant material was stronger.

History of MoM hip arthroplasty

The 1950s saw the development of two generations of MoM hip arthroplasties [221, 327], which both failed due to high rates of implant loosening and concerns about metal hypersensitivity, malignity, and metallosis [79, 130]. The third generation of MoM hip arthroplasties was introduced by McMinn in the late 1990s who sought to address the problems of PE wear related to the Charnley hip arthroplasties [222]. These implants had been adjusted in metallurgy, radial clearance, and sphericity, and they had demonstrated lower volumetric wear rates than the conventional MoP THA [75] and low initial failure rates [50, 222] (Figure 1). Due to these improvements and promising early results, the orthopedic community had high expectation for third-generation hip MOM arthroplasties [316], and both MoM resurfacing hip arthroplasty (RHA) and total stemmed MoM THA gained global popularity [22]. However, from 2008 to 2010, a growing number of reports revealed that revision rates were higher than anticipated [7, 248]. In April 2010, the British Medicines and Healthcare Products Regulatory Agency (MHRA) published a medical device alert regarding wear-related soft-tissue reactions seen in MoM hip arthroplasties [223]. In August 2010, the medical device company DePuy (Paramount Drive, Raynham, MA, U.S.) issued a voluntary recall of the ASR RHA and the ASR XL THA [84]. Two other MoM hip arthroplasty designs were also recalled; Durum by Zimmer was recalled already in 2007 due to "inadequacies in surgical techniques and instruction" [81], and the R3 by Smith & Nephew was recalled in 2012 [82].
In Denmark, The Danish Orthopedic Society (DOS) recommended examination of all patients with MoM hip articulations, and advised against further use of any type or brand of MoM hip articulation in March 2012 [73].

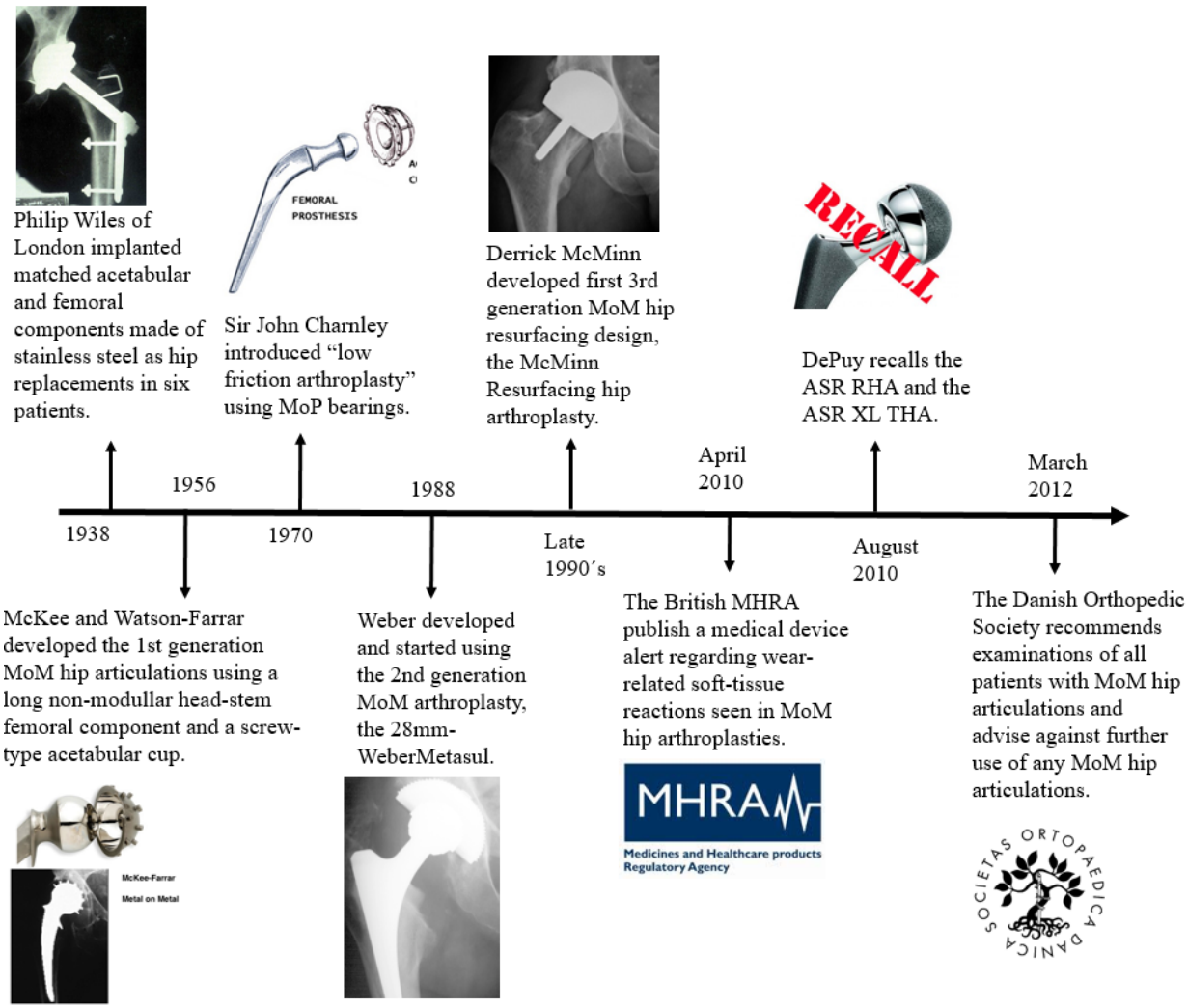


Figure 1 A short overview of the history of MoM and MoP hip arthroplasties

MoP THA, MoM THA and MoM RHA

Operation with conventional-stemmed THA involves surgical removal of the head and proximal neck of the femoral bone and the subchondral bone in the acetabulum. Afterwards, a metal stem with either a metallic or a ceramic head is inserted into the femoral medullar canal, and a metallic cup with a PE liner is inserted into the acetabular cavity (Figure 2). In the elderly with poor bone quality, implant components are most often inserted by use of bone cement, whereas in younger patients with good bone quality, cementless fixation with osseointegration into the implant surface coatings is usually preferred.

In MoM hip arthroplasty, no liner is typically interpositioned between the femoral head and the acetabular cup. Thereby, larger head-neck ratios may be achieved and larger-diameter femoral head sizes can be used (Figure 3). In that way, MoM hip arthroplasty more closely mimics natural human anatomy. This technique was therefore expected to lower dislocation rates, increase range-of-motion (ROM), and provide greater stability and balance in the hip joint [46]. Furthermore, metal alloy hardness and expected lower wear-rates were proposed to prolong implant lifetime beyond 15-20 years [39].

Even more advantages were expected in MoM RHA, since this method preserves the bone at the femoral head and neck (Figure 4). This was thought to reduce stress shielding at the proximal femur owing to a more normal physiological loading of the femur, and to allow for easier revision surgery of the femoral component. During the late 1990s and early 2000s, MoM THA and RHA were therefore considered an excellent choice for younger patients with high PA levels.

Figure 2 The principle of THA with a metallic cup in the acetabulum and a metallic stem in the femoral bone, and the Bi-Metric femoral stem with the Mallory-Head acetabular cup and the Arcom Ringloc UHMWPE liner (Biomet, Inc., Warsaw, IN, USA)

Figure 3 The M2a-Magnum MoM THA device (Biomet Inc., Warsaw, IN, USA).

Figure 4 The principle of MoM RHA, and the ReCap Resurfacing System (Biomet Inc., Warsaw, IN, USA).

Screening protocols in MoM hip arthroplasty

The undesirable side effects of MoM hip arthroplasties triggered official safety alerts and market withdrawal of some MoM hip arthroplasty designs [81, 82, 85, 223]. Furthermore, different screening protocols were published by several authorities: The European guidelines [113] (Appendix 1), the United States Food and Drugs Administration [83] (Appendix 2), The Hip Society Ohio [195] (Appendix 3), the American Association of Hip and Knee Surgeons, the American Academy of Orthopedic Surgeons, and the Hip Society [180] (Appendix 4), MHRA of the United Kingdom [224] (Appendix 5), and The DOS [74] (Appendix 6). These screening programs all included a combination of clinical examination, anterior-posterior (AP) pelvic and lateral hip radiographs, measurements of chromium and cobalt levels, and cross-sectional imaging in the form of magnetic resonance imaging (MRI), ultrasound (US), or computed tomography (CT).

Chromium and cobalt metal-ion levels

All bearing surfaces undergo some degree of wear whereby material is lost from the bearing surfaces. Strong correlations have been found between serum and joint fluid metal-ion measurements of chromium and cobalt, and between wear rates from the bearing surfaces and serum metal-ion measurements of chromium and cobalt [56, 120]. Metal-ion measurements of systemic exposure have therefore been assumed to reflect local exposure, and metal-ion measurements of chromium and cobalt levels along with clinical examination have therefore been used for screening for high-wearing and poorly functioning MoM hip arthroplasties. Different screening protocols suggest dissimilar cut-off values of chromium and cobalt levels. The UK MHRA suggests a limit of 7 ppb (which equals 7 μg/l) for both chromium and cobalt, which is similar to the recommendations of The DOS [74, 224]. An overview of units used for metal-ion measurements is presented in Appendix 7. Since a rather low sensitivity of 52% was reported for these cut-off value for detecting failed MoM hip arthroplasties [117], alternative cut-off values were suggested. Hart et al. suggested 5 pbb for both cobalt and chromium [117]; Van der Straeten et al. suggested 4 ppb for cobalt and 4.6 pbb for chromium for unilateral MoM RHA, and 5 ppb for cobalt and 7.4 ppb for chromium for bilateral MoM RHA [319]; and Sidaginamale et al. proposed 5 ppb for cobalt and 8.4 ppb for chromium to detect increased wear [292]. The different nature of these guidelines raised the question: “When does the elevated metal-ion measurements become clinically relevant?” Using elevated metal-ion measurements as a single indication for revision surgery has therefore been discouraged [121]. Furthermore, consensus is lacking on which matrix (whole blood or serum) to use for the metal-ion analyses, and different papers suggest either whole blood [51] or serum [201]. Different confounding factors such as high PA [167], renal insufficiency [143], nutritional supplements, and work or leisure-related chromium or cobalt exposure should be noted when interpreting the metal-ion levels [74, 83]. Elevated serum chromium and cobalt metal-ion measurements might be seen during the first 6-12 months after surgery due to a “running-in” phase [132], but thereafter a “steady-state” phase with lower metal-ion measurements should be reached [132]. Metal-ion measurements can be used as a screening tool for poorly functioning MoM hip arthroplasties only when the “running-in” phase has ended [319].

MoP THA and problems with PE wear debris

In the early 1960s, the orthopedic surgeon Sir John Charnley introduced the "low-friction arthroplasty", which consisted of three elements; a metal femoral stem, an ultra-high molecular weight polyethylene (UHMWPE) acetabular cup, and acrylic bone cement for bone fixation (Figure 1) [37]. Sir Charnley also advocated the use of small femoral heads, since he had recognized that a smaller bearing area would reduce generation of PE wear particles. In general, the concepts of his "low friction arthroplasty" is identical to the principles used today, and therefore Sir John Charnley have been considered the father of modern THA. Although implant survivorship of Charnley's "low friction arthroplasty" reportedly reached >80% at 20 years and 78% at 35 years after surgery, implant failure due to osteolysis and aseptic loosening secondary to PE wear particles limits implant longevity and remains the main cause of revision surgery [28, 31]. The amount of wear debris generated by the PE liner has been associated with periprosthetic osteolysis and eventually aseptic loosening [76, 115, 251, 264, 283]. A literature review of the association between PE wear rates and osteolysis in MoP THA found that the degree of osteolysis increased when the PE wear rate increased [76]. It was also reported that osteolysis was rarely present at PE wear rates below 0.1 mm/year [76]. Furthermore, PE wear rates above 0.2 mm/year have been associated with a high risk of revision surgery 20 years after surgery, and rates above 0.3 mm/year have been associated with a nearly 100% risk of revision surgery at 10 years [283].

Higher PE wear rates have been found in young and active patients [283], and PE wear rates have been associated with patients' PA levels rates rather than with time *in situ* [198, 282]. Many attempts have therefore been made to improve PE wear characteristics to increase the long-term survival of MoP THA. Highly cross-linked PE (HXLPE) was marketed in the early 1980s. HXLPE is formed by UHMWPE irradiated above the normal sterilization dose of 25 to 40 kGy. The wear particles and the wear volume of HXLPE are smaller [100, 116]. However, the total number of wear particles generated has been found to be comparable to that of UHMWPE [271]. Some studies suggest that HXLPE wear particles are more biologically active in initiating osteolysis [78, 100]. At the same time, authors report that HXLPE outperforms UHMWPE in terms of wear characteristics and long-term implant survival [23, 175, 176]. Later, vitamin-E-diffused HXLPE was introduced [252]. These liners were believed to have even better wear characteristics and better mechanical and fatigue properties than HXLPE [252]; and recent studies have shown promising results of vitamin-E-diffused HXLPE [109, 236, 294, 295].

In Denmark, the majority of acetabular cups (47.7%) used during 1995-2015 were cementless and the most frequently used cups was the Trilogy cup (Zimmer Biomet) with either a standard UHMWPE or a Longevity cross-linked PE liner (n = 32.153) [335].

Wear-related failure of MoM THA and RHA

Much attention has been devoted to the failure modes associated with metal-wear debris generated from the bearing surfaces. Even though the volumetric wear of MoM hip arthroplasties *in vitro* is very low and the wear particles are much smaller than those released from PE bearings, the number of metal-wear particles generated is 13-500 times higher than in PE bearings [70].

Various terms have been used to describe the side effects of the nano-sized metal particles, which spread in the body - both locally and systemically;

- Pseudotumors: A description of cystic and mixed or solid masses in relation to the hip joint that are neither malignant nor infective [254].
- Metallosis: This term is used about the soft tissue surrounding a metallic implant when it turns dark due to the metal wear debris from the implant [108].
- ALTR: Adverse Local Tissue Reaction. This term includes all adverse reactions from both mechanical and biological sources in failed hip arthroplasties [284].
- ARMD: Adverse Reaction to Metal Debris. This "umbrella" term includes metallosis, Aseptic Lymphocyte-dominated Vasculitis-Associated Lesion (ALVAL), pseudotumors, and implant failures associated with pain. This term describes implant failure caused by wear debris from the implant and was suggested by Langton D.J [185].
- ALVAL: Aseptic Lymphocyte-Dominated Vasculitis-Associated Lesion: This term is used for the histologic evaluation of a pseudotumor (grading system 0 - 10). Histopathologically, ALVAL are described as cell-mediated (type IV) hypersensitivity reactions characterized by perivascular lymphocytic infiltrate, fibrinous exudate, macrophage accumulation, and tissue necrosis [29, 333].
- Muscle atrophy: Moderate-to-severe muscle atrophy in either gluteal or external rotator muscles in patients with unexplained pain and MoM hip arthroplasties has been related to the metal-based disease process [12, 235, 337].

Except for the metal-wear-related failure modes in MoM hip arthroplasty, other failure modes are similar to those seen in conventional hard-on-soft THA with other bearing surfaces. These failure modes include aseptic loosening, dislocation, periprosthetic fracture (typically femoral neck fractures in MoM RHA), and deep infection [248, 335].

Factors associated with increased metal wear debris and metal-ion levels

Factors associated with increased metal wear and metal-ion levels can roughly be divided into three main categories:

1. Surgery-related factors: implant positioning, surgeons' learning curve.
2. Implant-related factors: diametrical clearance, arc of coverage, contact-patch-to-rim distance, trunnion, modular neck, implant loosening and type.
3. Patient-related factors: gender, size of the femoral component, activity level.

Surgery-related factors

MoM RHA surgical procedures have been described as difficult and unforgiving, and have been associated with a steep learning curve [267]. Associations between steep inclination angels and metal-ion measurements [55, 187] and between steep inclination angels and wear from the bearing surfaces [55, 120] have been demonstrated and it seems that accurate component positioning is very important in MoM hip arthroplasty. Several authors [55, 104, 179, 187] refer to Lewinnek's "safe zones" of 30-50° for inclinations and 5-25° for anteversions [192] as an optimal position to avoid high wear rates in MoM hip arthroplasty. Lewinnek's "safe zones" were originally based on prevention of dislocation in 28mm stemmed MoP THAs, but it seems that the zones may be valuable in MoM hip arthroplasty as well [179].

Implant-related factors

A reduced diametrical clearance (the distance between the articulating surfaces) and a lower arc of coverage of the acetabular cup (the angle subtended by the articular surface of the acetabular cup) have both been shown to cause edge loading (wear area crossing over the rim of the acetabular cup), which leads to increased wear rates and metal-ion levels of chromium and cobalt [185, 186, 218, 315]. Others have shown that the contact-patch-to-rim distance (the smallest distance between the center of the wear patch and the rim of acetabular cup) may predict up to 67.7% of the variability in wear rates and metal-ion levels in MoM RHA [218]. Furthermore, reduced contact-patch-to-rim distance has been shown to increase metal-ion levels [184, 191, 338]. Loosening of implant components results in micromotions between the bone and the loose component, which in turn leads to production of metal-ion particles. These metal-ion particles may induce third-body abrasion on the articulating surfaces, which contributes to further production of metal-ion particles [40].

Metal-ion measurements have been reported to be higher in MoM THA than in MoM RHA with identical bearing surfaces [93, 298]. However, since there is no difference in wear rates of bearing surfaces of MoM THA and MoM RHA [216], corrosion at the taper-trunnion junction has been suspected to be one of the main reasons for the higher metal-ion measurements in MoM THA than in MoM RHA [137, 158, 190].

Other implant-related factors such as implant coating [196], manufacturing process [32], variance in modular junctions [189], and use of adaptor sleeve [190] may also influence the amount of metal-wear debris and metal-ion levels.

Patient-related factors

Metal-ion levels have been found to be higher in females than in males [55, 118]. This has been suggested to be due to a general use of smaller femoral head sizes in females. The use of smaller femoral head sizes increases the risk of edge loading because of the smaller surface-bearing area, which is less tolerant of rotational component malalignment than larger femoral head sizes [87]. However, the female preponderance is reported to persist after adjustment for femoral head sizes and to remain a risk factor for elevated metal-ion levels according to one study [118], while other studies did not find that female gender was an independent risk factor [99, 122,

211]. PA has so far shown conflicting results; some *in vitro* and *in vivo* studies report an effect on metal-ion levels [21, 167]; however, other *in vivo* studies have not been able to verify an effect [131, 325].
Metal debris may also originate from other sources such as the bone-cement, cement-implant, or implant-bone interface (especially if the implant is loose), or from wires, screws, or delaminated metallic coatings [149]. This explains why increased metal-ion measurements may also be found among other bearing types such as MoP THA and MoC THA [16, 49, 110, 113, 200].

Cystic, mixed- and solid pseudotumors

Pseudotumors are defined as periprosthetic cystic, mixed, or solid masses that are neither infective nor malignant [254]. Cystic pseudotumors are more frequent than the mixed or solid ones, and most often they are located posteriorly/laterally to the hip joint, whereas the mixed or solid types are usually located to the iliopsoas bursa [9, 119, 123, 231, 246]. Pseudotumors have been described in asymptomatic patients [20, 34]; however, several presentations with nerve palsy, swelling, pain, and discomfort (mostly located to the groin area) have also been reported [15, 202]. The mixed or solid types have more often been associated with pain [20, 44, 125, 128] and increased metal-ion levels [44, 93, 306]. Pseudotumors have been associated with high cup inclination angels [187], leading to increased metal wear debris [177] and, consequently, high systemic levels of chromium and cobalt [35]. However, pseudotumors have also been found in patients with well-positioned cups and low systemic levels of chromium and cobalt [34, 69, 86, 217].
The pseudotumor prevalence range is 9-59% in MoM THA [9, 20, 227] and 4-28% in MoM RHA [15, 178, 281]. Prevalences this wide are assumed to reflect variable inflammatory responses to the wear debris from the bearing surfaces, but different radiological interpretations have also been offered [12]. Even though pseudotumors have mainly been associated with MoM hip arthroplasties, some case reports and smaller studies also report pseudotumors in patients with other bearing surfaces like CoP and MoP [16, 17, 30, 225, 288].
Various pseudotumor grading systems have been published [6, 34, 119, 128, 217], but since they focus on different subjects (size (<50mm / >50mm), appearances (cystic / mixed or solid), and wall thicknesses (<3mm / >3mm)), it is difficult to directly compare results between studies that use different grading systems (Table 1). One study found that the reliability of the Anderson system exceeded that of the system proposed by Hart/Matthies et al. 2012 and that of Hauptfleisch et al. 2012 [323]. The clinical significance of different pseudotumor grades remains controversial. Since many cystic pseudotumors have been found among asymptomatic patients, it has been suggested that the location of the pseudotumors simply reflects the surgical approach used for implantation [80, 203, 278]. Recently, it was shown that pseudotumors in MoM THA/RHA patients change in size/type between two cross-sectional images [4, 77, 124, 270, 322].

Table 1 Overview of the three published MRI pseudotumor grading systems

	Anderson et al. 2010	Hart/Matthies et al. 2012		Hauptfleisch et al 2012	
Grade A	Normal Normal post-operative appearances including seromas and small hematomas	Type 1	Pseudotumor Flat, thin-walled (<2 mm); fluid-like content	Type 1	Pseudotumor Thin-walled cystic mass (cyst wall <3 mm)
Grade B	Infection Fluid-filled cavity with high signal T2 wall; inflammatory changes in soft tissues, ± bone marrow edema	Type 2a	Pseudotumor Thick-walled (>2 mm) or irregular walls; fluid-like content	Type 2	Pseudotumor Thick-walled cystic mass (cyst wall >3 mm, but less than the diameter of the cystic component)
Grade C1	Mild MoM disease Peri-prosthetic soft-tissue mass with no hyperintense T2W fluid signal or fluid-filled peri-prosthetic cavity; either <5 cm maximum diameter	Type 2b	Pseudotumor Thick-walled (>2 mm) or irregular walls; atypical fluid	Type 3	Pseudotumor Mainly solid mass
Grade C2	Moderate MoM disease Peri-prosthetic soft-tissue mass/fluid-filled cavity >5 cm diameter or C1 lesion with either of following: 1) muscle atrophy or edema in any muscle other than short external rotator; or 2) bone marrow edema: hyperintense on Short Tau Inversion Recovery (STIR)	Type 3	Pseudotumor Solid		
Grade C3	Severe MoM disease Any of the following: 1) fluid-filled cavity extending through deep fascia; 2) tendon avulsion; 3) intermediate T1W soft-tissue cortical or marrow signal; 4) fracture				

Physical activity and wear of hip arthroplasties

Hip arthroplasty in young and active patients has been a challenge for the orthopedic hip surgeons for decades due to wear-related problems. Reports have shown that these patients have a higher risk of aseptic loosening and subsequent revision surgery than older THA patients [42, 71, 72]. Therefore, knowledge of the potential side effects of PA in patients with hip arthroplasties is important, and it has been shown that PE wear particles produced from the bearing surfaces in MoP THA are associated with patients' levels of PA rather than with the

time *in situ* [198, 282]. Some authors suggested that a similar relationship between patient activity, wear from articulating surfaces, and measurements of systemic metal-ion levels is present in MoM hip arthroplasties [53, 256], but evidence for this is limited and the few publications available have conflicting results. Two hip simulator studies reported higher wear rates during imitated jogging motions [33, 148], and a 10% rise in cobalt levels was found in two patients with Metasul 28-mm MoM hip arthroplasties after completing 800m of walking [97]. Additionally, Khan et al. investigated 15 patients with MoM hip articulations after a 1-hour treadmill run and reported an increase in cobalt (13%) and chromium (11%) levels [167]. In contrast, chromium and cobalt levels in seven patients with MoM hip arthroplasties who participated in a high-activity week and a low-activity week were statistically similar [131], and no difference was found in metal-ion levels in a triathlete with a Birmingham Hip Resurfacing arthroplasty before, during, and after the race [53].

Assessment of patients' physical activity

PA has been reported to be a significant contributor to general health [239], whereas being physically inactive has been found to be a strong risk factor for mortality globally [181, 253]. Much effort has therefore been devoted to obtaining quantitative data on the importance of PA to patients' health [239]. In the orthopedic field, knowledge of the effectiveness of orthopedic treatment (e.g. comparisons before and after rehabilitation or surgical interventions) is also important.

Knowledge of patients' PA can be obtained with questionnaires like the University of California and Los Angeles (UCLA) activity-level rating scale [339], the Tegner score [308], and the Activity Rating Scale [207]; by telephone surveys [61] and step counters [168]. Most recently, three-dimensional (3D) accelerometers were introduced. 3D accelerometers makes it possible to obtain objective and detailed descriptions of patients' everyday activities during long-time follow-ups [230, 285]. A review evaluating 12 different instruments with which to assess PA in patients with osteoarthritis of the hip or knee recommended using accelerometers for activity monitoring [309]. Additionally, the use of accelerometers was recently reported to be the most appropriate method for monitoring PA in orthopedic patients [296]. Currently, several brands and types of accelerometers are commercially available. Before deciding on which one to use, the following important questions should be considered:

- Should the study population wear a single accelerometer or multiple accelerometers?
- What is the cost of the accelerometer and the chargers?
- What is the ideal body position for the accelerometer (thigh, upper arm, lower back, wrist)?
- What is the battery duration of the accelerometer?
- What is the minimal time pr. day the device should be worn?
- For how many days should the accelerometer should be worn?
- How much data should be obtained?
- Is there a need for water-proof accelerometers?

- How should the accelerometer be attached to the body (tape/strips)?
- How should the data be analysed/processed (which software programme, use-friendliness).
- What is the quality and availability of technical support

Furthermore, it should be determined whether the study population needs detailed verbal or written instructions/protocols on how and when to wear the accelerometers, how to charge them, and how to return them safely to the research department.

Imaging screening modalities used for MoM hip arthroplasties

Plain radiographs

As for conventional MoP THA, plain radiographs of MoM THA/RHA can provide important information on fractures, osteolysis, cysts, radiolucent lines, and heterotopic ossifications. They can also be used for measuring implant positioning (inclination and anteversion) (Figure 5) [269] and for detection of radiolucent lines as a sign of implant loosening. In MoM RHA, serial images with plain radiographs can help detect worsening of femoral neck narrowing, which is commonly seen [133]. Still, the clinical significance of femoral neck narrowing remains unclear [96].

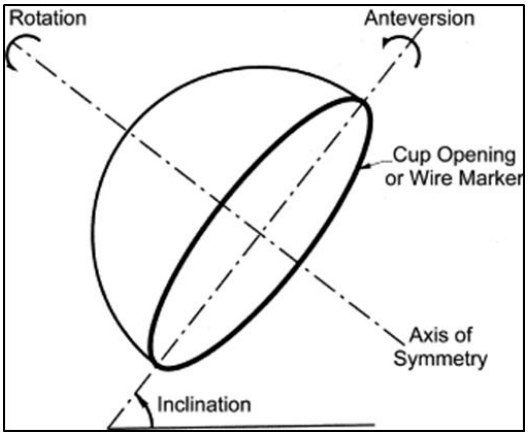


Figure 5 Illustration of cup inclination and anteversion angels.

Dual-energy X-ray absorptiometry (DXA) scans

Plain radiographs are too insensitive and inaccurate to detect small changes in bone mineral density (BMD). DXA scans allows detection of even small changes in BMD at a lower radiation dose than with plain radiographs or CT scans [154] (the precision error for BMD measurements of the femoral neck has been reported at 1.4% [18]. In cementless THA, resorption of the proximal femoral bone (Gruen Zone 1 and 7) has been reported to be a common phenomenon [174, 219, 244]. Resorption is thought to be caused by stress shielding, meaning that the bone load is reduced due to altered biomechanics induced by the implant [142], which occurs in accordance with Wolf´s law which states that;

"*bone in a healthy person or animal will adapt to the loads under which it is placed. If loading on a particular bone increases, the bone will remodel itself over time to become stronger to resist that sort of loading. The inverse is true as well: if the loading on a bone decreases, the bone will become less dense and weaker due to the lack of the stimulus required for continued remodeling*" [89, 329].

The bone around conventional THAs is most often analyzed in the seven regions described by Gruen et al. [106]. Due to the differences in stem size and shape between THA and RHA, this method is not suitable for RHA. Different approaches for analyzing the bone around RHA implants have been proposed; and different sizes, numbers (2-9), and placements of regions of interest (ROIs) have been suggested [45, 170, 193, 250, 257, 299]. However, no method has yet become the "gold standard".

Radiostereometric analysis (RSA)

Using plain radiographs to identify implant migration at an early stage has been found to be an insensitive method [205]. Since Göran Selvik and his co-workers developed RSA in 1974, it has been considered the "gold standard" for measurements of implant loosening owing to its high accuracy and precision [88, 226, 287, 289]. RSA has been used mainly for measurement of early implant migration, which has been shown to be a strong predictor of future implant loosening and revision surgery [127, 163, 241, 262, 263, 277]. However, RSA has also been used for multiple other purposes such as evaluation of growth plate integrity, joint kinematics, fracture healing, and femoral head penetration into the acetabular component [162, 274, 275, 303, 317].
Two analytical methods can be used for measuring implant migration; the marker-based method where tantalum markers are placed on the implant and in the host bone (Figure 6), thereby creating two rigid bodies [289, 290]; alternatively, the model-based method may be used in which a 3D surface model (created from a reverse-engineered model or a CAD model provided from the implant manufacture) is matched to the outer contour of the implant on the stereoradiograph by mathematical algorithms (Figure 7) [159, 160, 197].

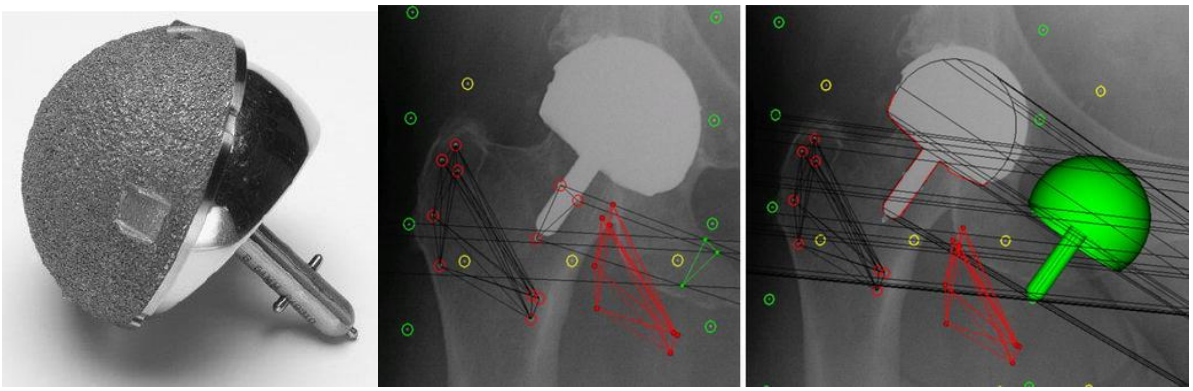


Figure 6 The ReCap resurfacing system with three tantalum markers attached to the pin of the femoral stem (Figure to the left) [26].

Figure 7 CAD model of the ReCap resurfacing stem femoral in the RSA program (Figure to the right) [197].

The high accuracy and precision of the RSA method makes it possible to conduct studies with small patient groups [318]. RSA is therefore a unique and suitable method for pre-marketing assessment of fixation of new implant designs, implant coatings, and types of bone cement [165]. Many authors have emphasized the importance of "a stepwise introduction" of new implants and bone cements before they are released to the market [164, 206, 238]. The following steps have been recommended: (1) preclinical tests (mechanical tests done by machines), (2) 2-year clinical RSA trials (ideally randomized), (3) large-scale multicenter clinical RSA studies (ideally randomized), and (4) postmarked surveillance in national registers (Figure 8).

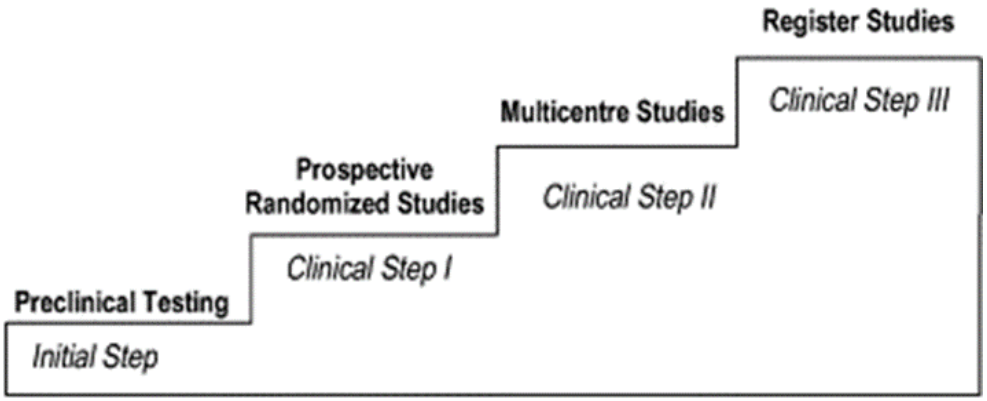


Figure 8 The stair-case principle of "a stepwise introduction" of new bearings, cements, and surgical techniques was introduced by Henrik Malchau in 2000 [206].

The importance of evaluating new types of bone cement in small patient groups before market release is neatly captured by the example of the Boneloc cement (Biomet, Warsaw, IN, USA), which was put on the market in 1991. Boneloc cement was designed to have a lower curing temperature (43°C instead of the traditional 80°C) and a decreased release of toxic monomers. Theoretically, this would reduce local cell death and thereby the incidence of aseptic loosening of implants. However, despite these theoretical advantages, many failures were observed in clinical practice due to aseptic loosening of implants fixed with Boneloc cement. Shortly thereafter, two clinical RSA studies on Boneloc cement were conducted: one study of 19 patients with total knee articulations [243] and another one of 11 patients with MoP THAs [310]. The results of these RSA studies supported the clinical observations of implant loosening, and Boneloc fixed implants migrated significantly more than implants fixed with conventional bone cement. Unfortunately, the results of these two studies were published only after Boneloc cement had been used in many patients. The 5-year postoperative revision rate of implants fixated with Boneloc cement was 14 times higher than for implants that were fixed with conventional cement [90]. Premature implant failure in thousands of patients would have been prevented if introduction of the Boneloc cement had followed the procedure of "a stepwise introduction".

Furthermore, an RCT study as demonstrated that the uncoated, uncemented Interax Total Knee (Styrker-Howmedica, Rutherford, New Jersey) had excessive migration patterns [237]. Because of the RSA results, the manufacturer discontinued production of the tibial components. Additionally, Luites et al. found a non-stabilizing migration pattern of the ProxiLock femoral stem (Zimmer, Warsaw, Indiana), which also caused production of these stems to be discontinued [199].

Ideally, all new MoM hip arthroplasty components should be studied in small-scale RSA studies prior to their market release; however, only a few brands have been investigated [26, 107, 136, 146, 147, 197, 259]. These studies all reported good fixation and stabile implants, which indicates that the cause of failure and revision surgery in MoM hip arthroplasty have other reasons than implant migration.

Magnetic resonance imaging (MRI), ultrasound (US), and computed tomography (CT)

MRI, US, and CT scans have all been recommended by the authorities as imaging screening modalities that can be used to detect ARMD and pseudotumors [74, 83, 224].
MRI has commonly been used as a screening modality in patients with MoM hip arthroplasties as it allows for excellent differentiation between soft and hard tissues, and identifies soft-tissue abnormalities like pseudotumors, muscle atrophy, tendon inflammation, and synovial thickening [27, 235]. However, MRI of metallic implants produces metal artefacts. The image quality can be improved by the use of special metal artifact reduction sequences (MARS) [36]; however, this also increases the scan time [94]. Recently, two new metal artifact reduction methods were developed: slice encoding for metal artifact correction (SEMAC) and multi-acquisition variable-resonance image combination (MARVIC) [38, 171]. These two techniques can be used alone or in combination (MARVIC-SEMAC). Without increasing the scan time, they allow for assessment of osteolytic lesions [171]. MRI is contraindicated in patients with pacemakers, defibrillators, or other implanted electronic devices, including cochlea implants and nerve stimulators [180, 331].

Like MRI scans, US scans allow for good soft-tissue differentiation. Other advantages include low costs and the fact that US is not limited by metal artefacts to the same degree as MRI scans [80, 245]. A further advantage of US is the possibility to obtain guided biopsies, fluid needle aspirations, or injections, which can be performed during the US examination. However, US is also dependent on the radiologist's experience, and the opportunity for retrospective re-grading is limited [180]. Furthermore, it may be difficult to scan large and obese patients since the resolution of US decreases with tissue depth. CT scans may be helpful when estimating component orientation and fixation, and for detection of osteolysis, fractures, and heterotopic ossification. CT scans can also be used to detect pseudotumors; however, MRI and US outperform CT for this purpose [272], and CT is associated with a high dose of ionizing radiation. [24].

Patient-reported outcome measures (PROMs)

THA is considered a successful surgical procedure for end-stage osteoarthritis of the hip joint, and THA has been shown to relieve pain efficiently, provide better functional capacity, and improve health-related quality of life [155, 157, 336]. In fact, patients with low scores of health-related quality of life who suffer from pain preoperatively have scores of health-related quality of life comparable to those of the age and gender-matched general population along with a significant decrease in pain 1 year after surgery [273]. Several factors like age [150, 273], gender [273], Body Mass Index (BMI) [152], preoperative function [3], surgical approach [151,

260], noise from the bearing surfaces [324], socio-economic status [3], cemented versus uncemented THA [273], unilateral versus bilateral THA [273], and patients' expectations and occupation [153] have been shown to influence the sum of PROMs.

Some short-term and mid-term comparative studies have investigated the clinical outcome scores between patients with MoM THA/RHA and patients with MoP THA or CoC THA [228, 265, 305, 316]. At 2 years after surgery, Vail et al. compared components of the Harris Hip Score (HHS) in MoM RHA and MoP THA. After controlling for gender, age, and preoperative function, they found statistically significantly higher activity and ROM scores of the HHS in the MoM RHA group than in the MoP THA group [316]. Similarly, Polland et al. evaluated patients with MoM RHA and MoP THA who had been matched on gender, age, preoperative activity level, and BMI at 5-7 years after surgery, and found similar Oxford Hip Scores (OHS) and complication rates between the two groups; however, patients with MoM RHA had higher scores on the UCLA activity-level rating scale [265]. MoM RHA and CoC THA have also been reported to yield comparable scores of HHS within an excellent range at 2 years after surgery [228].

Within recent years, some countries have introduced nationwide assessment of PROMs from patients before and after surgical procedures (e.g. hip arthroplasty) [41, 52, 67, 273]. Such routine collection of PROMs is, among others, intended to supplement register data, identify failures from the patients' point of view, increase the sensitivity of register-based analysis, and monitor and improve surgical outcomes.

Revision rates and postoperative functional outcomes

The National Institute for Health and Care Excellence (NICE) currently recommends a 10-year all-cause revision rate of 5% or less for primary THA [240]; however, data from the large joint registers reveal that revision rates of MoM hip arthroplasties exceed this benchmark.

In the 2014 Australian Hip Arthroplasty Register report, the 15-year all-cause revision rate was 13.3% for MoM RHA and 21.8% for MoM THA [7]. Similarly, the 13th National Joint Registry (NJR) Annual report for England, Wales, Northern Ireland, and the Isle of Man showed a 12-year all-cause revision rate of 13.6% for MoM RHA and 22.1% for MoM THA [247]. In Denmark, the 10-year all-causes revision rate of MoM RHA was reported to be 10.8% [335] (Figure 9) and the 7-year (10-year data not available) all-cause revision rate of MoM THA was 5.7% [334].

MoM RHA was supposed to favor revision surgery on the femoral side and to improve the chance of good postoperative results in case of needed revision surgery; however, postoperative results have unfortunately showed no difference regarding blood loss, operating time, clinical outcomes score, or complication rates when compared with MoP THA or MoM THA [8, 64, 95]. Poor functional outcomes have been reported for MoM THA/RHA patients who were revised due to metal-wear-related failures, e.g. progressive soft-tissue destructions, which can be observed in asymptomatic and seemingly well-functioning MoM hip arthroplasties [102, 194]. Consequently, some authorities and surgeons have recommended a low threshold for revision surgery in patients with metal-related failures [58, 83, 102, 108, 224]. However, other

studies have found good or excellent functional outcomes (based on results of OHS or HHS) following metal-wear-related revision surgery [54, 58, 209].
A recent systemic review on the outcomes of MoM hip arthroplasties revised due to metal-related failures concluded that the few studies available on this subject were of low quality (level 4) and limited by small study populations with short-term postoperative follow-up [208]. Due to this lack of evidence, there is no general threshold yet for when revision surgery due to metal-wear-related failures should be performed [212]. This is also reflected in the various recommendations on "which patients, and when to revise" suggested by several authorities and researchers [74, 83, 113, 180, 195, 224] (Appendix 1 to 6).

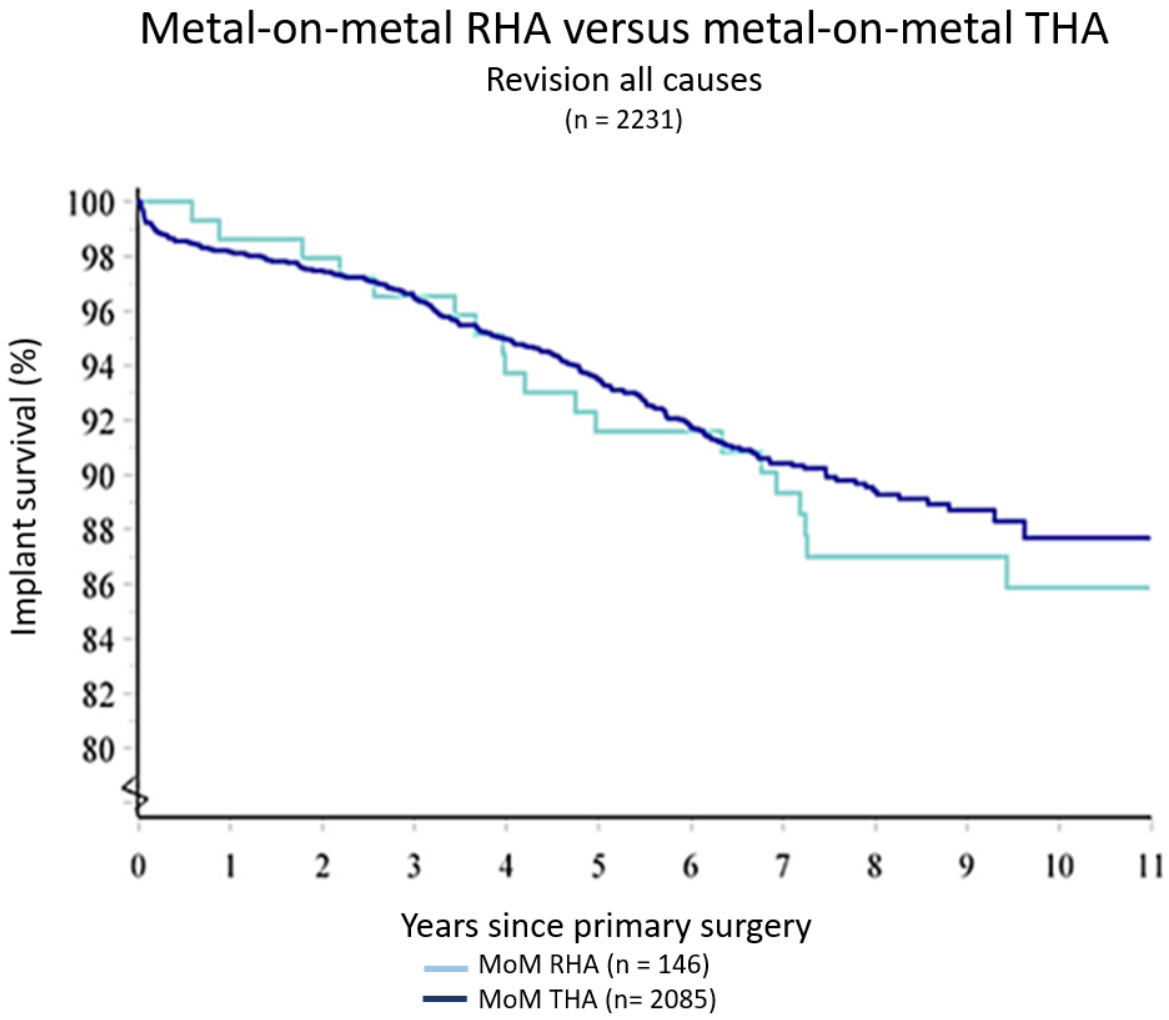


Figure 9 Survival curves (revision all-causes) of MoM THA and MoM RHA from the Danish Hip Arthroplasty Register 2016 [335].

4. Aim of the thesis

National Joint Registers reveal that MoM THA and RHA longevity is inferior to MoP THA longevity. Revision surgery of MoM THA and RHA has been associated with undesirable side effects of metal wear-debris generated from the bearing surfaces such as pseudotumors. However, pseudotumors have also been found in relation to MoP THA, and they may be related to risk factors other than metal wear debris. Deeper knowledge on this subject is important for the development and introduction of future implant types to improve patient safety.

The main aims of this thesis were:

1) To estimate the pseudotumor prevalence in MoM THA, MoM RHA, and MoP THA.

2) To investigate the effect of PA on metal-ion measurements and pseudotumor dynamics in the three bearing types during a 1-year follow-up.

3) To study differences in cup fixation and pseudotumor formation with an AntLat and a Post surgical approach for insertion of MoM RHA.

The specific aims of the four studies were:

Study I

The purpose of this cross-sectional study was to evaluate pseudotumor prevalence and pseudotumor classification in patients with MoM THA, MoM RHA, and MoP THA. Furthermore, we compared chromium and cobalt metal-ion measurements, clinical outcome scores, and conventional radiographs between the three bearing types and between patients with and without a pseudotumor.

Study II:

This 1-year longitudinal study aimed to investigate the correlation between patients' daily PA level, metal-ion measurements, and pseudotumor dynamics, as well as changes in pseudotumor classification/size during 1 year.

Study III

This randomized clinical trial (RCT) was conducted to investigate if the AntLat surgical approach, which preserves the blood supply to the femoral head, provides superior outcomes of implant stability, periprosthetic BMD, and clinical outcome scores than the Post surgical approach in patients with MoM RHA at 2 years after surgery.

Study IV

The objective of this cross-sectional mid-term follow-up study of a randomized patient group was to compare the location, grade, and prevalence of pseudotumors and muscle atrophy in patients allocated to MoM RHA by the AntLat or the Post surgical approach.

5. Materials & methods

Study design

Study I

A cross-sectional clinical study of patients with MoM THA, MoM RHA, or MoP THA at mean 7.1 (range: 0.2 - 21.5) years postoperatively (level of evidence: 3).

Study II

A 1-year prospective, clinical cohort study with five cross-sectional analyses (every third month) of patients included in Study I (level of evidence: 3). An illustration of investigations and follow-ups is presented in Table 2.

Study III

A prospective, randomized, patient-blinded clinical trial with 2 years of follow-up (level of evidence:1b).

Study IV

A subgroup analysis of a randomized, controlled clinical trial (Study III) at mean 5.3 (3.2 – 7.7) years after surgery (level of evidence: 2b).

Table 2 Illustration of investigations and follow-up in Study II

Method	Baseline/Day 1	3 months	6 months	9 months	12 months
MARS MRI scan	X	X	X	X	X
Blood sample	X	X	X	X	X
3D accelerometer		X	X	X	X
Conventional radiograph	X				
PROMs					
HHS	X				
OHS	X				
HAGOS	X	X	X	X	X

Ethics and permissions

All patients included in the studies of this thesis gave informed written consent to participate before entering the studies. All examinations were designed and carried out in compliance with the Helsinki II Declaration and current laws on personal data protection and patients' rights.

Study I and II

The study was approved by the Central Denmark Region Committee on Biomedical Research Ethics (03.17.2014; Journal no.: 1-10-72-65-14) and by the Danish Data Protection Agency (02.17.2014; Journal no.: 2007-58-0010; Trial no.: 1-16-02-87-14).

Study III

The study was approved by the Central Danish Region Committee on Biomedical Research (Journal no. M-20070082; issue date 29 August 2007) and by the Danish Data Protection Agency (Protocol no. 2007-41-1559; issue date 5 December 2007). The project was registered with www.clinicaltrials.gov (Clinical Trials Study ID number; 20070082).

Study IV

The study was reported to the Central Danish Region Committee on Biomedical Research who judged that it was a quality study of the ReCap Hip Resurfacing System (Journal no. 1-45-70-1-17) and therefore required no formal approval. The study was approved by the Danish Data Protection Agency (Journal no. 2012-58-0005).

Patients

Study I and II

The study population investigated in these two studies involved the same cohort of 111 patients (50 females, 61 males) with a total of 148 THAs (67 females, 81 males). Patients were identified and recruited from five former local research projects on MoM and MoP hip arthroplasties. The overall inclusion criteria of these five studies were primary osteoarthritis of the hip, acceptable BMD on preoperative DXA scan (T-score > - 1), age between 18 and 65 years, and informed written consent to participate. The overall exclusion criteria of the five studies were vascular or neuromuscular disease in the operated leg, fracture sequelae, avascular necrosis of the femoral head, women planning pregnancy, alcohol abuse, and daily intake of nonsteroidal anti-inflammatory drugs (NSAIDs), K-vitamin antagonists, or loop diuretics. A more detailed description of the inclusion and exclusion criteria in each study can be found in the published papers [134, 135, 138, 139].

Study I

A total of 111 patients (50 females, 61 males) with a total of 148 THAs (67 females, 81 males) were included between 19 May and 17 July 2014. Patients were divided into three groups: (1) MoM THA (n = 30), (2) MoM RHA (n = 47), and (3) MoP THA (n = 71). Baseline demographics of patients in the three groups are presented in Table 3.

Table 3 Descriptive baseline characteristics of patients with MoM THA, MoM RHA, and MoP THA. Values are mean (range) [141]

Articulation	MoM THA	MoM RHA	MoP THA	*p*-value
Number of patients	30	47	71	-
Sex (males/females)	22/8	29/18	30/41	0.01[a]
Age at follow-up	55 (30 - 70)	58 (39 - 73)	66 (45 - 77)	0.00 [b]
Years since operation	7.3 (5.3 – 8.3)	5.6 (2.4 – 9.4)	8.1 (0.2 – 21.5)	0.00[b]
Implant side, right/left	15/15	30/17	33/38	0.17[a]
Inclination cup angle (°)	44.4 (32.4 – 57.1)	42.9 (30.4 - 52.2)	43.9 (28.9 - 61.2)	0.57[a]
Anteversion cup angle (°)	22.1 (8.6 – 36.6)	16.9 (4.9 - 36.9)	23.9 (3.3 - 44.3)	0.00[a]

[a] Analysis of variance.
[b] Kruskal-Wallis rank test.

Study II

Patients in this study had already been enrolled in Study I. Patients in Study II were divided into two groups; (1) MoM hip articulations (n = 77) composed of MoM THA (n = 30) and MoM RHA (n = 47)), and (2) MoP THA (n = 71). Baseline demographics of the patients in the two groups are presented in Table 4.

Table 4 Descriptive baseline characteristics, outcome scores of questionnaires, activity, and chromium and cobalt measurements at all follow-ups in patients with MoM THA/RHA and MoP THA [140].

Articulation	MoM THA/HRA	MoP THA	*p*-value
Patients and implants			
Number of patients	77	71	-
Sex (male/female)	51/26	30/21	0.01[a]
Age at follow-up	59.1 (51.3 – 64.4)	68.3 (60.9 – 69.9)	0.00[b]
Years since operation	7.1 (4.6 – 7.6)	8.9 (4.7 – 10.7)	0.00[b]
Implant side, right/left	45/32	32/39	0.10[a]
Inclination cup angle (°)	43.5 (42.2 – 44.8)	43.8 (42.2 – 45.5)	0.74[a]
Anteversion cup angle (°)	18.7 (17.0 – 20.5)	23.9 (21.4 – 26.5)	0.00[a]
Questionnaires			
HHS at baseline	100 (96 - 100)	98 (94 - 100)	0.03[b]
OHS at baseline	47 (45 -48)	46 (43 - 48)	0.23[b]
HAGOS baseline[c]	95 (77.5 - 100)	85 (72.5 - 100)	0.14[b]
HAGOS 3 months[c]	95 (67.5 - 100)	90 (70 - 100)	0.61[b]
HAGOS 6 months[c]	92.5 (75 - 100)	90 (80 - 100)	0.90[b]
HAGOS 9 months[c]	95 (75 - 100)	90 (77.5 - 100)	0.78[b]
HAGOS 12 months[c]	90 (75 - 100)	85 (75 - 100)	0.37[b]
Physical activity level[d] (%)			
3 months	12.66 (11.62 – 13.69)	13.43 (12.13 – 14.72)	0.35[a]
6 months	11.82 (10.81 – 12.83)	12.33 (10.50 – 14.17)	0.61[a]
9 months	11.12 (10.19 – 12.05)	10.94 (9.35 – 12.53)	0.84[a]
12 months	13.15 (12.20 – 14.09)	13.34 (11.66 – 15.03)	0.83[a]

[a] Analysis of variance. Values are mean (95% confidence interval)
[b] Two-sample Wilcoxon rank-sum (Mann-Whitney) test. Values are median (interquartile range)
[c] Clinical outcome scores of HAGOS subscale "Hip-Related Quality of Life"
[d] Physical activity level includes the mean time spent walking, bicycling, and performing high-impact activities (%) during total daily wear-time

Study III and IV

The MoM ReCap Resurfacing System (Biomet Inc., Warsaw, IN, USA) was used at our institution between January 2006 and January 2012. During this period, 110 patients were operated with the MoM ReCap Resurfacing System by two orthopedic surgeons specialized in hip arthroplasty surgery. Of these 110 patients, 37 were operated with the AntLat approach (ad modum Watson) [57] and the remaining 73 were operated by the Post approach (ad modum Moore) [57].

Study III

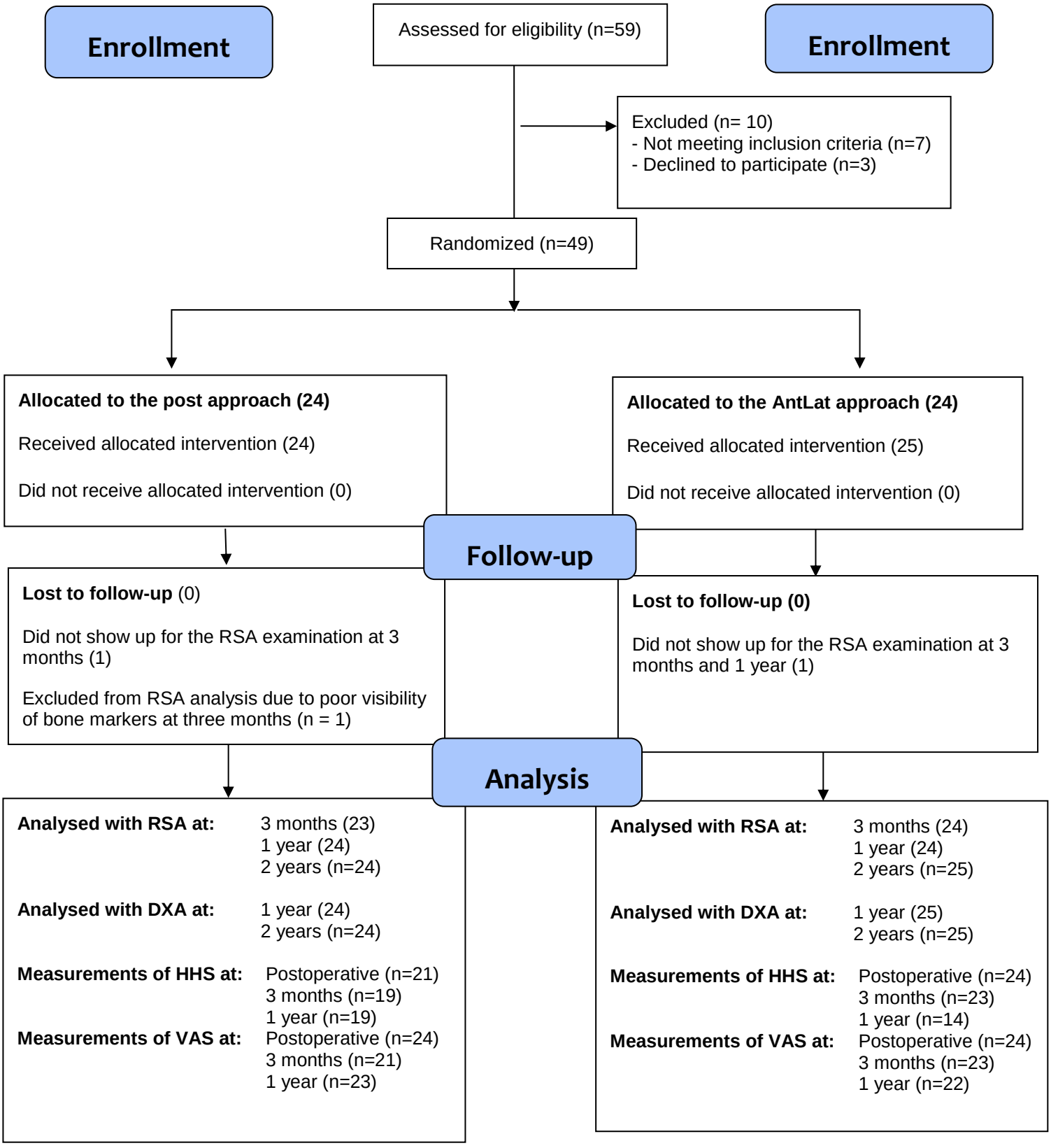
This RCT study was carried out between November 2008 and January 2012 where 49 patients (28 males) were included. Patients were allocated to surgery with MoM RHA by either the AntLat surgical approach (n=25) or the Post surgical approach (n=24) by opening sealed envelopes prior to surgery. Two experienced orthopedic hip surgeons undertook all operations using standard equipment provided by the manufacturer. All patients were blinded regarding the surgical approach used for implantation. Inclusion criteria were primary or secondary (due to mild or moderate dysplasia) osteoarthritis of the hip, acceptable BMD on pre-operative DXA scan (T-score >-1), and age 30-60 years. Exclusion criteria were vascular or neuromuscular disease of the lower extremities, fracture sequelae of the hip/acetabulum, avascular necrosis of the femoral head, women planning pregnancy, alcohol abuse, and daily intake of NSAIDs, K-vitamin antagonists, and loop diuretics. Postoperatively, the hospital physiotherapists instructed all patients in a home-based training program that allowed full weight bearing. During the first 6 weeks, patients were advised limited adduction, but no other restrictions applied. Baseline demographics of all patients are presented in Table 5 and Figure 10.

Table 5 Descriptive baseline characteristics of the patients, implants, and surgery. Values are mean (range) [139].

	Post approach	AntLat approach	*p*-value[a]
Number of patients	24	25	-
Sex (male/women)	15/9	13/12	0.47
Age at operation	47 (32-60)	53 (44-61)	0.01
Implant side, right/left	13/9	12/8	0.48
Femoral head size (mm)	50 (50-60)	48 (48-64)	0.49
Inclination cup angle (°)	39.4 (32.6 – 47.6)	41.6 (21 – 50.7)	0.07
Anteversion cup angle (°)	9.7 (3.6 – 21.8)	14.1 (3.4 – 24.8)	0.008
Stem position (neutral/valgus/varus)	15/9/0	21/4/0	0.09
Stem position (neutral/anterior/posterior)	23/1/0	24/1/0	0.97
Time of surgery (min)	106.5 (75 - 140)	103.3 (75 - 120)	0.45
Blood loss during surgery (ml)	297.7 (150 - 600)	344.5 (100 - 700)	0.12

[a] Satterthwaite's t-test.

Figure 10 CONSORT flow diagram showing the inclusion/exclusion process and follow-up until 2 years of follow-up [139].



Study IV

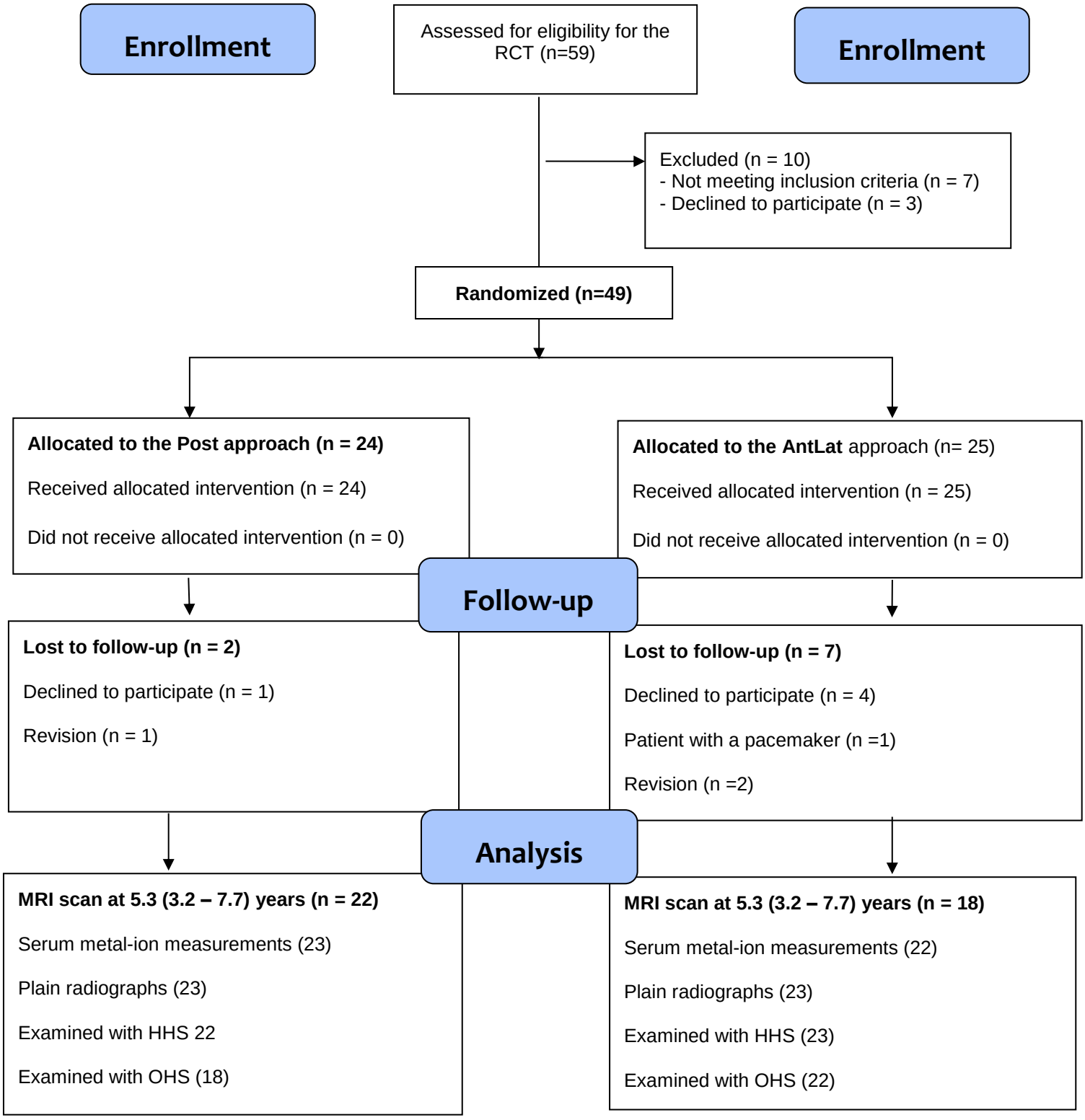
Patients included in the principal RCT study (Study III) were invited to participate in an additional follow-up examination of their MoM RHA at mean 5.3 (3.2 – 7.7) years after surgery. Five patients declined to have an MARS MRI scan (four AntLat, one Post), three patients had been revised (two AntLat, one Post), and one patient had a pacemaker (AntLat) and could not be MRI scanned. This left 40 patients with MARS MRI scans (18 AntLat, 22 Post) (Figure I) at 5.3 (3.2 – 7.7) years of follow-up. Demographics of patients in Study IV are presented in Table 6 and Figure 11.

Table 6 Descriptive baseline characteristics of the patients and implants. Values are mean (range).

	Post approach	AntLat approach	*p*-value[a]
Number of patients	24	25	-
Sex (male/women)	15/9	13/12	0.47
Age at operation, mean (range)	47 (32-60)	53 (44-61)	0.01
Implant side, right/left	16/8	19/6	0.48
Femoral head size (mm), mean (range)	50 (44-54)	48 (42-58)	0.49
Inclination cup angle (°)	40.4 (30.4 – 50.1)	41.2 (27.5 – 52.2)	0.60
Anteversion cup angle (°)	11.5 (4.9 – 22.5)	15.3 (6.1 – 27.5)	0.02

[a] Satterthwaite's t-test.

Figure 11: CONSORT flow diagram showing the inclusion/exclusion process for the original RCT study, and follow-up for the sub-study at mean 5.3 (3.2 – 7.7) years after surgery.



Implants

Study I and II

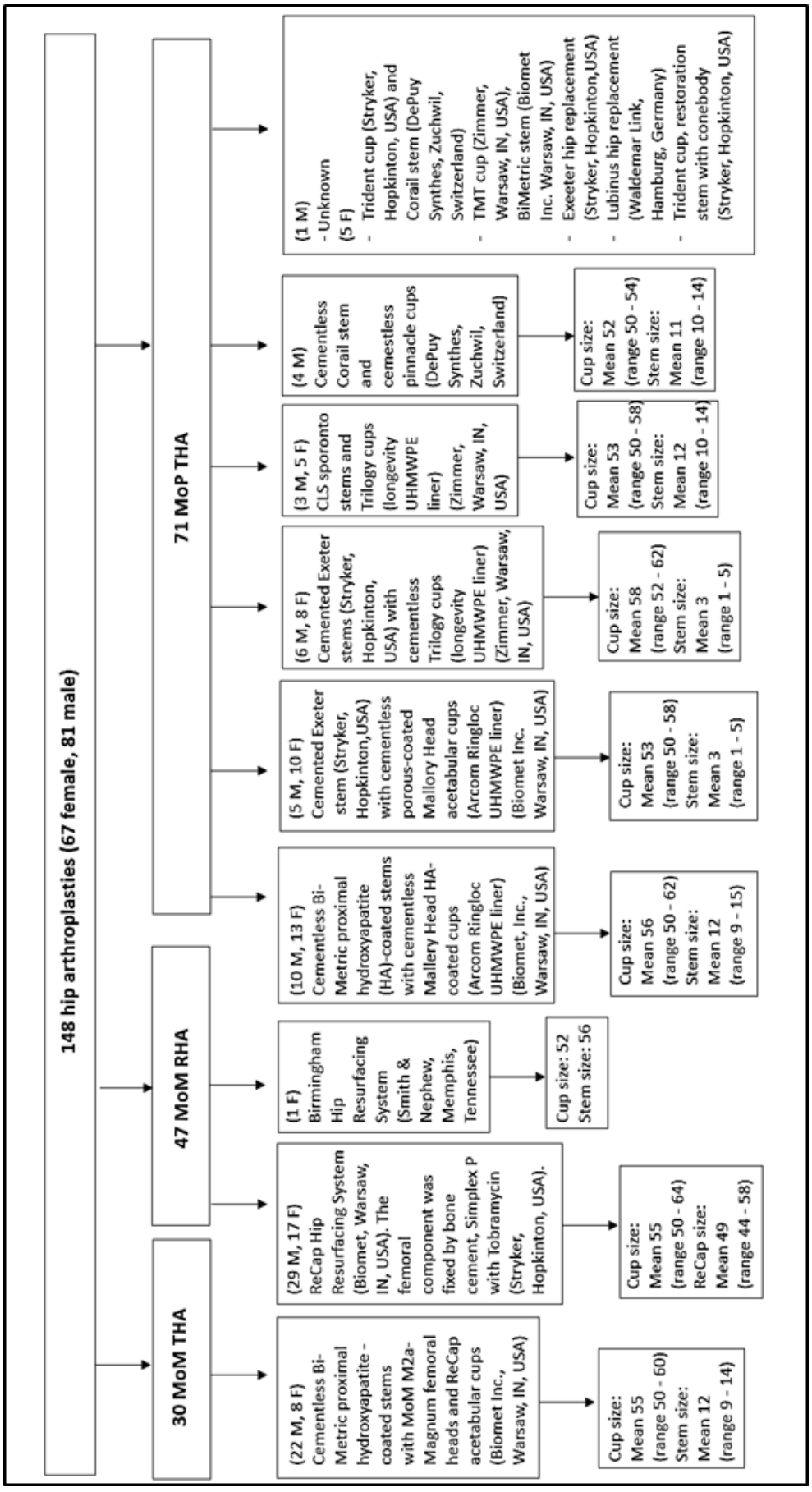
All MoM and MoP THAs were inserted with a Post surgical approach; the MoM RHAs were inserted with either a Post (ad modum Moore) [57] (n = 38) or an AntLat (ad modum Watson) [57] (n = 9) surgical approach. An overview of implant details used in Study I and II is presented in Figure 12.

MoM THAs: All MoM THAs were cementless Bi-Metric proximal HA-coated stems with MoM M2a-Magnum femoral heads and ReCap acetabular solid shells (Biomet Inc., Warsaw, IN, USA) (Figure 3). The ReCap acetabular press-fit cup and the M2a-Magnum head are made of "as-cast" high carbon cobalt chromium molybdenum alloy. The system is modular at the head-neck junction. Head size is dependent upon cup size with neck length being adjusted via adaptors inserted into the femoral head. The outer diameter of the ReCap cup is fully hemispherical (180°) with four rim indentations for stable attachment of the locking impaction device. It is 6 mm thick at the dome and an average of 3 mm thick at the rim. The radial clearance level of the M2a-Magnum articulation is maintained at 75 to 150 μm [13]. The stem and taper are made of a titanium, aluminium, and vanadium alloy, and lateralized stems have an increased taper and trunnion length.

MoM RHAs: The majority of MoM RHAs included were MoM ReCap Hip Resurfacing arthroplasties (Biomet Inc., Warsaw, IN, USA) (Figure 4) (1 patient had Birmingham Hip Resurfacing (BHR) (Smith & Nephew, Memphis, Tennessee)). The ReCap Hip Resurfacing System consists of a cemented cobalt chrome femoral component and a cementless titanium non-hydroxyapatite-coated closed pore porous-coated acetabular component with a cobalt chrome core fixed by press fit. The femoral component was fixed by bone cement, Simplex P with Tobramycin (Stryker, Hopkinton, USA). The radial clearance level of ReCap resurfacing system ranges from 75 to 150 μm [13].

MoP THAs: Different brands of MoP THAs were included. A majority (n=38) of the acetabular cups were cementless hydroxyapatite (HA)-coated or porous-coated Mallory-Head acetabular cups (Biomet, Inc., Warsaw, IN, USA) with an Arcom Ringloc UHMWPE liner (Biomet, Inc., Warsaw, IN, USA) (Figure 2). A majority of the femoral stems were cementless Bi-Metric proximal HA-coated stems (n=23) (Biomet, Inc., Warsaw, IN, USA) (Figure 2) or cemented Exeter stem (n=29) (Stryker, Hopkinton, USA). Details on the remaining MoP THAs can be found in Figure 12.

Figure 12 Presentation of the different types and brands of hip articulations included in the Study I and Study II [140, 141].



Study III and IV

Patients in these two studies all received the ReCap Hip Resurfacing System (Figure 4), consisting of a cemented cobalt chrome femoral component and a cementless titanium non-HA-coated closed pore porous-coated acetabular component with a cobalt chrome core fixed by press fit. The femoral component was fixed by bone cement, Simplex P with Tobramycin (Stryker, Hopkinton, USA).

Interventions

MARS MRI scans

Study I, II and IV

The MRI set-up and follow-up

MARS MRI of the pelvis and proximal one third of both femurs was performed using two identical 1.5 T Philips Ingenia MRI scanners (Koninklijke Philips Electronics NV, Eindhoven, The Netherlands) (Figure 13). A protocol with five sequences was used (Table 7). During MRI scans, patients were placed in standardized positions; supine with the body parallel with the examination table, internally rotated hips, and feet fixated with a band (Figure 14). Patients in Study I had one baseline MRI scan at mean 7.1 (range: 0.2 - 21.5) years after surgery. Patients in Study II patients had four additional MRI scans with 3-month intervals (in total 5 MRI scans during 1 year) (Table 1). Patients in Study IV had one MRI scan.

Table 7 have been published in [140, 141].

Table 7 Details of magnetic resonance imaging parameters used in this study

Pulse sequence name	TE (ms)	TR (ms)	TI (ms)	ST (mm) / gap (mm)	FOV	Matrix size	BW (Hz/pixel)	Coil
Coronal T1W MARS	15	450-650	-	2.5 / 1	360x450	380x356	438,6	Sense Body 16ch
Coronal STIR MARS	40	4000-8000	130	3.5 / 1	400x454	364x320	434,7	Sense Body 16ch
Coronal T2W MARS	80	3000-7000	-	2.5 / 1	360x450	380x316	438,6	Sense Body 16ch
Axial T1W MARS	16	450-650	-	2.5 / 1.5	400x454	420x348	437,7	Sense Body 16ch
Axial STIR MARS	40	4000-8000	130	3.5 / 1.5	360x447	276x272	435,5	Sense Body 16ch

W: Weighted
TSE: Turbo spin echo
STIR: Short tau inversion recovery
TE: Time of echo (ms, millisecond)
TR: Time of repetition (ms, millisecond)
TI: Time of inversion (ms, millisecond)
ST: Slice thickness (mm, millimeter)
FOV: Field of view
BW: Band width

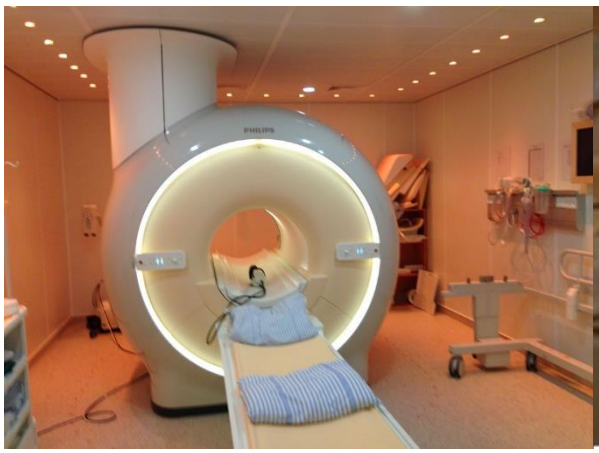
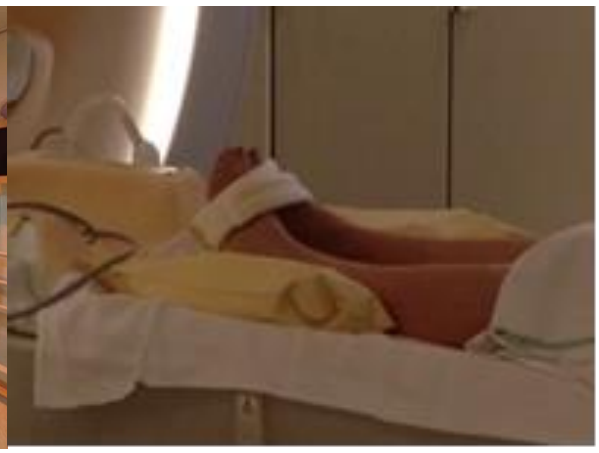



Figure 13 The MRI scanner used for examinations in Study I and II
Figure 14 A patient lying in the standardized positions used for MRI scans with internally rotated hips and feet fixed with a band. A cloth was positioned between patients' thighs due to the long scan time and the risk of heat conduction

MRI analyses

The MRI scans were assessed on a PACS workstation (Agfa Impax, Belgium, version 6.3.1.8000) and evaluated in consensus between two observers; one experienced musculoskeletal radiologist and researcher (LR) and one MD (MHH). Both were blinded to patients' serum-ion measurements, clinical details, and radiographs. Pseudotumor findings were classified according to the Anderson grading system (Figure 1), which has the highest intra-observer and inter-observer reliability of the currently used systems [6, 323]. In addition to the Anderson grading system, the pseudotumor type (fluid/mixed or solid) and anatomical location (anterior-lateral or posterior-lateral to the greater trochanter, or located to the iliopsoas bursa) were noted. In contrast to the Anderson grading system, patients with a C1 lesion and muscle atrophy or edema in any other muscles than the short external rotators were not classified as C2, since different surgical approaches have been shown to cause muscle atrophy in other muscle groups than the short external rotators [2].
In Study IV, muscle atrophy was assessed as a decrease in volume and appearance of fatty change relative to the contralateral side according to the classification system proposed by Pfirrmann et al. [261] (Table 8). Grade 0–4 was evaluated individually for the gluteus maximus, medius, and minumus, the obturatorius internus and externus, the illiopsoas, the abductors, and the piriformis muscle. For obliquely running muscles, multiple planes were taken into consideration before grading.

Table 8 Muscle atrophy grading system by Phirrmann et al 2005 used to evaluate hip muscle atrophy

Atrophy grade	Description
0	Normal – no fat steaks present
1	Some fat steaks present
2	Fat evident, but less fat than muscle
2	Equal amounts of fat and muscle
4	More fat than muscle

Accelerometer-based measurements of physical activity

Study II

Accelerometer setting and clinical application

A commercially available 3D accelerometer (Axivity, Newcastle upon Tyne, England), which determines the acceleration of body parts in three planes, was used to measure type and duration of activity in patients (Figure 15). The accelerometer was set at 100Hz and ±8 g. The patients were instructed to mount the accelerometer on the lateral side on the right thigh with Fixomull tape (3M, USA) (Figure 16) and to wear it during all wake hours. Patients wore the accelerometer for periods of mean 15 (range: 10 – 21) days with a minimum of 8 hours of wear time per day. The accelerometer was worn before the MARS MRI scans at 3, 6, 9, and 12 months.

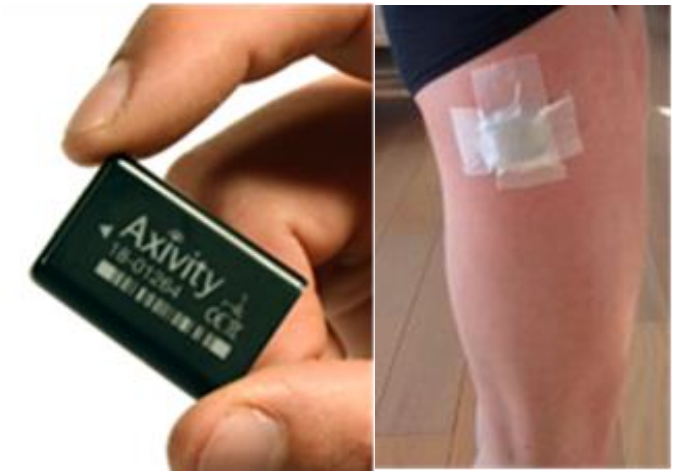


Figure 15 The 3D Axivity accelerometer used for monitoring patients' PA.
Figure 16 The 3D Axivity accelerometer firmly fixated to the lateral side of the right thigh with Fixomull tape.

Accelerometer data analyses

All data were visually split into separate days using a MatLab-script designed for the purpose, and non-worn periods were removed. Thereafter one person analyzed all accelerometer-based activity data. The raw acceleration signal was analyzed using the inclinometer function of the accelerometer and algorithm-based peak detection methods in Matlab (MATLAB R2010a, The Mathworks Inc., Natick, Massachusetts, USA) based on previously published principles [215, 266]. Briefly, the accelerometer's orientation was calibrated within a period of level walking, that had been manually selected in the dataset. Within this walking period, the average magnitudes of the three acceleration vectors and the gait cycle frequency (Hz) were derived to allow further differentiation between activities. Standing periods were distinguished from sitting periods based on the direction of the gravitation vector. Walking was distinguished from other upright activities (all classified as standing) by application of heuristic rules to the gait cycle frequency. A walking period was classified when at least five consecutive heel strike

peaks were detected, with 0.6Hz and 5min walking bouts. More detailed information on the accelerometer and its clinical application has been given in a previous study [286].

Surgical approach

Study III

Patients were allocated to surgery with MoM RHA using the AntLat surgical approach (ad modum Wattson) [144] or the Post surgical approach (ad modum Moore) [144]. The AntLat approach was performed with a skin incision along the anterolateral aspect of the hip. Thereafter, the anterior third of the gluteus medius and gluteus minimus muscle insertions to the femoral bone were cut, and the anterior part of the joint capsule was opened (Figure 17 A). The Post approach was used with a skin incision facing the posterior part of the hip. The fibers of the gluteus maximus muscle were separated, and the tendons from the external rotators were cut through. Finally, the posterior part of the joint capsule was opened (Figure 17 B). Two experienced orthopedic hip surgeons undertook the operations using standard equipment provided by the manufacturer.

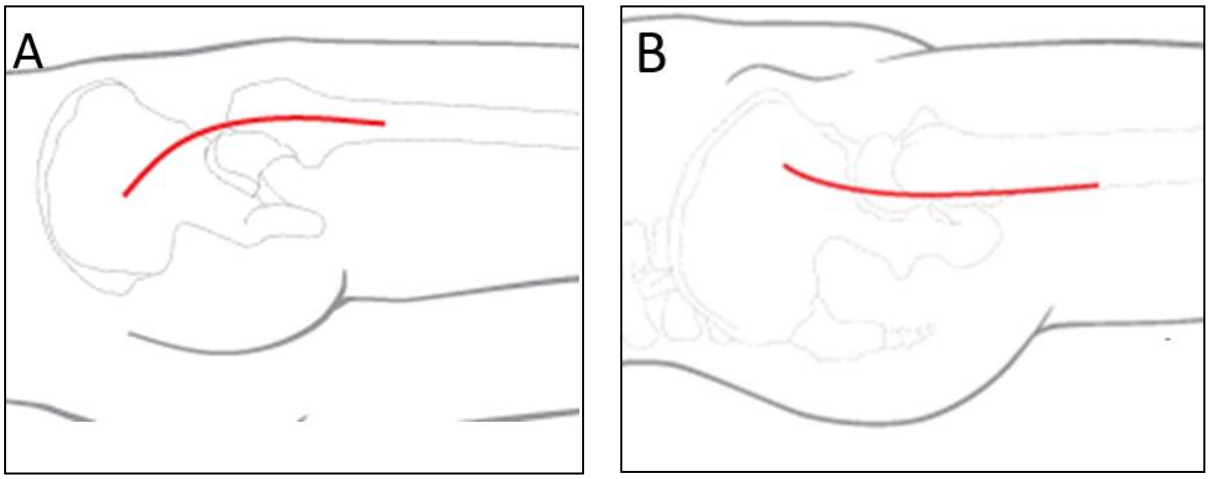


Figure 17 A The skin insertion for the AntLat surgical approach.
Figure 17 B The skin insertion for the Post surgical approach.

RSA

Study III

Surgery and follow-ups

For RSA measurements, eight to ten tantalum markers (one mm) were inserted into the greater and lesser trochanter regions, and six to eight tantalum markers were inserted into the periacetabular bone during surgery. RSA stereoradiographs were obtained using a uniplanar setup with the patient in a standardized position: supine, body parallel with the examination

table, the big toes pointing straight up, and the calibration box placed under the examination table. Stereoradiographs were obtained within the first postoperative week and at the 3-month follow-up and at follow-up at 1 and 2 years. Implant migration was assessed at all follow-up stereoradiographs using the postoperative stereoradiograph as the reference.

RSA setup

A standardized RSA setup was used to obtain all stereoradiographs. The set-up consisted of two synchronized ceiling-fixed roentgen tubes (Arco-Ceil/Medira; Santax Medico, Aarhus, Denmark) with a 40^{o} angle between them, along with a uniplanar carbon calibration box (Box 24, Medis Specials, Leiden, The Netherlands) (Figure 18). The uniplanar calibration box defines the 3D coordinate system by a bottom layer of fiducial markers and an upper layer of control markers (Figure 19). The first step in RSA analysis is calibration of the stereoradiograph according the known 3D position of the fiducial markers and the control markers in the calibration box. The fiducial markers are used to calculate the position of the implant (cup and stem) models to the point with the shortest distance between the projection lines. The control markers are used to calculate the exact position of the x-ray source.

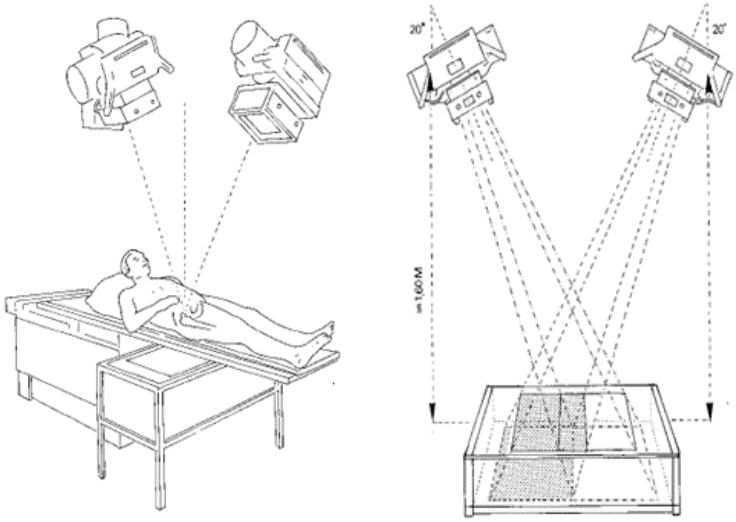


Figure 18 A standardized RSA setup showing the two roentgen tubes with a 40^{o} angle between x-ray projections (Figure to the left) [318].
Figure 19 The uniplanar calibration box which defines the 3D coordinate system by a bottom layer of fiducial markers and an upper layer of control markers (Figure to the right) [318].

Precision of the method

The precision of the RSA analyses was assessed by "double examinations" of all patients at the 1-year follow-up, where two sets of stereoradiographs from the same patient were recorded within a 10-15-minute interval [145, 318]. Between the two examinations, the patients changed position by either standing or sitting before returning to the standard supine position on the X-ray table. The first stereoradiograph was used as reference in migration analysis of the double

examinations, and the calibrated difference in implant displacement between the two stereoradiographs represents the systematic error of the RSA system (bias) and should (optimally) equal zero. The standard deviation of the difference between the two stereoradiographs (SD dif.) reflects the precision of the RSA results. The coefficient of repeatability (CR) (±1.96 x SD dif.) reflects the lower limit at which it is possible to detect prosthetic migration on the individual basis of the system [5, 145] (Table 9).

Table 9 Measurement error of RSA based on for double-examination stereo radiographs for translations and rotations. Mean difference represents the systematic error of the system. SD dif. is the random variation within the method comparing the double examinations. CR (±1. 96 x SD dif.) reflects the precision on the individual patient level [139].

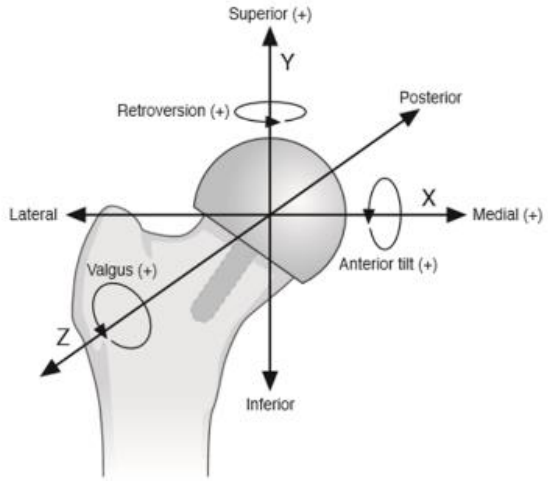
Femoral component	Translation (mm)				Rotation (°)			
Axis	X	Y	Z	TT[a]	X	Y	Z	TR[b]
Mean dif.	0.02	0.02	-0.06	0.01	0.04	-0.01	-0.05	-0.02
SD dif.	0.14	0.12	0.40	0.31	0.39	0.28	0.33	0.33
CR [c]	0.27	0.24	0.78	0.61	0.76	0.55	0.65	0.65
Cup	Translation (mm)				Rotation (°)			
Axis	X	Y	Z	TT[a]	X	Y	Z	TR[b]
Mean dif.	0.05	0.03	-0.01	-0.11	-0.21	0.19	-0.09	-0.05
SD dif.	0.50	0.15	0.44	0.44	0.84	0.65	1.01	0.89
CR [c]	0.98	0.29	0.86	0.86	1.65	1.27	1.98	1.74

[a] The total translation was calculated using the 3D Pythagorean theorem (TT= $\sqrt{(x^2 + y^2 + z^2)}$.
[b] The total rotation was calculated using the 3D Pythagorean theorem (TR= $\sqrt{(x^2 + y^2 + z^2)}$.
[c] CR = Coefficient of Repeatability (±1.96 x SD dif.).

RSA analyses

All RSA analyses of implant migrations were performed by two experienced RSA technicians. Stereoradiographs were analyzed using 3D computer-aided design (3D CAD) surface model/marker models [159, 160, 197]. The CAD models used for RSA analyses were created using 5000 triangles, and they were implemented into the model-based RSA software by the software provider (RSAcore, Leiden, The Netherlands). Translations (implant movement along the axes) were expressed as x-translations (medial/lateral direction), y-translations (superior/inferior direction), and z-translations (anterior/posterior direction). Rotations were expressed as rotations about the x-axis (anterior/posterior tilt), rotations about the y-axis (retroversion/anteversions), and rotations about the z-axis (valgus/varus tilt) (Figure 20 and 21). The total translation (TT) and the total rotation (TR) were calculated by use of the Pythagorean theorem as TT= ($\sqrt{(x^2 + y^2 + z^2)}$. The distribution of the implant and femoral bone markers can be assessed using the condition number (CN), and an upper limit of ≤150 has been suggested

[318]. The mean CN of the markers was 17.69 ± 5.04 in the femur and 56.22 ± 15.82 in the acetabulum. The rigid body error (RBE) represents the stability of the markers. In the analysis of the markers, the mean RBE was 0.14 ± 0.05 in the femur and 0.19 ± 0.07 in the acetabulum. The rigid body Match threshold was set to 0.50 mm.



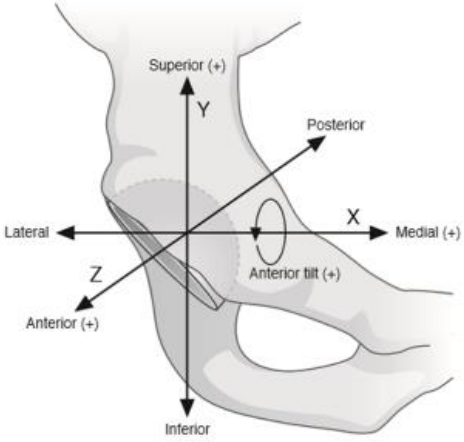


Figure 20 Illustration of directions, translations, and rotations for the ReCap resurfacing femoral component [139].
Figure 21 Illustration of directions of translations and rotations for the ReCap acetabular component [139].

DXA scans

Study III

DXA set-up end follow-up

Postoperatively (within 1 week after surgery) and at the 1 and the 2-year follow-up, quantitative measurements of periprosthetic BMD (g/cm^2) were acquired by DXA scans with a Lunar Prodigy Advance 2005 DXA scanner (General Electric, Chicago, IL, USA). Patients were placed in standardized positions: supine, body parallel with the examination table, big toes pointing straight up, and fixation of the feet to a device. The postoperative DXA scan served as baseline for the subsequent scans as recommended by Kröger et al. [173]. To verify system reliability, calibration was performed daily with two different phantoms according to the manufacturer's guidelines.

DXA analyses

All DXA scans were analyzed using the enCORE version 11.40 software (GE Healthcare, Madison, WI, USA). This software uses a tissue detection algorithm to differentiate between bone, soft tissue, and metallic implants. No specialized software was available for creating the femoral neck regions of the MoM RHA. Customized ROIs were therefore created in a template that was applied at the baseline scan with ROIs evenly distributed on either side of the implant stem. Subsequently, the ROIs were copied to the follow-up scans. The BMD of the femoral

neck was analyzed in two models: (A) in a 2-ROI model with a sub-region medial (Med) and lateral (Lat) to the pin of the femoral component as suggested by Penny et al. [257]; and (B) in a 6-ROI model with three regions medial (M1-3) and three regions lateral (L1-3) to the pin of the femoral component as suggested by Kishida et al. [170] (Figure 22).

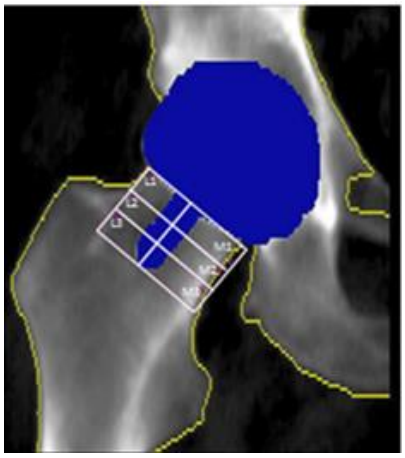


Figure 22 The 6-ROI model with three regions lateral (L 1-3) and three regions medial (M 1-3) to the pin of the femoral component [139].

Conventional radiographs

Study I, II, III, and IV

All patients included in these four studies had a postoperative standardized weight-bearing AP pelvic and lateral hip radiograph taken. Another set of AP pelvic and lateral hip radiographs was obtained at baseline/inclusion (Study I and II), at the 2-year follow-up (Study III), and at the 5.3-year (range: 3.2 – 7.7 years) follow-up. All radiographs were evaluated in consensus between two observers (SSJ, MHH), and patients' postoperative radiographs were compared to their follow-up radiographs. The femoral bone around the stems was reviewed for presence of radiolucent lines > 1 mm and signs of osteolysis in the seven Gruen zones in THA [105] or zones by Kishida et al. in RHA [170]. The periacetabular bone was reviewed for radiolucent lines > 1 mm and signs of osteolysis in the three DeLee Zones [62]. Heterotopic calcification was scored according to Brooker grades I-IV, depending on the severity of ectopic bone growth [25]. Femoral narrowing was calculated in Study III and IV using the method described by Hing et al. [133]. In Study III, stem location of neutral, valgus, or varus position (relative to the center line of the femoral neck) was evaluated [57].

Cup position

Study I, II and IV

Cup inclination and anteversion angles were measured digitally by PolyWare Pro 3D Digital vs. 5.10 (PolyWare 3D Digital version 5.10; Draftware Developers, Conway, SC, USA) [65, 66]. The PolyWare program determines the position of the implants by edge detection on the

AP pelvic radiograph (Figure 23). By manually fitted points on the contour of the femoral head and acetabular cup, the program creates an ellipse for the components with a midpoint that overlaps the center of rotation and then calculates inclination and anteversion angles using complex mathematical curve-fitting methods [65, 66]. The acetabular cup and femoral head are visualized using 3D models of the specific implants models according to the manufacturer's specifications (Figure 24). Cup inclination and anteversion angles were measured using the latest AP pelvic radiographs.

Study III

In Study III, measurements of cup inclination and anteversion were read from the model-based RSA software (RSAcore, Leiden, The Netherlands). The 3D acetabular cup model was precisely fitted to the contour of the cup on the individual 2-year stereoradiographs. The position of the acetabular cup was thereafter read from the z-axis (inclination angles) and x-axis (anteversion angles).

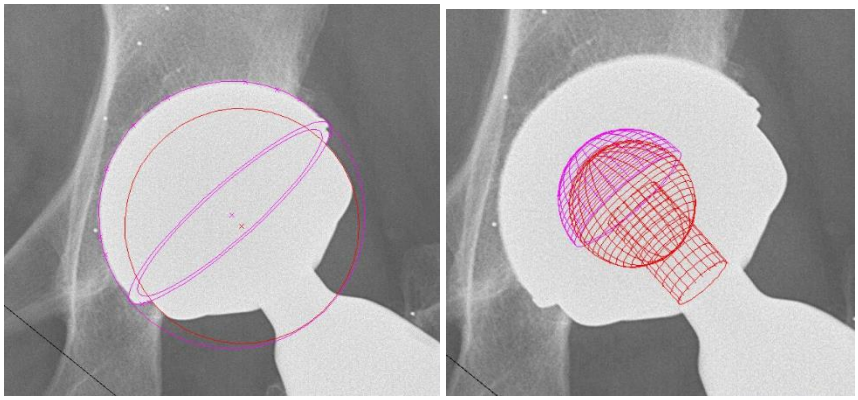


Figure 23 Illustration of edge detection of the acetabular cup and the femoral head on the anterior-posterior pelvic radiograph.
Figure 24 The acetabular cup and the femoral head are visualized by a 3D model (the CAD model is not supposed to fit perfectly with the THA implant).

Serum-ion measurements of chromium and cobalt

Study I, II, III and IV

In the four studies, blood samples of chromium and cobalt were collected according to published international and national guidelines [73, 201]. Blood was collected in Trace Element Serum 6.0ml (13x100 mm) KFK359 tubes (REF 368380) (Becton Dickinson, Franklin Lakes, NJ, USA) [10] and centrifuged to separate serum. To eliminate any form of metal contamination, analyses were completed using an inductively coupled plasma mass spectrometry (ICP-MS) at Vejle Regional Hospital, Denmark. C-reactive protein (CRP), creatinine, and estimated glomerular filtration rate (eGFR) were analyzed to screen for infection and renal impairment. In Study II, the blood samples were collected just before the MRI scan at the five follow-ups.

Clinical outcome scores

Harris Hip Score (HHS)

Study I, II, III and IV

HHS covers domains of pain, daily activities (stair use, using public transportation, sitting, and managing shoes and socks), gait (limp, support needed, and walking distance), and range of motion. Intra-class correlations have been proven good to excellent [242]. A PhD student (MHH) examined patients in Study I and II with HHS at baseline, and patients in Study III and IV were examined by an orthopedic hip surgeon before surgery and at 3 months and 1 year after surgery (Study III), and at 5.3 (3.2 – 7.7) years after surgery (Study IV).

Oxford Hip Score (OHS)

Study I, II, and IV

The OHS is a validated patient-reported outcome questionnaire used to evaluate disability and pain following hip arthroplasty [52]. It comprises a 12-item questionnaire with patients selecting one of five possible answers for each question. We used the modified OHS scoring system proposed by Murray et al., in which each question is scored from 0 (worst outcome) to 4 (best outcome). Hence, OHS outcomes ranged from 0 (worst outcome) to 48 (best outcome) [232]. Patients in Study I and II completed the OHS at baseline, and patients in Study IV completed the OHS at 5.3 (3.2 – 7.7) years after surgery.

The Copenhagen Hip and Groin Outcome Score (HAGOS)

Study II

HAGOS consists of six separate subscales entitled Pain, Symptoms, Physical function in daily living, Physical function in Sport and Recreation, Participation in Physical Activities, and Hip and/or Groin-related Quality of Life. The questionnaire has shown intra-class correlation coefficients ranging from 0.82 to 0.91 for the six subscales [311]. Patients in Study II completed the HAGOS questionnaire at baseline, and at the 3, 6, 9 and 12-month follow-up.

The Visual Analog Scale (VAS) for pain

Study III

VAS for pain assesses the average level of pain during daily living associated with having a hip implant [68]. The scale ranges from 0 to 10, where 0 equals “no pain” and 10 equals “worst imaginable pain”. Patients in Study III filled out the VAS for pain postoperatively and at 3 months and 1 year after surgery.

Statistics

In general, p-values below 0.05 were considered statistically significant for the tests. All analyses were performed using Stata software version 13 (StataCorp LP, College Station, Texas, USA).

Study I

Primary and secondary endpoints

The primary endpoint was pseudotumor prevalence evaluated with MARS MRI. The secondary endpoints were measurements of chromium and cobalt serum-ion levels, clinical outcome scores, and conventional radiographs.

Sample size

No scientific data were available for an *a priori* sample size calculation, but patients with a hip arthroplasty from five former local research projects were invited to participate.

Statistics

All continuous variables were tested for normality (Shapiro-Wilk test). Analysis of variance was used to compare parametric demographic variables between the three bearing types, and Kruskal-Wallis test was used to compare non-parametric variables. Differences in pseudotumor prevalence, serum metal-ions, and clinical outcome scores between the three bearing types and between patients with and without a pseudotumor were analyzed using multiple regression, adjusting for sex, age, and time since arthroplasty. Given the small number of patients in some sub-group analyses, Fischer's exact test was used to compare some of the parameters.

Study II

Primary and secondary endpoints

The primary endpoints were measurements of PA and metal-ion levels. The secondary endpoints were estimation of pseudotumor prevalence, change in pseudotumor grades over time, and clinical outcome scores.

Sample size

No scientific data were available for an *a priori* sample size calculation, but patients with a hip arthroplasty from five former local research projects were invited to participate.

Statistics

Data were checked for normality by Q plot and histograms. Analysis of variance was used to compare parametric demographic variables between the two groups, and the two-sample Wilcoxon rank-sum test (Mann-Whitney) was used to compare non-parametric variables.

Multiple regression analysis showed no difference between MoM THA and RHA regarding the influence of activity level, cadence, and sex on the levels of chromium and cobalt at any follow-up ($p>0.54$). We therefore chose to pool MoM THA and MoM RHA patients into one group to achieve more statistical power in the analysis. Multiple regression analysis was performed to assess the effect of patients' daily PA on serum-ion measurements of chromium and cobalt and on pseudotumor size at all follow-ups. We adjusted for sex, inclination angles, and time since surgery because these variables have been shown to affect serum-ion levels of chromium and cobalt and pseudotumor prevalence [9, 14, 118, 120].

Study III

Primary and secondary endpoints

The predefined primary endpoint was implant migration at 2 years. Secondary endpoints were measurements of periprosthetic BMD, serum-ion measurements, conventional radiographs, and clinical outcome scores.

Sample size

An *a priori* sample size calculation was performed using RSA data. Based on an estimated clinically significant difference of 0.6 mm and a SD of 0.7 mm between groups [276], the *a priori* sample size calculation required 22 patients in each group to achieve 80% power at a 0.05 significance level. Due to potential dropouts, we planned to include 25 patients in each group, but since The DOS advised against further the use of any MoM hip articulations before study inclusion had been completed, only 24 patients were included in the Post group.

Statistics

All continuous variables were tested for normality (Shapiro-Wilk test). When data were not normally distributed, non-parametric tests (Mann-Whitney U-test and Wilcoxon rank-sum test) were used. When data were normally distributed, Satterthwaite's t-test was used. Calculation of the correlation coefficient (r) of independent variables was made using the Spearman correlation analysis when the data were not normally distributed and the Pearson correlation analysis when the data were normally distributed.

Study IV

Primary and secondary endpoints

The primary endpoint was pseudotumor prevalence at 5 years of follow-up evaluated with MARS MRI. The secondary endpoints were grades of muscle atrophy, measurements of chromium and cobalt serum-ion levels, clinical outcome scores, and conventional radiographs.

Sample size

No *a priori* sample size calculation was performed in Study IV as the study was originally planned as an RCT study with sufficient sample size to compare implant migrations with RSA between groups (Study III).

Statistics

All continuous variables were tested for normality (Shapiro-Wilk test). When data were not normally distributed, non-parametric tests (Mann-Whitney U-test and Wilcoxon rank-sum test) were used. When data were normally distributed, Satterthwaite's t-test was used. The correlation coefficient (r) of independent variables was calculated using the Spearman correlation analysis when the data were not normally distributed and the Pearson correlation analysis was used when the data were normally distributed.

6. Summary of results

Study I

The primary aim of this cross-sectional case-control study was to evaluate the pseudotumor prevalence and type detected by MARS MRI scans in patients with MoM THA, MoM RHA, and MoP THA. The secondary aim was to compare measurements of chromium and cobalt serum-ion levels, clinical outcome scores, and conventional radiographs across the three bearing types and between patients with and without a pseudotumor.
Three hypotheses were investigated: (1) Patients with MoM THA or RHA have a higher prevalence of pseudotumors than patients with MoP THA. (2) Patients with MoM THA or RHA have elevated metal-ion measurements compared with patients with MoP THA. (3) Patients with a solid or mixed pseudotumor have higher metal-ion measurements and lower clinical outcome scores than patients without a solid or mixed pseudotumor.

Results

Pseudotumors

MARS MRI scans of 30 MoM THA, 47 MoM RHA, and 71 MoP THAs were evaluated according to the Anderson grading system (Table 1). The pseudotumor prevalence was statistically similar in the three bearing types with 13 of 30 (43%) in MoM THA, 13 of 47 (28%) in MoM RHA, and 29 of 71 (41%) in MoP THA, (p=0.10). A significantly lower prevalence of mixed or solid pseudotumors was found in MoM THA (n=3) and MoM RHA (n=0) than in MoP THA (n=10) (Table 10 and 11, Figure 25 - 29).

Table 10 Detailed presentation of fluid-filled and mixed or solid pseudotumors in patients with MoM THA, MoM RHA, and MoP THA [141].

Articulation	MoM THA	MoM RHA	MoP THA
Total number of hips	30	47	71
Total number of fluid pseudotumors	10	13	19
Sex (male/female)	8/2	11/2	9/10
Location (AL, PL, ILB)	0/10/0	2/11/0	0/8/11
Communication (Yes/No or not applicable)	4/6	8/5	5/14
Width, mean (range) (mm)	40.5 (10 - 77)	46 (12 - 100)	46 (16 - 82)
Depth, mean (range) (mm)	19.5 (4 - 56)	31 (5 - 72)	19 (3 - 60)
Height, mean (range) (mm)	18 (5 - 34)	17 (4 - 33)	19 (5 - 41)
Total number of mixed or solid pseudotumors	3	0	10
Sex (male/female)	2/1	-	5/5
Location (AL, PL, ILB)	0/1/2	-	0/5/5
Communication (Yes/No or not applicable)	2/1	-	5/5
Width, mean (range) (mm)	68 (44 - 101)	-	76 (41 - 202)
Depth, mean (range) (mm)	44 (37 - 48)	-	51 (16 - 120)
Height, mean (range) (mm)	24 (18 - 32)	-	33 (13 - 111)

Location: The anatomical location of the pseudotumor: AL = Antero-lateral of the greater trochanter, PL = Posterior-lateral of the greater trochanter, and ILB = located to the iliopsoas bursa

Table 11 Results of the MARS MRI evaluations according to the Anderson classification. Additional to the Anderson classification, pseudotumors were categorized as fluid or mixed/solid appearance [141].

Articulation	MoM THA	MoM RHA	MoP THA	*p*-value
Total number of patients	30	47	71	-
Grade A "Normal or Acceptable"	17	34	42	0.11[a]
Grade B "Infection"	0	0	0	-
Grade C1 "Mild MoM Disease"	7	7	15	0.38[a]
Fluid	6	7	12	0.64[a]
Mixed or solid	1	0	3	0.42[b]
Grade C2 "Moderate MoM Disease"	6	6	12	0.28[a]
Fluid	4	6	7	0.36[a]
Mixed or solid	2	0	5	0.16[b]
Grade C3 "Sever MoM Disease"	0	0	2	0.70[b]
Fluid	0	0	0	-
Mixed or solid	0	0	2	0.70[b]
Total number of pseudotumors	13	13	29	0.10[a]
Total number of fluid pseudotumors	10	13	19	0.40[a]
Total number of mixed or solid pseudotumors	3	0	10	0.01[b]

[a] Multiple regression analysis (adjusting for risk factors of sex, age, and time since the arthroplasty)
[b] Fisher's exact test

Serum-ion measurements

Serum-ion measurements of cobalt of mean 2.45 (range: 0.59 – 5.60) µg/L were significantly higher in hips with a mixed or solid pseudotumor than in hips without a mixed or solid pseudotumor; mean 1.34 (range: 0.59 – 5.9) µg/L (p = 0.00). Serum-ion measurements of chromium of mean 2.24 (0.59 - 9.74) µg/L in hips with a mixed or solid pseudotumor were similar in hips without a mixed or solid pseudotumor; mean 1.75 (range: 0.59 - 9.74) (p = 0.09).

Clinical outcome scores

HHS of mean 93.6 (range: 76 - 100) was significantly lower in hips with a mixed or solid pseudotumor than in hips without a mixed or solid pseudotumor; mean 97 (range: 78 - 100) (p=0.01). Likewise, OHS of mean 38 (range: 10 - 48) in hips with a mixed or solid pseudotumor was significantly lower than in hips without a mixed or solid pseudotumor; mean 45 (30 - 48) (p = 0.00). Serum-ion measurements of chromium and cobalt and clinical outcome scores of HHS and OHS in the three bearing types are presented in Table 12.

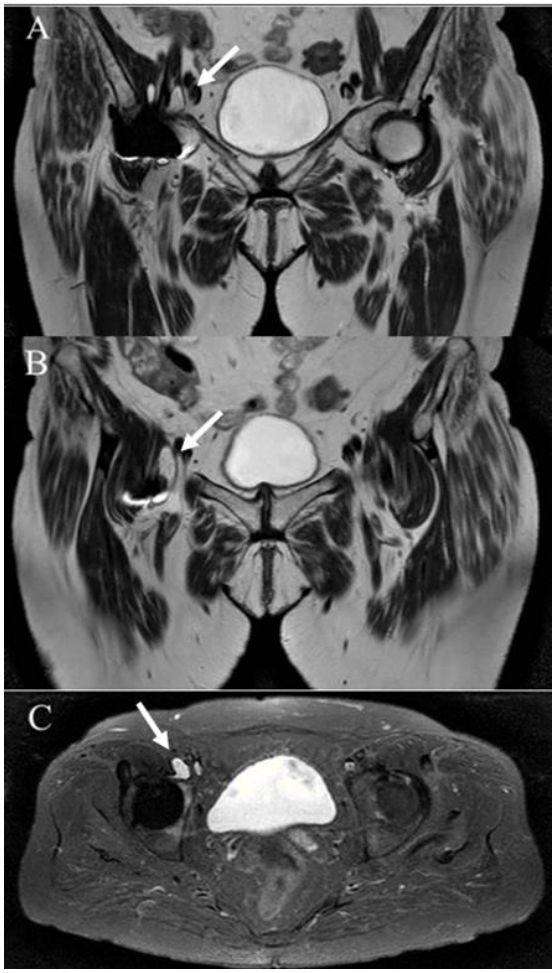
Conventional radiographs

Examination of the conventional radiographs showed that radiolucent lines around the cup were present in two MoM THAs (in DeLee Zone I), zero MoM RHAs, and eight MoP THAs (three in DeLee Zone I and three in DeLee Zone I and II). Osteolysis around the cup were found in zero MoM THAs, three MoM RHAs (all in DeLee Zone I), and seven MoP THAs (six in DeLee Zone I and three in DeLee Zone I and II). Radiolucent lines around the femoral stems were seen in zero MoM THAs, seven MoM RHAs (all distal around the tip of the stem), and two MoP THAs (one in Gruen Zone I and one in Gruen Zone VII), and osteolyses around the femoral stems was not observed in any MoM THA or MoM RHA, but seven MoP THAs had osteolyses (four in Gruen Zone I, and three in Gruen Zone I and VII).

Table 12 Scores of the Harris Hip Score (HHS), the Oxford Hip Score (OHS) and the Copenhagen Hip and Groin Outcome Score (HAGOS) and measurements of chromium and cobalt serum-ions at mean 7.1 (range: 0.2 - 21.5) years after surgery. Values are mean (range) [141].

Articulation	MoM THA	MoM RHA	MoP THA	*P*-value[a]
HHS (30/47/71)	98.3 (89 - 100)	97.6 (76 - 100)	95.9 (76 - 100)	0.08
OHS (29/47/66)	46.2 (36 - 48)	44.9 (31 - 48)	43.6 (10 - 48)	0.39
HAGOS (27/45/68)				
Symptoms	92.9 (71 – 100)	90.1 (32 - 100)	85.1 (3.6 - 100)	0.20
Pain	95.2 (75 - 100)	94.5 (65 - 100)	86.8 (0 - 100)	0.06
Function in Daily Living	96.3 (65 - 100)	91.2 (20 - 100)	86.5 (0 - 100)	0.18
Sport and Recreation	85.9 (47 - 100)	83.8 (16 - 100)	64.5 (0 - 100)	0.04
Physical Activities	87 (25 - 100)	73.3 (0 - 100)	64.5 (0 - 100)	0.05
Hip-Related Quality of Life	85.6 (35 - 100)	83.3 (10 - 100)	78.5 (0 - 100)	0.19
Chromium (µg/L)	3.01 (0.59 – 9.74)	2.26 (0.59 – 9.74)	0.98 (0.59 – 6.90)	0.00
Cobalt (µg/L)	2.02 (0.59 – 5.45)	1.53 (0.59 – 5.96)	1.14 (0.59 – 5.90)	0.03

[a] Multiple regression analysis (adjusting for risk factors of sex, age, and time since the arthroplasty).



F**igure 25** Coronal (A and B) and axial (C) MARS MRIs of a 68-year-old female with a right side MoP THA (Mallory Head, BiMetric Stem) and a pseudotumor located to the iliopsoas bursa. Her serum serum-ion levels of chromium and cobalt were 2.7 µg/L and 4.1 µg/L [141].

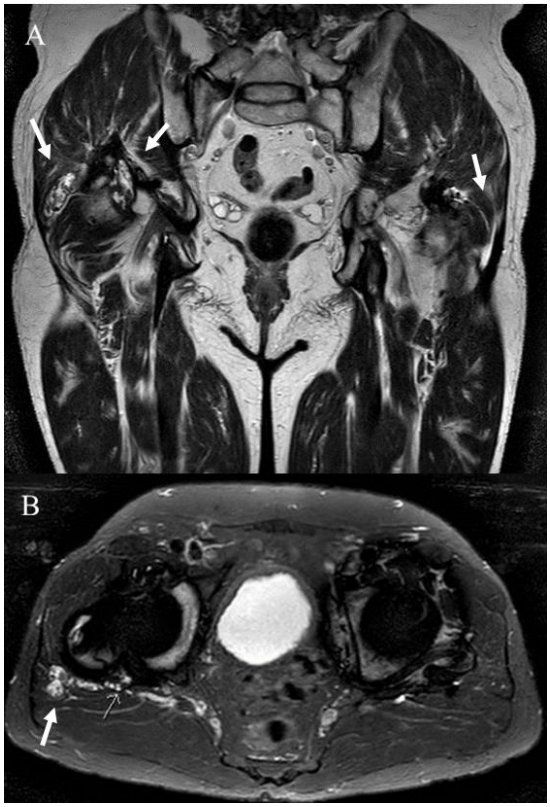


Figure 26 Coronal (A) and axial (B) MARS MRIs of a 64-year-old male with bilateral MoP THA (right side: Mallory Head, Exeeter stem; left side: Pinnacle cup, Corail stem). The pseudotumor on the right side is a mixed type; on the left side a cystic type. His serum-ion levels of chromium and cobalt were 0.6 µg/L and 0.7 µg/L [141].

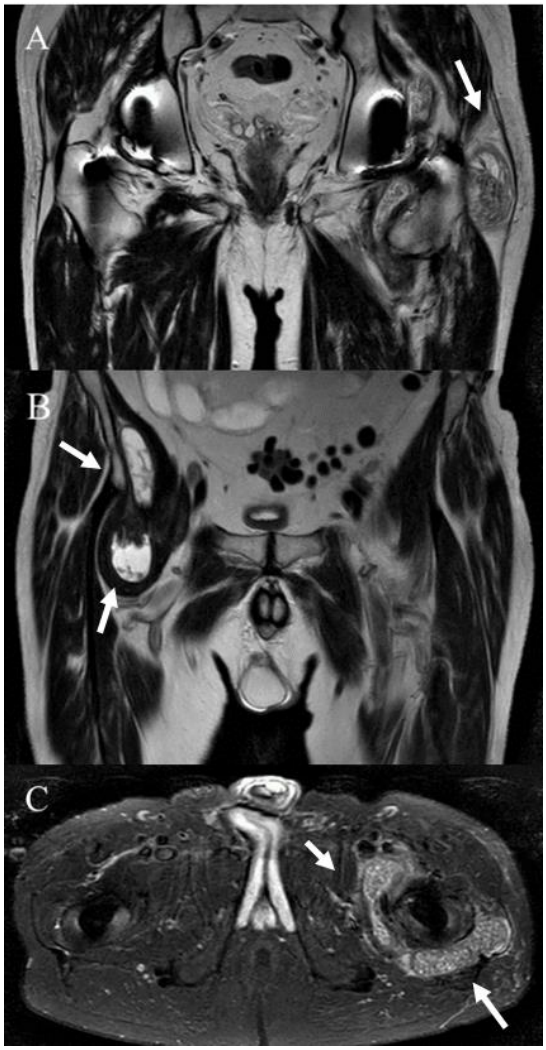


Figure 27 Coronal (A and B) and axial (C) MARS MRIs of a 71-year-old male with bilateral MoP THA (Right + left side: Mallory Head, BiMetric stem). Both pseudotumors are mixed type. His serum-ion levels of chromium and cobalt were 0.6 µg/L and 1.1 µg/L, respectively [141].

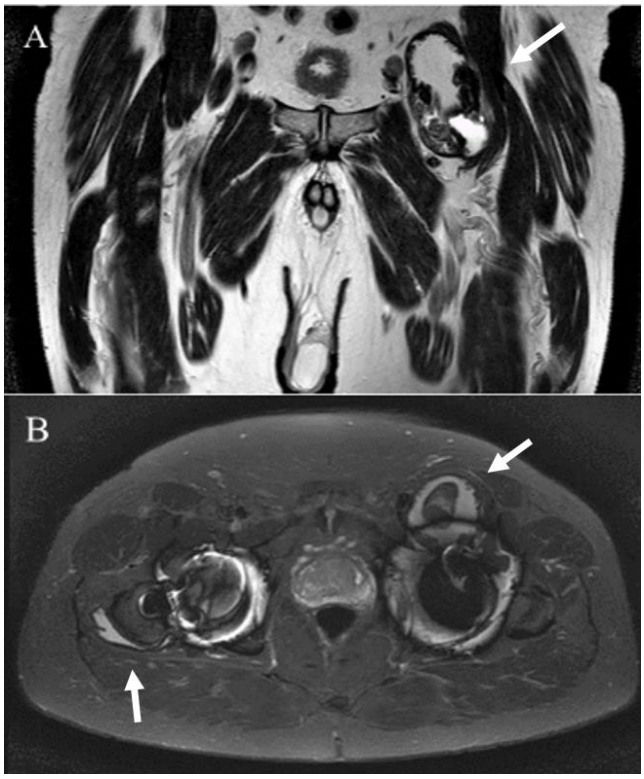


Figure 28 Coronal (A) and axial (B) MARS MRIs of a 71-year-old male with bilateral MoP THA (right + left side: Trilogy cup, BiMetric stem). Mixed type pseudotumors were found bilaterally. His serum-ion levels of chromium and cobalt were 3.9 µg/L and 5.9 µg/L, respectively [141].

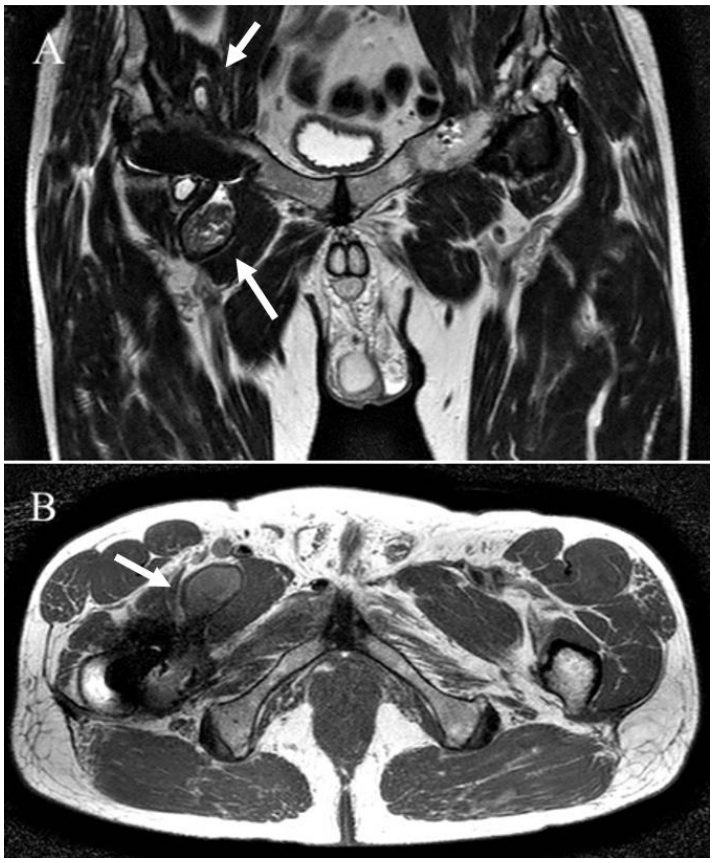


Figure 29 Coronal (A) and axial (B) MARS MRIs of a 54-year-old male with right side MoM THA (M2a-Magnum, BiMetric stem) and a mixed pseudotumor located to the iliopsoas bursa. His serum-ion levels of chromium and cobalt were 1.4 µg/L and 2.8 µg/L, respectively [141].

Study II

The primary aim of this longitudinal study was to investigate the relationship between patients' daily PA and metal-ion measurements of chromium and cobalt, and the relationship between patients' daily PA and changes in pseudotumor size. The secondary aim was to examine changes in pseudotumor type over time. Three hypotheses were investigated: (1) There is a relationship between the PA level and metal-ion measurements of chromium and cobalt in MoM THA/RHA patients. (2) There is a relationship between the PA level and the size of cystic pseudotumors. (3) Minor changes in pseudotumor size/type take place within one year.

Results

Physical activity, serum-ion measurements, and pseudotumors

MoM THA/RHA patients' daily PA and serum-ion measurements of chromium were significantly related at all follow-ups ($p < 0.01$). A similar relationship was not found for patients with MoP THA (Table 13, Figure 30 and 31). Neither MoM THA/RHA patients' nor MoP THA patients' daily PA was related to serum-ion measurements of cobalt or to changes in pseudotumor size ($p>0.30$) (Table 14).

Table 13 Multiple regression analysis on the effect of total activity (defined as the sum of walking, cycling, and high activity measurements) on measurements of chromium and cobalt (µg/L) in patients with MoM THA/RHA and MoP THA at 3, 6, 9, 12, and 24 months. Adjustments were made for sex, inclination angle, and time since surgery in the multiple regression model [140].

Articulation	MoM THA/RHA				MoP THA			
	Adj. R^{2} [b]	β [c]	95% CI	*p*-value	Adj. R^{2} [b]	β [c]	95% CI	*p*-value
Activity and chromium								
3 months (66/56) [a]	0.25	0.13	0.01 – 0.24	0.03	- 0.05	- 0.02	-1.08 – 0.03	0.35
6 months (61/48) [a]	0.28	0.17	0.05 -0.28	0.006	- 0.08	0.01	-0.40 -0.04	0.96
9 months (65/49) [a]	0.29	0.18	0.06 – 0.29	0.003	- 0.08	0.01	- 0.50 -0.06	0.83
12 months (63/51) [a]	0.23	0.17	0.04 – 0.30	0.01	-0 06	0.01	-0.03 – 0.06	0.53
Activity and cobalt								
3 months (66/56) [a]	0.12	0.05	- 0.01 – 0.12	0.12	0.15	-0 03	- 0.11 – 0.41	0.39
6 months (61/48 [a])	0.16	0.07	- 0.01 – 0.14	0.04	0.11	0.01	- 0.06 – 0.08	0.81
9 months (65/49) [a]	0.16	0.06	- 0.01 – 0.13	0.08	0.09	0.02	- 0.05 – 0.08	0.62
12 months (63/51) [a]	0.11	0.06	- 0.02 – 0.15	0.18	0.14	0.02	- 0.05 – 0.08	0.55

[a] Number of MoM THA/RHA patients / Number of MoP THA patients.
[b] The percentage of variance in metal-ion measurements which can be explained by patients PA level, sex, inclination angle, and time since surgery.
[c] The degree of change in metal-ion measurements for every 1-unit (1%) change in patients' activity level.

Table 14 Multiple regression analysis on the effect of total activity (defined as the sum of: walking, cycling, and high activity measurements) on the pseudotumor volume (cm^3) in patients with MoM THA/RHA and MoP THA at 3, 6, 9, 12 and 24 months. Adjustments were made for sex, inclination angle, and time since surgery in the multiple regression model [140].

Articulation	MoM THA/RHA				MoP THA			
	Adj. R^{2} [b]	β [c]	95% CI	*p*-value	Adj. R^{2} [b]	β [c]	95% CI	*p*-value
Activity and pseudotumor volume (cm^3)								
3 months (64/55) [a]	0.02	0.02	- 0.04 – 0.08	0.46	0.01	0.01	-0.03 – 0.04	0.70
6 months (60/49) [a]	0.05	0.02	- 0.23 – 0.07	0.39	0.01	0.01	-0.04 – 0.07	0.61
9 months (65/49) [a]	0.02	- 0.01	- 0.06 – 0.04	0.81	- 0.05	0.01	- 0.04 – 0.06	0.64
12 months (63/51) [a]	0.06	- 0.02	- 0.05 – 0.01	0.30	0.05	0.01	-0.04 – 0.06	0.73

[a] Number of MoM THA/RHA patients / Number of MoP THA patients.
[b] The percentage of variance in pseudotumor volume that can be explained by patients' PA, sex, inclination angle, and time since surgery.
[c] The degree of change in metal-ion measurements for every 1-unit (1%) change in patients' activity level.

Figure 30 Mean serum-ion levels of chromium and cobalt at baseline, 3, 6, 9, and 12 months of follow-up [140].

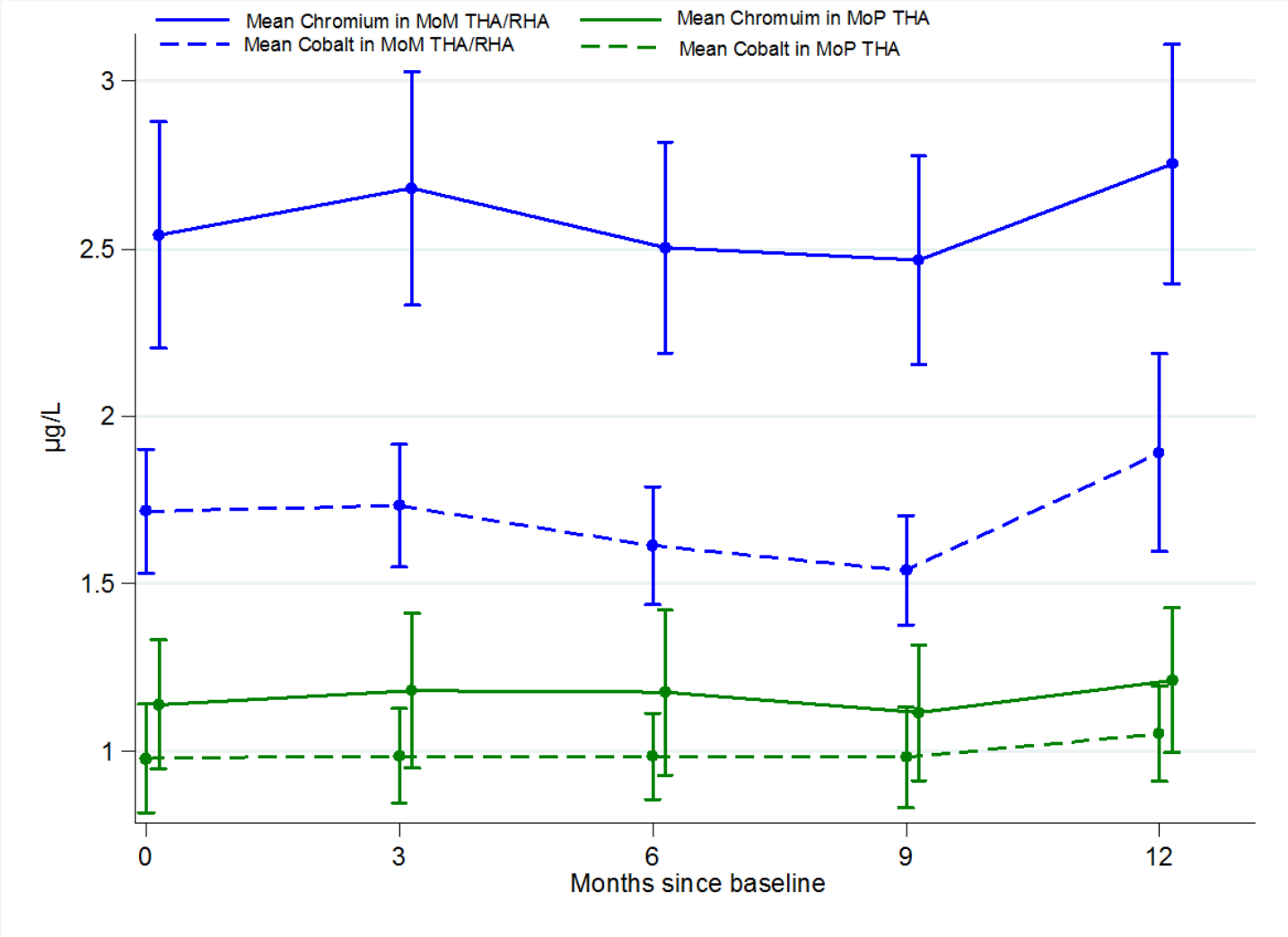


Figure showing the mean serum-ion levels of chromium and cobalt in MoM THA/RHA patients and MoP THA patients at baseline (mean 7.1 (range: 0.2 - 21.5) years after surgery), 3, 6, 9, and 12 months of follow-up. The error bars represent the SD of the mean chromium and cobalt levels.

Figure 31 Mean daily physical activity level at 3, 6, 9, and 12 months of follow-up [140].

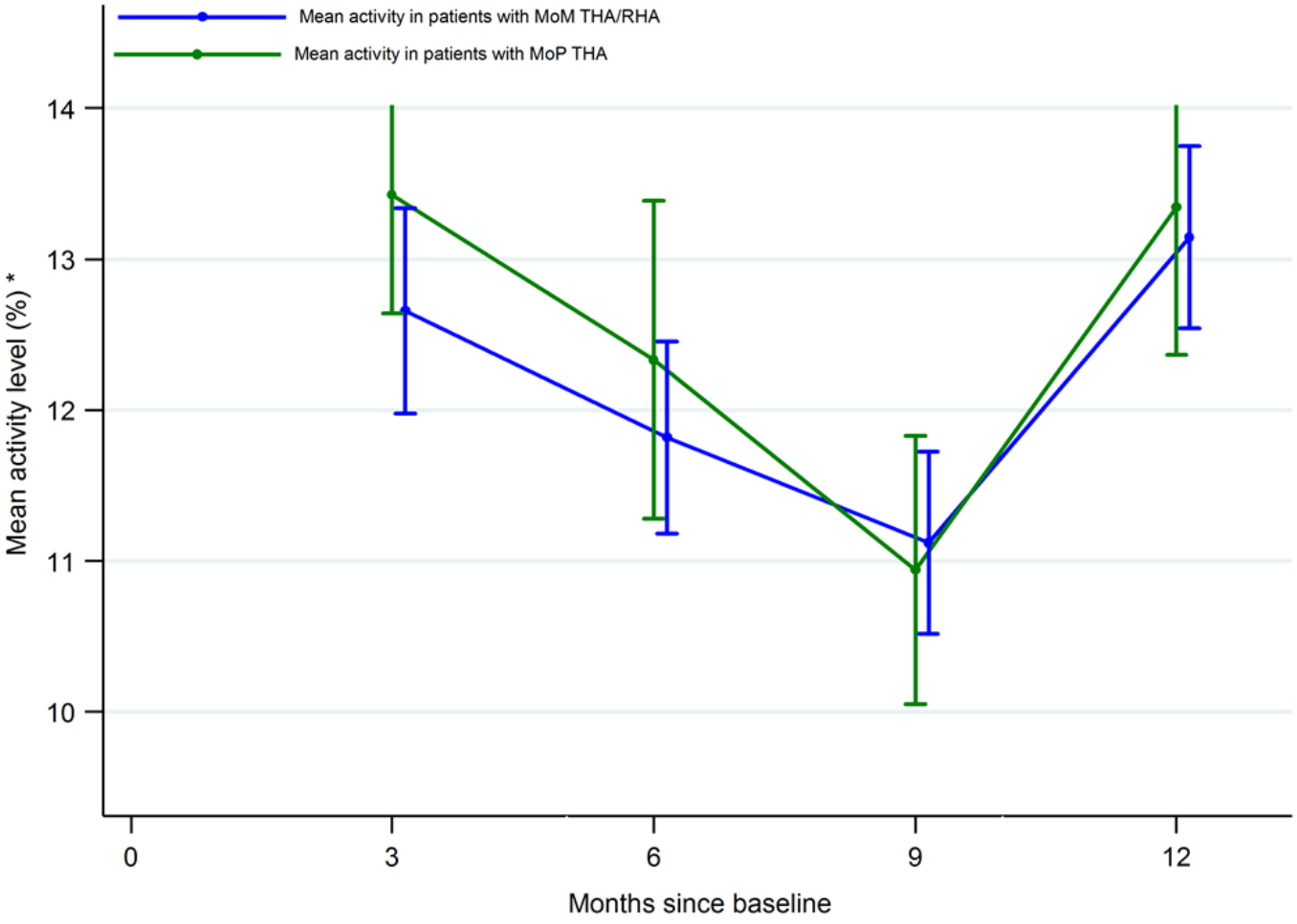


Figure showing the mean daily physical activity level (*defined as combined walking, bicycling, and high-impact activity in percentage of total daily accelerometer wear time) in MoM THA/RHA patients and MoP THA patients at 3, 6, 9, and 12 months of follow-up. The error bars represent the SD of the mean activity level (%).

Changes in pseudotumor type over time according to the Anderson grading system

Baseline MARS MRI evaluations showed that pseudotumors were present in 26 of 77 (34%) MoM THA/RHAs and 29 of 71 (41%) MoP THAs mean 7.1 (range: 0.2 - 21.5) years after surgery (Table 15). MARS MRI evaluations of all patient at the five follow-ups showed that 10 of 26 (38%) pseudotumors in MoM THA/RHA and 8 of 29 (28%) pseudotumors in MoP THA changed classification according to the Anderson grading system during the 1-year follow-up (Table 16). Changes in classification occurred between grades A, C1, and C2. The exact changes are shown in Table 16. The anatomical location and the pseudotumor appearance (cystic, solid type, or mixed type) did not change between the follow-ups.

Table 15 was published in [140].

Table 15 Results of the MARS MRI evaluations according to the Anderson classification. Additional to the Anderson classification pseudotumor appearance (fluid or mixed/solid) were recorded.

	Baseline		3 months		6 months		9 months		12 months	
Articulation	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA
Total number hips	77	71	69	63	68	56	68	52	65	56
Pseudotumors	26	29	22	25	23	24	22	23	23	25
Grade A "Normal or Acceptable"	51	42	47	38	45	32	46	29	42	31
Grade B "Infection"	-	-	-	-	-	-	-	-	-	-
Grade C1 "Mild MoM Disease"	15	15	13	14	14	14	12	14	15	15
Fluid	14	12	12	12	13	11	11	12	13	12
Mixed or solid	1	3	1	2	1	3	1	2	2	3
Grade C2 "Moderate MoM Disease"	11	12	9	9	9	10	10	9	8	10
Fluid	9	7	8	4	8	5	9	4	8	5
Mixed or solid	2	5	1	5	1	5	1	5	0	5
Grade C3 "Sever MoM Disease"	0	2	0	2	0	0	0	0	0	0
Fluid	0	0	0	0	0	0	0	0	0	0
Mixed or solid	0	2	0	2	0	0	0	0	0	0

Table 16 was published in [140].

Table 16 Descriptive data of patients with pseudotumors that changed Anderson classification during the study period.

Pt.	Articulation	Gender	Age (yr)	Location [a]	MRI signal [b]	HHS	MRI 1 Baseline [c]	MRI 2 3 months [c]	MRI 3 6 months [c]	MRI 4 9 months [c]	MRI 5 12 months [c]
MoM THA/RHA											
1.	M2a-Magnum/Bimetric stem	Female	64	PL	Mixed	100	C2	C2	C2	C2	C1
2.	ReCap Resurfacing	Female	60	PL	High	100	A	C1	C1	C1	C1
3.	ReCap Resurfacing	Male	49	PL	High	96	A	A	A	A	C1
4.	ReCap Resurfacing	Male	39	PL	High	100	C1	C2	C1	C1	C1
5.	ReCap Resurfacing	Female	54	PL	High	95	A	A	C1	C1	C1
6.	ReCap Resurfacing	Female	55	PL	High	100	C1	C1	C1	C2	C2
7.	M2a-Magnum/Bimetric stem	Male	54	PL	High	100	C1	C1	A	A	A
8.	M2a-Magnum/Bimetric stem	Male	62	PL	High	100	C1	A	C1	C1	C1
9.	M2a-Magnum/Bimetric stem	Male	52	PL	High	89	C2	C1	C1	C2	C2
10.	M2a-Magnum/Bimetric stem	Male	50	PL	High	100	C2	C1	C2	C1	C1
MoP THA											
1.	Pinnacle cup, corail stem	Male	65	PL	High	100	C1	A	C1	C1	C1
2.	Mallory head/Exeeter stem	Female	69	PL	High	100	A	A	A	A	C1
3.	Lubinus hip arthroplasty	Female	69	ILB	High	91	C1	C1	C1	C1	C2
4.	Trilogy cup, CLS sporonto	Male	48	PL	High	90	C2	C1	A	A	A
5.	Trilogy cup/Bimetric stem	Female	68	PL	High	98	C1	A	-	-	-
6.	Mallory head/Exeter stem	Male	72	ILB	High	94	C2	C1	C2	C1	C1
7.	Mallory head/Exeter stem	Male	69	PL	High	84	A	A	A	C1	C1
8.	Mallory head/Bimetric stem	Female	60	PL	High	100	A	A	C1	C1	A

[a] The anatomical location of the pseudotumor: PL = Posterior-lateral of the greater trochanter, and ILB = located to the iliopsoas bursa.

[b] High MRI signal intensity is associated with fluid content, and low signal intensity is associated with solid content

[c] Grading according to the Anderson Classification and chromium and cobalt levels (Chromium / Cobalt) (µg/L) at the time of follow-up

Study III

The aim of this RCT study was to investigate if the AntLat approach, which preserves the blood supply to the femoral head, provided outcomes for both cup and stem components that are superior to those of the Post approach in patients with MoM RHA. Three hypotheses were evaluated: (1) The AntLat approach provides cup and femoral component fixation superior to that of the Post approach. (2) The AntLat approach increases the periprosthetic BMD around the femur component more than the Post approach. (3) Patients operated by the AntLat approach have better outcome scores of HHS and lower VAS for pain than patients operated by the Post approach.

Results

RSA

At 3 months, total translations (TT) of the acetabular ReCap cups of mean 1.00 (SD: ± 0.70) mm and total rotations (TR) of mean 2.44 (SD: ± 1.36) ° in the AntLat group were significantly higher than TT of mean 0.64 (SD: ± 0.45) mm and TR of mean 1.39 (SD: ± 1.17) ° in the Post group, (p=0.04) (p=0.002). At 1 and 2 years, all cup migrations were similar in the AntLat group and the Post group (Table 17). Between 3 months and 2 years, seven cups (five AntLat and two Post) had individual TT migrations above the precision limit (0.86 mm) of TT (range 0.99 – 1.85 mm), and 10 cups (seven AntLat and three Post) had TR migrations above the precision limit (1.74) of TR (range 1.87 – 2.86) °. All migrations of the ReCap femoral component were comparable between groups at all follow-ups (p>0.11) (Table 18). On the femoral side, seven components (two AntLat and five Post) had individual TT migrations above the precision limit (0.61 mm) of TT (range 0.72 – 1.82 mm), and eight components (two AntLat and six Post) had individual TR migrations above the precision limit (0.65 °) of TR (range 0.86 – 1.95) ° between 3 months and 2 years.

Table 17 Migrations of the ReCap acetabular component as mean (SD) along and about the 3 orthogonal axes measured with RSA at 3 months and 1 and 2 years after surgery. Examinations were performed in total (Post approach/ AntLat approach); 23/24 patients at 3 months, 24/24 patients at 1 year, and 24/25 patients at 2 years. Values are mean (SD) [139].

	Post approach	AntLat approach	*p*-value[a]
Translations (mm)			
Medial/lateral (x-axis)			
3 months	0.17 (0.40)	0.18 (0.55)	0.99
1 year	0.21 (0.55)	0.28 (0.46)	0.39
2 years	0.16 (0.63)	0.15 (0.72)	0.92
Proximal/distal (y-axis)			
3 months	0.36 (0.31)	0.37 (0.34)	0.90
1 year	0.40 (0.31)	0.48 (0.37)	0.55
2 years	0.40 (0.33)	0.55 (0.59)	0.56
Anterior/posterior (z-axis)			
3 months	0.09 (0.45)	0.21 (0.95)	0.58
1 year	0.36 (0.84)	0.35 (0.86)	0.98
2 years	0.39 (0.86)	0.39 (1.16)	0.74
Total translation[b]			
3 months	0.64 (0.45)	1.00 (0.70)	0.04
1 year	0.88 (0.80)	0.99 (0.72)	0.35
2 years	0.98 (0.77)	1.37 (0.87)	0.07
Rotations (°)			
Anterior/posterior tilt (x-axis)			
3 months	-0.16 (1.05)	0.12 (0.63)	0.59
1 year	0.24 (2.52)	0.09 (1.59)	0.73
2 years	0.32 (2.64)	0.08 (1.80)	0.70
Anteversion/retroversion (y-axis)			
3 months	-0.03 (0.87)	-0.33 (1.43)	0.75
1 year	-0.32 (1.95)	-0.26 (1.51)	0.98
2 years	-0.45 (0.45)	-0.33 (1.70)	0.85
Valgus/varus tilt (z-axis)			
3 months	0.01 (1.22)	-0.40 (1.74)	0.30
1 year	-0.34 (1.21)	-0.58 (1.57)	0.43
2 years	0.01 (1.59)	-0.73 (1.81)	0.27
Total Rotation[c]			
3 months	1.39 (1.17)	2.44 (1.36)	0.002
1 year	2.21 (2.61)	2.32 (1.43)	0.13
2 years	2.92 (2.55)	2.68 (1.61)	0.80

[a] Paired Wilcoxon signed-rank test.

[b] The total translation was calculated using the 3D Pythagorean theorem ($TT= \sqrt{(x^2 + y^2 + z^2)}$).

[c] The total rotation was calculated using the 3D Pythagorean theorem ($TR= \sqrt{(x^2 + y^2 + z^2)}$).

Table 18 Migrations of the ReCap femoral component as mean (SD) along and around the three axes measured with RSA at 3 months, 1 year, and after surgery. Examinations were performed in total (Post approach / AntLat approach); 23/24 patients at 3 months, 24/24 patients at 1 year, and 24/25 patients at 2 years. Values are mean (SD) [139].

	Post approach	AntLat approach	*p*-value[a]
Translations (mm)			
Medial/lateral (x-axis)			
3 months	-0.02 (0.26)	-0.04 (0.25)	0.95
1 year	0.08 (0.56)	-0.08 (0.16)	0.12
2 years	0.04 (0.56)	-0.07 (0.22)	0.39
Proximal/distal (y-axis)			
3 months	-0.02 (0.26)	0.02 (0.13)	0.71
1 year	-0.14 (0.73)	0.00 (0.18)	0.78
2 years	-0.16 (0.77)	-0.09 (0.24)	0.37
Anterior/posterior (z-axis)			
3 months	-0.18 (0.58)	-0.02 (0.42)	0.24
1 year	-0.35 (0.68)	0.02 (0.41)	0.08
2 years	-0.25 (0.69)	0.14 (0.54)	0.09
Total translation[b]			
3 months	0.56 (0.42)	0.43 (0.26)	0.35
1 year	0.78 (0.91)	0.44 (0.18)	0.27
2 years	0.79 (0.91)	0.49 (0.42)	0.14
Rotations (°)			
Anterior/posterior tilt (x-axis)			
3 months	0.19 (0.45)	-0.07 (0.42)	0.11
1 year	0.14 (0.59)	0.02 (0.33)	0.39
2 years	-0.12 (0.67)	0.08 (0.41)	0.62
Anteversion/retroversion (y-axis)			
3 months	0.01 (0.31)	-0.09 (0.31)	0.25
1 year	-0.03 (0.46)	-0.05 (0.29)	0.85
2 years	-0.02 (0.45)	0.00 (0.34)	0.87
Valgus/varus tilt (z-axis)			
3 months	-0.16 (0.50)	0.05 (0.38)	0.23
1 year	-0.43 (1.74)	0.07 (0.35)	0.27
2 years	-0.45 (1.78)	0.06 (0.39)	0.25
Total rotation[c]			
3 months	0.63 (0.45)	0.56 (0.33)	0.79
1 year	1.02 (1.65)	0.50 (0.26)	0.17
2 years	1.04 (1.71)	0.52 (0.41)	0.38

[a] Paired Wilcoxon signed-rank test.

[b] The total translation was calculated using the 3-D Pythagorean theorem ($TT= \sqrt{(x^2 + y^2 + z^2)}$).

[c] The total rotation was calculated using the 3D Pythagorean theorem ($TR= \sqrt{(x^2 + y^2 + z^2)}$).

Dual-energy X-ray absorptiometry scans (DXA)

At 1 year after surgery, the periprosthetic BMD since postoperative in ROI M1 decreased to mean 98.58 ± 8.75% in the AntLat group and increased to mean 107.16 ± 11.18% in the Post group (p=0.01). At 2 years after surgery, the periprosthetic BMD remained reduced to mean 99.47 ± 9.05% in the AntLat group and increased to mean 107.16 ± 11.18% in the Post group, (p=0.01). In the entire region medial to the stem, the periprosthetic BMD from after surgery to 1-year follow-up was decreased to mean 98.45 ± 8.57% in the AntLat group and increased to mean 105.57 ± 11.07% in the Post group (p=0.02). However, at 2 years, measurements of mean 99.83 ± 9.10% in the AntLat group were comparable to mean measurements of 105.60 ± 10.77% in the Post group (p=0.05) (Table 19).

Table 19 Bone mineral density in the eight ROIs as percentage of baseline (postoperative) values up to 2 years after surgery. Examinations were performed in total (Post approach / AntLat approach); 24/25 patients at 1 year and 24/25 patients at 2 years. Values are mean (SD) [139].

ROI	Post approach	AntLat approach	*p*-value [a]
L 1			
1 year	132.21 (49.83)	112.16 (26.66)	0.08
2 years	134.57 (37.96)	118.59 (37.83)	0.15
L 2			
1 year	111.46 (37.75)	103.25 (21.73)	0.35
2 years	107.35 (28.33)	109.57 (23.47)	0.77
L 3			
1 year	107.22 (29.99)	100.36 (20.95)	0.36
2 years	101.55 (20.01)	101.29 (22.88)	0.97
M 1			
1 year	106.35 (10.19)	98.58 (8.75)	0.01
2 years	107.16 (11.18)	99.47 (9.05)	0.01
M 2			
1 year	101.23 (10.22)	96.97 (8.10)	0.11
2 years	102.08 (11.29)	97.34 (9.14)	0.11
M 3			
1 year	110.15 (22.09)	100.62 (14.87)	0.06
2 years	109.60 (20.58)	103.18 (14.48)	0.21
Lat			
1 year	116.32 (37.84)	104.58 (18.91)	0.17
2 years	113.58 (27.51)	108.73 (23.29)	0.50
Med			
1 year	105.57 (11.07)	98.45 (8.57)	0.02
2 years	105.60 (10.77)	99.83 (9.10)	0.05

[a] Satterthwaite's t-test.

Clinical outcome measures and serum-ion measurements

The AntLat group and the Post group had similar clinical outcome scores of HHS and VAS after surgery and at 3 months and 1 year (p>0.09); and serum-ion measurements of chromium and cobalt approximately 3 years after surgery were similar in the groups (p>0.74) (Table 20).

Conventional radiography, implant position, and complications

Comparison of the postoperative and the 2-year conventional radiographs showed femoral neck narrowing of mean 12 ± 0.80% in the AntLat group, which was similar to the mean narrowing of 9.0 ± 0.50% in the Post group (p=0.21). At 2 years postoperatively, cup inclination angles of mean 41.6 (range: 21 – 50.7) ° in the AntLat group were similar to the angles in the Post group; mean 39.4 (range: 32.6 – 47.6) ° (p=0.07). However, cup anteversion angles of mean 14.1 (range: 3.4 – 24.8) ° in the AntLat group were statistically significantly different from the mean of 9.7 (range: 3.6 – 21.8) ° in the Post group (p=0.008) (Table 20). No patients had undergone revision surgery at the time of the 2-year follow-up.

Table 20 Scores of the Harris Hip Score (HHS), the Visual Analogue Scale (VAS) for pain, serum-ion measurements and cup inclination and anteversion values of HHS and VAS are mean (SD). Values of chromium, cobalt, inclinations, and anteversions are mean (range) [139].

	Post approach	AntLat approach	*p*-value
HHS			
Postoperative	59.8 (10.6)	60.1 (14.6)	0.70[a]
3 months	86 (12.8)	90.1 (10.31)	0.24[a]
1 year	91 (9.9)	89.2 (14.2)	0.89 [a]
VAS			
Postoperative	51.8 (18.6)	51.8 (19.2)	0.97[a]
3 months	11.3 (15.6)	10.7 (17.8)	0.80[a]
1 year	10.6 (11.9)	6.9 (14.38)	0.09[a]
Chromium (µg/L)			
3 (1 – 5.2) year	2.20 (0.59 - 10.5)	1.87 (0.64 – 4.50)	0.91[a]
Cobalt (µg/L)			
3 (1 – 5.2) year	1.59 (0.59 – 7.26)	1.37 (0.59 – 4.96)	0.74[a]
Inclination cup angle (°)	39.4 (32.6 – 47.6)	41.6 (21 – 50.7)	0.07[b]
Anteversion cup angle (°)	9.7 (3.6 – 21.8)	14.1 (3.4 – 24.8)	0.008[b]

[a] Two-sample Wilcoxon rank-sum (Mann-Whitney) test.
[b] Satterthwaite's t-test.

Study IV

The aim of this approximately 5-year cross-sectional follow-up study was to compare location, grade, and prevalence of pseudotumors and muscle atrophy in patients allocated to MoM RHA by the AntLat or the Post surgical approach. Three hypotheses were evaluated: (1) The location of pseudotumors reflects the route of the surgical approach. (2) The location of muscle atrophy differs with the AntLat and the Post approach. (3) The grades and prevalences of pseudotumors and muscle atrophy were similar with the AntLat and the Post approach.

Results

Pseudotumors

The 40 MARS MRI scans were evaluated according to the Anderson grading system. Pseudotumors were found in 7 of 18 (39%) patients in the AntLat group and 12 of 22 (55%) patients in the Post group, and the prevalence was statistically similar (p=0.33). Communication between the hip joint and the pseudotumor was seen in 11 patients (four AntLat, seven Post), and the communicating path followed the route used for implantation. Pseudotumors in the AntLat group were located antero-laterally to the hip joint, and in the Post group they were located postero-laterally to the hip joint (Figure 33 –35). No patients had solid or mixed-type pseudotumors. Descriptive data of patients with a pseudotumor are presented in Table 21.

Muscle atrophy

According to the classification system proposed by Pfirrmann et al.[261], grades of muscle atrophy of the caudal part of the gluteus medius and minimus were higher in the AntLat group than in the Post group ($p < 0.004$). The Post group had significantly higher grades of muscle atrophy of the short external rotator muscles (piriformis, obturator internus and externus) than the AntLat group, ($p < 0.001$) (Table 22).

Table 21 Descriptive data of patients with pseudotumors at approximately five years cross-sectional follow-up divided into two groups based on the surgical approach used

Pt.	Age	Side	Sex	Dimensions	Position	Anderson classification	Chromium	Cobalt	OHS	HHS	Anterversion	Inclination
Patients operated by the posterior approach												
4	56	R	F	36x19x8	LD	C1	2.14	1.12	43	100	7.3	39.5
6	54	R	F	73x12x29	LD	C2	14.10	11.15	-	100	7.8	34.7
7	38	L	M	27x52x19	LD	C2	5.63	2.67	47	100	16.9	33.5
10	32	R	M	28x49x19	LD	C1	1.24	1.07	46	99.75	5.0	37.3
28	60	L	M	41x14x19	L	C1	4.69	5.58	47	99.87	17.8	43.3
32	62	L	F	24x52x10	LD	C2	6.31	2.94	46	99.95	4.9	50.1
35	40	R	F	46x5x27	L	C1	2.60	1.23	42	97.95	10.2	30.4
41	47	R	F	15x9x8	LD	C1	6.96	4.27	48	100	6.9	42.9
42	55	R	M	35x2x18	L	C1	1.32	1.04	-	99.95	12.4	45.6
43	56	R	F	70x60x42	LD	C2	4.66	3.06	44	96.02	9.3	42.4
46	46	R	M	17x7x7	L	C1	1.44	0.83	40	95.6	22.5	46.9
47	37	R	M	50x65x18	LD	C2	0.63	0.78	41	100	21.7	38.5
Patients operated by the anterolateral approach												
14	48	L	F	15x4x10	L	C1	1.23	0.84	33	94.45	15.6	38
15	55	R	M	41x5x13	L	C1	2.02	2.17	47	96.02	11.3	45.3
17	50	L	F	40x28x17	AL	C1	1.17	0.88	44	100	18.2	34.7
25	60	R	M	67x33x34	AL	C2	0.75	0.65	48	99.95	12.3	43.7
31	50	R	M	78x42x32	AL	C2	1.52	0.96	47	100	6.1	41.9
45	56	L	M	47x20x6	L	C1	1.80	3.93	48	75.75	11.9	43
49	51	R	M	15x26x10	AL	C2	1.40	0.92	47	96.02	20.4	42

Age: age of the patient at the time of primary MoM RHA
Dimensions: Maximum depth, width and height in mm
Position: Anatomical location of the pseudotumor in relation to the greater trochanter, LD = latero-dorsal, L=Lateral, AL = Antero-lateral
Anderson Classification: C1 = Mild MoM disease, C2 = Moderate MoM disease
Chromium: Concentration of serum-ion chromium (µg/L)
Cobalt: Concentration of serum-ion chromium (µg/L)
Anteversion: Cup anteversion angles (°)
Inclination: Cup inclination angles (°)

Table 22 Grades and anatomical location of muscle atrophy. Data available from 21 patients operated by the Post approach and 18 patients operated by the AntLat approach.

	Grade of muscle atrophy	Post approach	AntLat approach	*p*-value[a]
Gluteus maximus	0	19	15	0.79
	1	2	2	
	2	0	1[1]	
	3	0	0	
	4	0	0	
Gluteus medius	0	18[2]	5[2]	0.001
	1	0	0	
	2	1[2]	3[2]	
	3	1[2]	5[2]	
	4	1[2]	5[2]	
Gluteus minimus	0	20	9	0.004
	1	0	1[3]	
	2	0	3[3]	
	3	1	3[3]	
	4	0	2[3]	
Piriformis	0	1	10	0.001
	1	5	2	
	2	2	3	
	3	1[1]	2	
	4	2	1	
Obturatorius internus	0	1	8	0.000
	1	0	5	
	2	1	1	
	3	7	1	
	4	12	3	
Obturatorius externus	0	1	12	0.000
	1	3	2	
	2	6	2	
	3	11	2	
	4	0	0	
Iliopsoas	0	20	15	0.59
	1	1	1	
	2	0	1	
	3	0	0	
	4	0	1[4]	
Adductors	0	21	16	0.21
	1	0	0	
	2	0	1	
	3	0	1[5]	
	4	0	0	

[a] Fischer´s exact test
[1]Located at the caudal part of gluteus maximus
[2]Located at the caudal part of gluteus medius
[3]Located at the caudal part of gluteus minimus
[4]Located at the caudal part of iliopsoas
[5]Located at adductor longus

Clinical outcome measures and serum-ion measurements

Clinical outcome scores and serum-ion measurements of chromium and cobalt were similar at the 5.3-year (range 3.2 – 7.7) follow-up (Table 23).

Conventional radiography, implant position, and complications

Measurements of femoral neck narrowing in the AntLat group were mean 11% (range: 3% to 27%) and statistically similar to the mean of 11% (range: 3% to 26%) in the Post group, (p = 0.65). Cup inclination angles of mean 41.2° (27.5 – 52.2)° in the AntLat group were comparable to mean angles of 40.4 (30.4 – 50.1)° in the Post group (p=0.60); but cup anteversion angles of mean 15.3° (6.1 – 27.5)° in the AntLat group were higher than the mean angles of 11.5° (range: 4.9–22.5) in the Post group (p=0.02) (Table 23). At 5.3 (3.2 – 7.7) years after surgery, three female patients had undergone revision surgery; two in the AntLat group were revised at 2.6 and 4.1 years after surgery, respectively, and in the Post group were revised at 2.7 years after surgery. The woman who underwent revision surgery at 2.6 years postoperative (from the AntLat group), reported severe pain in the groin area, and serum metal-ion concentrations of chromium and cobalt were 2.5 µg/L and 18.23 µg/L. CT scan showed a 90 x 24 x 55 mm cystic mass from the top of the trochanter major and distally (Figure 36). During revision surgery, the orthopaedic surgeon noticed black metallosis in the hip joint area, and biopsies from the pseudocapsule revealed ALVAL scores of 8-9. At 3 months after surgery, serum metal-ion levels of chromium and cobalt were decreased to 1.12 µg/L and 1.22 µg/L, and the patient described a reduction in pain. The two other patients who underwent revision surgery both experienced groin pain. They had serum-ion levels below the reference limits of 7 µg/L issued by The DOS, and both MRI and US scans were normal. After revision to MoP THAs, both patients were without pain.

Table 23 Scores of the Harris Hip Score (HHS), the Oxford Hip Score (OHS), serum-ion measurements of chromium and cobalt, and cup inclination and anteversion angles at 5.3 (3.2 – 7.7) years after surgery. Values are mean (range).

	Post approach	AntLat approach	p-value[a]
Harris Hip Score	97.4 (75.8 - 100)	94.2 (29 - 100)	0.57[a]
Oxford Hip Score	43.2 (31 - 48)	44.6 (15 - 48)	0.08[a]
Chromium (µg/L)	3.4 (0.59 - 14.1)	1.9 (0.65 – 4.1)	0.35[a]
Cobalt (µg/L)	2.51 (0.59 – 12.8)	1.68 (0.59 – 8.5)	0.47[a]
Inclination cup angle (°)	40.4 (30.4 – 50.1)	41.2 (27.5 – 52.2)	0.60[b]
Anteversion cup angle (°)	11.5 (4.9 – 22.5)	15.3 (6.1 – 27.5)	0.02[b]

[a] Two-sample Wilcoxon rank-sum (Mann-Whitney) test.
[b] Satterthwaite's t-test.

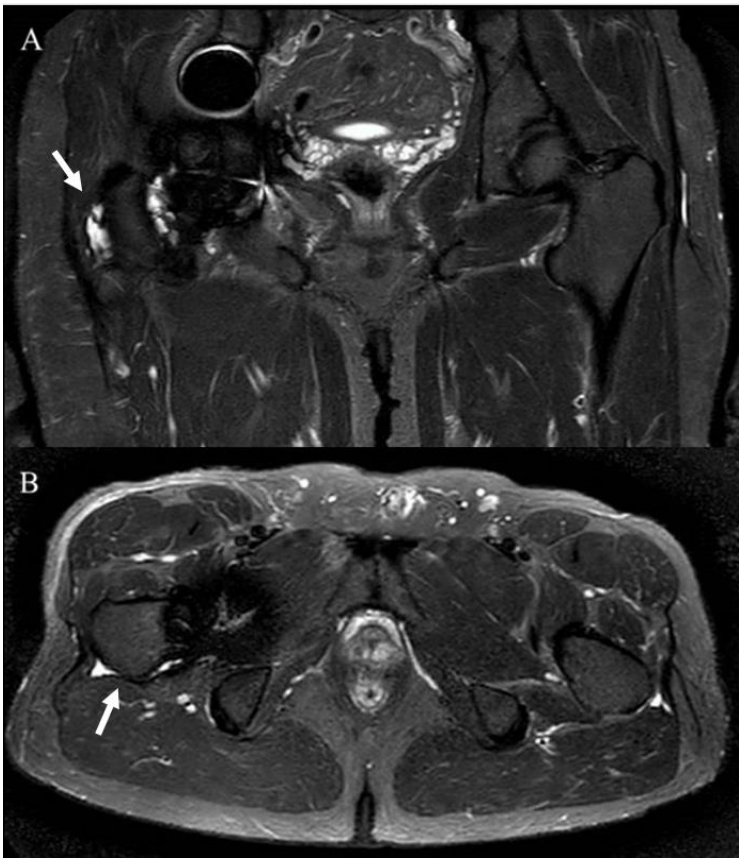


Figure 33 Coronal (A) and axial (B) MARS MRIs a 32-year-old male with a pseudotumor located latero-dorsalt to the greater trochanter, and communicating with the hip joint (pt. no. 10 in Table III).

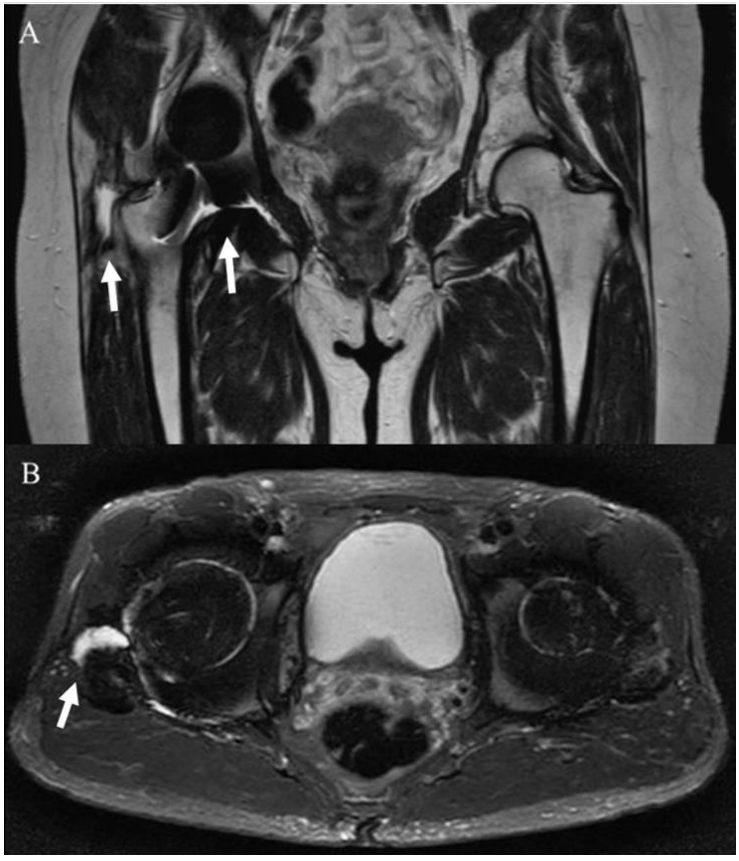


Figure 34 Coronal (A) and axial (B) MARS MRIs in a 60-year-old male with a pseudotumor located antero-laterally to the greater trochanter and communicating with the hip joint (pt. no. 25 in Table III).

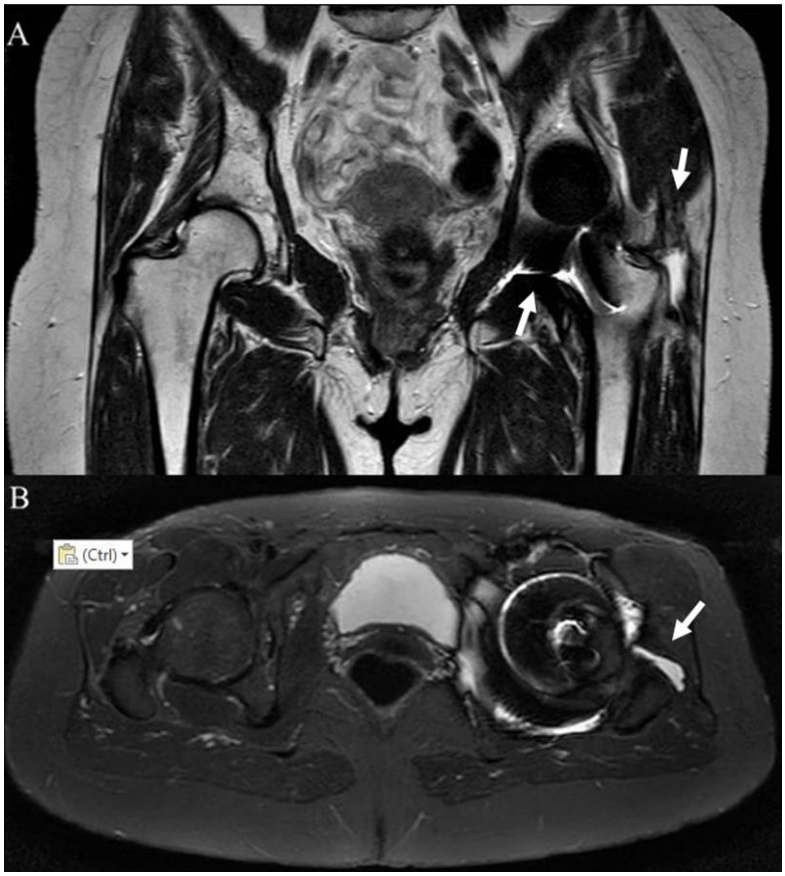


Figure 35 Coronal (A) and axial (B) MARS MRIs in a 50-year-old female with a pseudotumor located antero-laterally to the greater trochanter and communicating with the hip joint (pt. no. 17 in Table III).

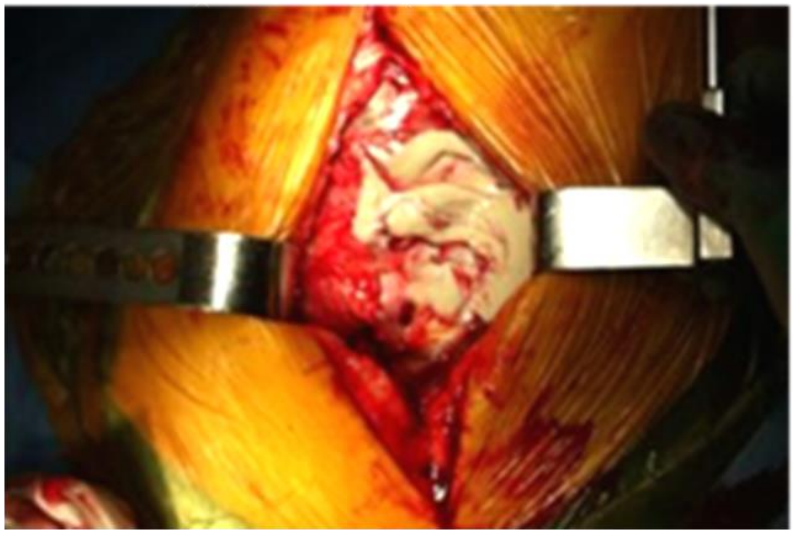


Figure 36 Picture of the 90 x 24 x 55 mm pseudotumor located at the top of trochanter major and reaching distally from there.

7. Discussion

Key findings

To the best of my knowledge, this is the first thesis on a relatively large population of MoM THA, MoM RHA, and MoP THA patients reporting an equal pseudotumor prevalence in the three bearing types and a higher number of mixed or solid pseudotumors in MoP THAs than in MoM THA/RHAs. This thesis also confirmed that the level of daily PA in patients with MoM THA/RHA was related to the patients' serum-ion measurements of chromium, but not to measurements of cobalt or pseudotumor size. Furthermore, comparison of the AntLat surgical approach with the Post surgical approach for insertion of the ReCap resurfacing hip system showed no clinical support for the theorized superiority of the AntLat approach in terms of implant fixation, periprosthetic BMD, and clinical outcome scores. Interestingly, MARS MRI scans showed that cystic pseudotumors were located on the surgical route used for implantation, and that muscle atrophy of the caudal part of the gluteus medius and minimus were common in the AntLat group, whereas muscle atrophy of the small external rotators was common in the Post group.

Interpretations of results and comparison with the literature

Wear-related issues

Serum-ion measurements of chromium and cobalt (Study I, III, IV)

We found a significant difference in mean serum-ion levels of chromium and cobalt between the three bearing types with the lowest levels in MoP THA, moderate levels in MoM RHA, and the highest levels in MoM THA (Study I). Previous studies have also found higher metal-ion levels in MoM THA than in MoM RHA [11, 93, 182]. Wear rates measured by polar measurement profiles from the bearing surfaces of failed MoM THA and MoM RHA have been found to be comparable [216], and corrosion at the head-neck taper junction in MoM THA has therefore been proposed as an explanation for the clinical differences in metal-ion levels between MoM THA and MoM RHA [137, 158, 188, 190]. In MoP THA, authors have suggested that a similar corrosion mechanism at the head-neck taper junction leads to elevated metal-ion levels and pseudotumors that on MRI scans present as pseudotumors in MoM hip arthroplasty [44, 288, 307, 328]. Metal-ion release from different brands of MoM THA has been reported to vary profoundly, with cobalt levels being lowest in patients with M2a-Magnum MoM THA and highest in patients with the Metasul THA (Zimmer, Warsaw, IN) [190]. The M2a-Magnum MoM THA design differs from that of other MoM THA brands in having has a titanium (Ti) sleeve between the head and the stem, which creates a Ti-Ti interface between the sleeve and the stem (Figure 37). It has been suggested that the Ti-Ti interface causes less corrosion and thereby less metal-ion release than Ti-CoCr and CoCr-CoCr interphases [234].

One study even reported similar metal-ion levels in the M2a-Magnum MoM THA and the ReCap Resurfacing system [182], whereas metal-ion levels were elevated in other MoM THA brands compared with the MoM RHA design with identical bearing surfaces (Durum, ASR; BHR, Conserve Plus) [11, 93, 182]. However, in agreement with our results (Study I), higher metal-ion levels in patients with the M2a-Magnum MoM THA than in the ReCap Resurfacing have also been identified [19], and other factors such as adapter sleeve length, thickness, and size, may also play a significant role for metal-ion generation [234].

Figure 37 The M2a-Magnum MoM THA device with a titanium sleeve (Biomet Inc., Warsaw, IN, USA).

Measurements of chromium and cobalt serum metal-ions in patients operated by the AntLat approach and by the Post approach were comparable after approximately 3 years (Study III) and 5 years (Study IV) of follow-up. In general, the mean metal-ion measurements of chromium and cobalt were comparable to those reported in previous studies on the ReCap resurfacing system inserted by a Post approach [19, 182]. However, one female patient (pt no. 6 in Table 21) in the Post group had chromium levels of 14.1 μg/L and cobalt levels of 12.8 μg/L at the follow-up after approximately 5 years. This level is above the 7 μg/L threshold suggested for Denmark [73]. The MARS MRI scan revealed a 90 x 24 x 55 mm cystic pseudotumor located latero-dorsally to the greater trochanter, but the patient experienced no pain, and her HHS scores were 100. We will continue to follow her closely with serum-ion measurements, MARS MRI scans, and clinical examinations to investigate any future destructive process in the soft tissue or bone. In line with former studies, our results (Study IV) showed a correlation between small femoral heads and elevated serum metal-ion measurements of chromium and cobalt [210, 292], and an association between female gender and elevated measurements of chromium and cobalt [9, 229].

Cystic, mixed- and solid pseudotumors in MoM THA/RHA and MoP THA (Study I, II, IV)

The results of this thesis show that the prevalence of periprosthetic lesions identified as pseudotumors on MARS MRI in MoM THAs is the same as that of MoM RHAs and MoP THAs. This result was based on MRI examinations performed using the currently available pseudotumor grading system, which has high intra-observer and inter-observer reliability [6, 323]. Previously, pseudotumors in relation to MoP THAs were described only in small studies and case-reports [16, 279, 288, 302]; this thesis (Study I and II) is the first to compare a relatively large series of MoM and MoP hip implants and to show that pseudotumor in MoP

THA is not a unique finding. A recent study on 28 MoM THAs, 36 MoM RHAs, and 33 CoP THAs reported a similar pseudotumor prevalence in the three bearing types [17]. Although cross-sectional imaging studies on hard-on-soft bearings are still rare, the results of the study performed by Bisseling et al. [17] and those presented in our study indicate that pseudotumors may be found regardless of the type of bearing surface used. Patients with a mixed or solid pseudotumor (3 MoM THAs and 10 MoP THAs) had significantly lower clinical outcome scores of HHS and OHS and higher serum-ion measurements of cobalt than patients with no pseudotumor or with cystic pseudotumor (Study I).

In agreement with this, previous studies on MoM THAs/RHAs and MoP THAs also found higher cobalt metal-ion levels [44, 93, 306] and lower clinical outcome scores [20, 44, 125, 128] in patients with mixed or solid pseudotumors. Furthermore, compared with cystic pseudotumors, mixed and solid pseudotumors have been associated with a more aggressive nature and various degrees of muscle atrophy, bone destruction, nerve palsy, swelling, pain, and poor outcomes of revision surgery [15, 102, 194, 202].

Like former studies, we found that cystic pseudotumors were mainly located postero-laterally to the hip joint, whereas mixed and solid pseudotumors were most commonly related to the iliopsoas bursa (Study I and II) [9, 119, 123, 231, 246]. Interestingly, we observed that the anatomical location of cystic pseudotumors followed the surgical route used for implantation (antero-lateral or postero-lateral) of the ReCap resurfacing system (Study IV). This theory has been proposed by other authors [80, 203, 278], but our study was the first to investigate and verify it.

The 1-year longitudinal study with five follow-ups (Study II) showed that 10 of 26 (38%) pseudotumors in MoM THA/RHA and 8 of 29 (28%) pseudotumors in MoP THA changed classification according to the Anderson Grading system. All changes in pseudotumor classification happened between grade A, C1 and C2, which corresponds to changes between “Normal appearance/No pseudotumor” (A), “Mild MoM Disease” (C1), and ”Moderate MoM Disease”(C2), and mainly reflect changes in pseudotumor size. The anatomical location and the pseudotumor appearance (cystic, solid, or mixed type) did not change between the follow-ups. Some other studies with two cross-sectional imaging examinations have also investigated changes in pseudotumor size/type over time [4, 77, 124, 270, 322]. Like our study, these studies reported minor changes in pseudotumor development. They also showed that, generally, changes were related to the size of cystic pseudotumors rather than to the pseudotumor’s appearance (cystic/mixed or solid). However, Almousa et al. [4] reported that one pseudotumor changed from cystic into solid, and Ebreo et al. [77] described one C2 pseudotumor that changed into a C3 pseudotumor that required revision surgery. It has also been shown that initially asymptomatic pseudotumors may become symptomatic with increasing pseudotumor size, and that may subsequently call for revision surgery [214]. However, it remains unclear if specific factors lead to these pseudotumor alterations and at which stage they become symptomatic and destroy their surroundings. We found that cystic pseudotumors were common in asymptomatic patients regardless of bearing type (Study I, II and IV). This is in agreement with previous studies describing large numbers of asymptomatic cystic pseudotumors [20, 34, 119]. The clinical relevance and significance of asymptomatic cystic pseudotumors has been debated. Because of the high prevalence asymptomatic cystic pseudotumors, Hart et al. suggested that the orthopedic community should be less concerned about the asymptomatic cystic pseudotumors and instead devote more attention to mixed and solid pseudotumors [119].

Since our results (Study IV) show that cystic pseudotumors classified as C1 and C2 follow the surgical route for implantation and therefore could be a normal postoperative finding, the author of this thesis supports the suggestion by Hart et al and, moreover, believes that revision surgery of asymptomatic, non-destructive cystic pseudotumors should be avoided.
It remains unclear if all periprosthetic soft-tissue lesions should be identified as genuine pseudotumors. Currently, it cannot be established from existing literature whether a specific location, size, or postoperative period suffices for classifying a periprosthetic fluid collection as an actual pseudotumor or a normal postoperative finding that may be found following any THA procedure. In addition, there is a demand for a more restrictive use of the term pseudotumor or use of an alternative term to describe the asymptomatic cystic pseudotumors [119].

Influence of PA on metal-ion levels and pseudotumor dynamics (Study II)

In patients with MoP THA, the volume of PE wear has been shown to be associated with patients' general PA level and with periprosthetic osteolysis [282, 283]. MoM THA patients with high PA levels undergo revision surgery due to aseptic loosening more frequently than MoP THA patients with lower PA levels [198]. PA is generally believed to be a patient-related factor essential for implant survival. However, only little research has been conducted into how daily PA levels in patients with MoM THA/RHA influence wear from the bearing surfaces and metal-ion release, and the few studies that do exist on the subject have opposing conclusions [21, 33, 53, 131, 167].
We found a strong correlation between MoM THA/RHA patients' daily PA level and serum-ion measurements of chromium, but a similar correlation was not verified in MoP THA patients. An activity-related increase in chromium of mean 11% has previously been observed by Khan et al. who obtained metal-ion levels in 15 patients with different MoM hip arthroplasty designs (Birmingham Hip Resurfacing, Cormet 2000 Resurfacing and Metasul THA) after 1 hour of running or fast walking on a treadmill [167]. Furthermore, *in vitr*o hip simulator studies have found an increase in metal-wear rates during imitated jogging motions [21, 33]. On the other hand, serum-ion measurements of chromium and cobalt in a triathlete with a BHR device did not change significantly before, during, or after a triathlon competition [53]. However, a significant rise in urinary chromium was observed immediately after and until 6 days after the triathlon competition [53]. Another study on seven patients with MoM hip articulations failed to verify a significant difference in serum-ion measurements of chromium and cobalt during a 2-week period, which included 1 week with high activity levels and a subsequent week with restricted activity levels [131].
The above-mentioned studies differ from our study concerning follow-up time, study design, population and regime, wherefore no direct comparison of the results and conclusions can be made. Moreover, previous studies examined the correlation between metal-ion measurements and acute changes in activity level, while we examined the correlation between metal-ion measurements and patients' daily PA levels (based on 14 days of activity monitoring). High-intensity workout and acute changes in PA might cause some dehydration, which potentially could bias the metal-ion measurements. Furthermore, these studies were limited by small study populations (15, 1, and 7 patients, respectively) and short-term follow-ups, whereas our study

had a relatively large study population, which was examined at several follow-ups during 1 year.
Study II revealed no correlation between patients' daily PA levels and changes in pseudotumor size/type. Changes in pseudotumor size/type over time in MoM THAs/RHAs and MoP THAs have been reported in previous studies using two cross-sectional imaging examinations [4, 77, 124, 270, 322]. Similarly, we found changes in pseudotumor size in both MoM THA/RHA and MoP THA patients within only 3-months periods. However, our results suggest that these changes were unrelated to changes in patients' daily PA levels, and further research on this topic is required to determine which factors cause these changes.

Clinical outcome scores (Study I, II, III and IV)

Regardless of bearing type, patients diagnosed with a mixed or a solid pseudotumor (3 MoM THAs and 10 MoP THAs) had higher metal-ion levels of cobalt and lower clinical outcome scores of HHS and OHS than patients with a cystic pseudotumor or no pseudotumor. This finding (Study 1) is in agreement with previous studies on MoM THAs, RHAs, and MoP THAs, which also reported a correlation between pain and mixed or solid pseudotumors [20, 44, 125, 128] and elevated metal-ion measurements [44, 93, 306].
In Study II, patients completed the HAGOS questionnaire at all follow-ups. We compared the outcomes of the subscale "Hip Related Quality of Life", which reports on any hip and/or groin-related problems, with its effect on patients' daily quality of life. We found similar outcome scores in MoM THA/RHA patients and MoP THA patients at all follow-ups. The HAGOS questionnaire is currently the only questionnaire available that specifically focuses on assessing groin problems [60]. A measurement on groin pain was important for our study, since pseudotumors have been associated with pain and discomfort mainly located to the groin area [15, 202]. The comparable outcome scores could reflect that the prevalence of pseudotumors was similar in MoM THA/RHA patients and MoP THA patients, and, furthermore, that patients in the two groups were comparable regarding the association between any hip and/or groin-related problem and their effect on daily quality of life.
The clinical outcome scores of HHS, 3 months and 1 year (Study III) and approximately 5 years (Study IV) after surgery were all similar in the AntLat and the Post group. In all patients, HHS scores were excellent (above 90) after approximately 5 years of follow-up. Similar results were reported by Van der Weegen et al. with mean HHS scores of 92 for 280 ReCap resurfacings [321] and by Gagata et al. who reported excellent HHS scores with mean 95.8 for 24 ReCap resurfacings [91].

Influence of the AntLat and the Post surgical approach on MoM RHA

Implant fixation of MoM RHA (Study III)

Ideally, all new implant brands, including MoM THA and HRA, should be examined according to the principle of stepwise introduction before being released [164, 206, 238]. However, only a few MoM HRA designs have been evaluated in RSA studies; two studies on the Birmingham

Hip component (BHR) (Smith & Nephew, Memphis, Tennessee) [98, 146, 147] were conducted, one on the Conserve Plus system (Wright Medical Technology, Arlington, Tennessee) [107] one on the ASR devise (DePuy, Warsaw, Indiana) [259], and two on the ReCap resurfacing (Biomet, Warsaw, Indiana) [26, 197].

Migrations of resurfacing femoral components inserted by the Post approach have generally been reported to be smaller than those reported for conventional stems [98, 146, 259]. Similarly, we found small migrations of the ReCap femoral component at 2 years after surgery regardless of which surgical approach was used, and all migrations were comparable between the AntLat and the Post group at all times measured. In both groups, migrations of both cups and stems were most pronounced during the first year. This is in agreement with the results of previous RSA studies of other MoM RHA designs [98, 146, 259] and conventional cemented femoral stems [59, 156, 163, 291].

RSA studies of conventional cemented stems have shown an association between subsidence measurements at 2 years and the risk of future implant failure [59, 156, 163, 320]. In a recent systematic review and meta-analysis of 24 RSA studies and 56 survival rate studies, van der Voort et al. found that a 2-year mean subsidence exceeding -0.15 mm in cemented stems was associated with revision rates due to aseptic loosening of more than 5% at 10 years after surgery [320]. A study comparable to that of van der Voort et al. has not been performed for resurfacing femoral components because RSA studies of these devises are few.

We found that mean subsidence at 2 years was -0.13 mm, which is below the acceptable limit of -0.15 mm for conventional cemented stems suggested by van der Voort et al. Compared to 2-year subsidence measures of the ASR femoral component of mean -0.06 mm [259] and the BHR femoral component of mean -0.01 mm [98], subsidence measures of the ReCap resurfacing femoral component were slightly more pronounced. It is difficult to give an exact explanation for this; however, different implant designs and cements may play a role as may differences in the analytical methods (marker-based RSA or model-bases RSA). In a clinical RSA study of the ReCap femoral component, Lorenzen et al. compared RSA estimates obtained with the marker-based method with those obtained with the model-based method [197]. At 5 years after surgery, subsidence was mean 0.04 mm with marker-based RSA versus mean -0.22 mm with model-based RSA [197], which shows that there is some difference in RSA results obtained with the two methods.

Results of the RSA analysis showed significantly higher cup migrations of TT and TR in the AntLat group than in the Post group at 3 months, but cup migrations at 1 and 2 years were similar in the two groups. The ReCap cups were inserted without cement. Achievement of initial stability thus relied on a tight mechanical press-fit fixation. Our results suggest that the mechanical press-fit fixation in the AntLat surgical approach was inferior to that obtained with the Post surgical approach for insertion of the ReCap acetabular cup. Both surgeons were highly experienced in using the anterior approach for hip surgery (Ganz osteotomy). Still, it is possible that the larger migrations found in AntLat group at 3 months could be explained by the fact that the surgeons were less experienced in using the more recent AntLat approach for insertion of hip arthroplasties than in using the standard Danish posterior surgical approach. However, the 1 and 2 year cup migrations were similar in the two groups. This demonstrates that surface osseo-integration and good secondary fixation of the cups took place in both groups. In addition,

all cups were stable between 1 and 2 years, and stable cups at 2 years after surgery have shown to be an important factor for good long-term results [241, 262]. Longstanding implant fixation in both groups should therefore be expected.

BMD in MoM RHA (Study III)

MoM RHA was expected to reduce stress-shielding and osteolysis at the proximal femoral bone due to a more natural physiological loading of the femur via the femoral neck than in conventional THA. Some short-term studies on different MoM RHA designs inserted by a Post surgical approach have found no difference or small effects at 1 to 2 years after surgery compared with the postoperative scenario, with a BMD increase mainly on the medial side of the femoral stem [43, 111, 258, 299]. Confirming this, Study III showed a BMD increase medial to the femoral stem in the Post group. In contrast to this, the AntLat group experienced a small BMD decrease at the medial side of the femoral stem at 1 and 2 years after surgery. In both the AntLat and the Post group, BMD had increased mostly on the lateral side of the femoral stem at 1 and 2 years after surgery. Comparable results were reported in two previous studies that used different MoM RHA designs; however, these studies used the same ROIs on the femoral neck as us in Study III; in patients with the the ASR device, Penny et al. found an increase in all three lateral ROIs [258], and Kishida et al. found an increase in L1 and L3 (no change in L2) (Figure 22) in patients with the BHR device [170]. Our results show that even though the Post approach sacrifices the medial circumflex artery and thereby a significant part of the blood supply to the femoral head, this does not negatively affect the periprosthetic BMD of the femoral neck. The BMD antero-lateral decrease from immediately after surgery until 2 years after surgery was below 1% in general, and although there was a statistically significant difference in the BMD measurements between groups, the clinical significance and any possible future consequences of these results are doubtful.

The anatomical location of muscle atrophy (Study IV)

Muscle atrophy in patients with MoM hip arthroplasties is included in the umbrella term “adverse reactions to metal debris” (ARMD), which is used to describe undesirable and unexpected side effects related to MoM hip articulations [185]. Muscle atrophy was a common finding in patients with MoM RHA (Study IV), and the anatomical location of the muscle atrophy in patients operated by the AntLat approach was different from that found in patients operated by the Post approach. Other research groups have described muscle atrophy in patients with MoM hip arthroplasties ranging from 22% to 90% [129, 278, 313]. For example, Toms et al. reported gluteus medius atrophy in 8 of 20 symptomatic hips and gluteus minimus atrophy in 9 of 20 [313]. Progressing gluteal muscle atrophy during a 1-year period was reported in 28 MoM THAs and 46 MoM RHAs inserted via a Post or a lateral surgical approach [12]. It has been suggested that muscle atrophy of the gluteus muscles occurs following the use of transgluteal surgical approaches [204], but gluteal muscle atrophy seen in patients operated through a Post surgical approach has been related to presence of ARMD [12]. We found muscle atrophy in the caudal part of the gluteus medius (grade 2 - 4) in 13 of 18 asymptomatic patients operated by the AntLat approach and in 3 of 21 patients (grade 2 - 4) operated by the Post

approach. However, these three patients (one male, two females) had low serum metal-ion levels of chromium (range: 0.67 – 2.7) and cobalt (range: 0.90 - 1.7) and good clinical outcome scores of HHS (range: 89 - 100) and OHS (range: 31 - 42). We could not verify any signs of ARMD on the MRI scans. In support of our results, a recent paper reported on muscle atrophy in patients operated with conventional MoP THA by the Post or the AntLat surgical approach, finding that muscle atrophy of the gluteus muscles was common in patients operated by the AntLat surgical approach [2]. Additionally, muscle atrophy of the short external rotator muscles (particularly obturator internus and piriformis) was detected in 17 of 22 patients operated by the Post approach, but two patients operated by the AntLat approach had no muscle atrophy of the obturator internus and piriformis muscles [225]. The results of the studies by Agten et al. [2] and Mistry et al. [225] support that the Post surgical approach may cause some muscle atrophy of the short external rotators, whereas the AntLat surgical approach may cause some muscle atrophy of the gluteus medius and minimus. This important issue is not considered in the Anderson classification, where muscle atrophy in any other muscles than the short external rotators is considered a pathological finding; and in our opinion, an updated version of Anderson classification may therefore be needed.

Implant positioning (Study III and IV)

Optimal positioning of the hip implant components has been found to be of great importance in conventional THA [47, 192, 255], and it has been argued that component positioning within an optimal zone is even more critical in MoM hip arthroplasties [103, 183, 218]. In addition, malpositioning of MoM THAs and RHAs has been associated with edge-loading, high metal-ion levels, and early implant failure [103]. Especially a steep cup orientation with an inclination angle above 50° has been reported to be a factor leading to high metal-ion measures [55, 183, 216, 325]. We found that the acetabular cup inclination angles were comparable in the AntLat group and the Post group (Study III and IV). However, two patients in the AntLat group had acetabular cup inclination angles above the limit of 50° (50.2° and 50.7°). Nevertheless, their metal-ion measurements of chromium and cobalt were comparable to those measured in the remaining patients, and they had no pseudotumors. Although there was a significant difference in the acetabular anteversion angles of the cup between the AntLat and the Post group, no difference was observed in metal-ion measurements of chromium or cobalt, pseudotumor prevalence, or clinical outcome scores of HHS or OHS. A possible explanation for this may be that all cups were generally well positioned. Moreover, the combined effect of the component size, inclination angle, arc of cover, and anteversion angle may play a bigger role for edge-loading than the anteversion angle alone [55, 183]. Additionally, pseudotumors have been found both in patients with well-positioned cups [69, 217] and in patients with mal-positioned cups [187, 268]; pseudotumor development hence seems to be multifactorial rather than solely dependent on acetabular cup malposition.

Revision rates (Study III and IV)

At 5.3 (3.2 – 7.7) years after surgery, three female patients (6.12%) with the ReCap resurfacing system had undergone revision surgery; two operated via the AntLat approach were revised at

2.6 and 4.1 years after surgery, and one operated via the Post approach was revised at 2.7 years after surgery (Study III and IV). Data from the Danish Hip Arthroplasty Registry show that 1380 patients received MoM RHAs of different brand types during 2004 to 2012. In 2013, 8.6% had been revised; and in 2016, the revision rate had increased to 10.8% [334, 335]. The 2016 report also reveals a huge variation in the revision rates between the orthopedic departments at different hospitals; from 5.2% (Bispebjerg Hospital) to 50% (Skodsborg Hospital). From 2012 to 2013, some departments reported a considerable increase in the revision rates, e.g. Herlev Hospital (from 16.1% to 32.7%) and Silkeborg Hospital (from 4.4% to 15.3%) [334]. This may reflect that the Danish media paid massive attention to the side effects of MoM hip arthroplasties during 2012, which probably has caused some insecurity for both patients and surgeons. Moreover, no clear guidelines were available to inform doctors which patients to revise and when to do so. Furthermore, the report shows some brand-specific differences in revision rate, with the highest rates being reported for ASR hip articulations (26.4%). It is possible that brand-specific differences in revision rates have been affected by general effect of implant recalls. The threshold for revision surgery may have been lower for specific MoM designs than for MoM hip arthroplasties in general. Revision rates of the ReCap Resurfacing System reported by The NJR show a 7-year cumulative percentage probability of revision of 7.79% [247]. This is close to the revision rate found in Study III (6.12%), where three female patients had undergone revision surgery at 5.3 (3.2 – 7.7) years after surgery. In agreement with this, larger studies with multivariable analysis of registry data report a higher risk of MoM RHA revision surgery in females than in males [1, 298]. Moreover, a recent meta-analysis reported a 2.5 times higher risk of MoM RHA revision surgery in females than in males [126].

Methodological considerations and limitations

Study design (Study I, II, III and IV)

Study I and II

Study I was designed as a cross-sectional study and Study II as a 1-year longitudinal study of patients included in Study I. Both studies were limited by the fact that comparisons were made between unmatched groups. A study design with age- and gender-matched groups would have been statistically stronger than a study design with unmatched groups. Although we tried to minimize the effect of the difference between groups by adjusting for potential confounders (sex, age, inclination angles, and time since the arthroplasty), our results may, nevertheless, be statistically biased due to factors related to patients, implants, or surgical techniques.

Study III and IV

Study III was conducted as a 2-year RCT study and Study IV as a cross-sectional mid-term follow-up study of the patients originally included in Study III who had been randomized to MoM RHA by two different surgical approaches. The observers performing the RSA analysis and the MRI evaluations in the two studies were blinded to the surgical approach used for insertion of the ReCap resurfacing system. All included patients were also blinded to the

surgical approach; however, it was not possible to blind the nurses or the orthopedic surgeons. Although the two studies investigated a randomized study population, some biological variation might still exist between the groups.

Selection bias (Study I, II, III and IV)

Study I and II

In Study I and II, patients with MoM hip articulations had already been followed according to the recommendations from The DOS. Thus, some patients (1 MoM THA and 3 MoM RHAs (originally included in Study III) from our department) with symptoms, pseudotumors, or high metal-ion levels had already been revised before the study started. Furthermore, when inviting patients to participate in Study I and II, some patients might have declined participation due to limited physical or mental resources or a long transportation time.

Study III

Although Study III was conducted as an RCT study, which is considered a very strong study design, the ReCap resurfacing arthroplasty may have appealed to a specific patient group, especially since the MoM RHA design had been branded as a "sports hip", and patients who did not consider themselves "sporty" might have declined the invitation to participate.

Study IV

Patients in Study IV who were not willing to participate in an additional follow-up of their MoM RHA could either be those who experienced no problems with their MoM RHA or those who did not have the extra energy to participate in further investigations.

Sample size calculation (Study I, II, III and IV)

Study I and II

No scientific data were available for an *a priori* sample size calculation, and therefore no sample size calculation was performed in Study I and II. Consequently, we do not know if the assessed pseudotumor prevalence was an accidental finding or if it reflects the "true" pseudotumor prevalence in MoM THAs/RHAs and MoP THAs. Additionally, several factors related to patients, implants, and surgical technique may have affected the pseudotumor prevalence.

It would have been interesting to investigate an even larger study population that also included MoC and CoC bearing types. However, such patient groups were unfortunately not available at our institution.

Study III

The *a priori* sample size calculation of Study III was based on RSA data from studies of conventional THAs, since no RSA data were available for resurfacing components. Ideally, the sample size calculation should have been performed using RSA data of studies of the ReCap resurfacing system. Alternatively, a sample-size calculation from another study of the ReCap resurfacing system could have been used.

Study IV

No *a priori* sample size calculation was performed in Study IV as the study was originally planned and dimensioned for an RCT study comparing RSA-measured implant migrations in different groups (Study III). One advantage of RSA studies is that only small sample sizes are necessary because of the high precision of this method. However, it is possible that the groups were too small for comparison of MRI results. However, since the two groups differed systematically in anatomical location of both pseudotumors and muscle atrophy, any difference noted is likely attributable to the surgical approach used for implantation rather than an expression of random variation.

Pseudotumor grading systems (Study I, II and IV)

Numerous pseudotumor definitions and pseudotumor grading systems have been published, all of which take different subjects contents into account such as size (<50mm / >50mm), apperance (cystic / mixed, or solid), and wall thickness (<3mm / >3mm) [6, 34, 119, 128, 217]. This diversity makes it difficult to directly compare results of pseudotumors reported in the orthopedic literature.

In 2014, van der Weegen et al. compared the three most commonly accepted MRI pseudotumor grading systems [323]. They reported that the Anderson grading system had the highest intra-observer and inter-observer reliability among the grading systems investigated [6, 323]. The Anderson Grading system consists of three categories; (A) “Normal”, (B) “Infection”, (C1) “Mild MoM Disease”, (C2) “Moderate MoM Disease”, and (C3) Severe MoM Disease. The classification by Hart/Matthies et al. is based on the MRI signal, the shape of the pseudotumor, and the appearance of the pseudotumor capsule. In this grading system, the pseudotumor is described as (1) “Thin-wallet, flat fluid-filled”, (2a) “Thick or irregular walls, fluid like, Not flat (2b) “Thick or irregular walls, atypical fluid”, and (3) “Solid, any shape” [119, 217]. Hauptfleisch et al. grade the pseudotumors into type I “Thin walled (<3mm), cystic mass”; type II “Thick walled (>3mm), cystic mass”; and type III “Mainly solid mass” [128].

In all MRI studies of this thesis (Study I, II and IV), pseudotumors were classified according to the Anderson grading system. We consider the strengths of this grading system to be its detailed description of each pseudotumor category; the inclusion of a grade A, which corresponds to “Normal or acceptable”; and its reliance on objective measures such as the pseudotumor size rather than MRI signal appearance or pseudotumor wall appearance, which leaves more space for rater variation. A limitations of the Anderson Grading system is that it does not put much weight on pseudotumor appearance (cystic, mixed, or solid), or on its anatomical location. This information is of clinical importance, and we therefore added them to our MRI evaluations. Recently, Smeekes et al. also compared the three MRI pseudotumor grading systems [297]. In contrast to van der Weegen et al. [323], they found that the classification by Hart/Matthies had

the best inter-observer reliability [297], but they concluded that, in general, all three grading systems simply had moderate agreement.
Both studies used a 1.5 Tesla MARS MRI scanner for pseudotumor evaluation. In the study by Smeekers et al., 240 MARS MRI scans were evaluated, whereas van der Weegen et al. evaluated only 49 MARS MRI scans. Smeekers et al. evaluated only patients with the M2a-38 MoM THA (Biomet, Warsaw, IN, USA); and before MRI evaluations were performed, the patients had been divided into a control group and groups that were either at high or low risk for developing a pseudotumor based on metal-ion levels, gender, cup inclination angle, and clinical symptoms. Van der Weegen et al. evaluated patients with three different types of hip articulations: the M2a-Magnum THA, the ReCap Resurfacing system, and the Mallory-head femoral component (Biomet, Warsaw, IN, USA), and the two observes were blinded to the patients' clinical status. It is difficult to judge which of these two studies is the more reliable. However, the MoM THAs and RHAs and some of the MoP THAs evaluated by van der Weegen et al. are identical those included in Study I and II of this thesis. Furthermore, blinding of the two observers adds some reliability to the study by van der Weegen et al.

MARS MRI scans as screening modality (Study I, II and IV)

MRI and US scans have both been recommended for initial pseudotumor screening in patients with MoM hip arthroplasties, since both permit excellent differentiation of the periprosthetic soft tissue [27, 80, 235, 245]. Both methods have some advantages and disadvantages for evaluations of MoM hip arthroplasties, and conclusions are inconsistent in studies comparing the diagnostic accuracy of the two methods for pseudotumors identification [94, 213, 246, 293].

We chose MARS MRI as the imaging modality for Study I, II, and IV because it outperforms US for evaluation of patients with MoM THA/RHAs and MoP THAs in several ways:

1. It allows retrospective image evaluation, which is advantageous when performing consensus evaluations (Study I, II and IV) (and if planning revision surgery).
2. It allows comparisons of serial MRI scans, which was necessary for conducting Study II.
3. It allows comparison with the contralateral hip, which was essential for grading muscle atrophy in Study IV.
4. It is less dependent on operator and examiner than US.

However, MRI also has some disadvantages compared with US:

1. It is more costly and more time-consuming.
2. The metallic hip implants produce metal artefacts, even with the newer MARS techniques, and we therefore struggled with the visibility of some periprosthetic areas.

3. MRI is contraindicated in some patients (e.g. patients with pacemaker, defibrillator, aneurysm clips); however, no patients were excluded on these grounds in the studies of the present thesis.
4. The main disadvantage is the limited potential for achieving biopsies from the pseudotumors found in MoM and MoP hip arthroplasties. The combination of MARS MRI and histology matching would probably have given a more precise description of the pseudotumor type and may have established causality between pseudotumors and bearing types.

With the present study set-up, we had to perform retrospective evaluations and comparisons of serial scans, and we therefore considered MARS MRI scans to be the best screening tool for Study I, II, and IV.

Blood versus serum metal-ion measurements (Study I, II, III, and IV)

Several authorities and authors recommend the use of systemic metal-ion measurements as a screening tool for poorly performing MoM hip arthroplasties [73, 83, 113, 180, 223]. However, guidelines on whether whole blood or serum should be used for analysis of chromium and cobalt concentrations are not universally accepted. The MHRA and the FDA both recommend the use of whole blood, whereas The DOS [73] and Kwon et al. [180] recommend the use of serum metal-ions. Daniels et al. reported that whole blood measurements were more accurate than serum measurements in reflecting systemic metal-ion exposure and should therefore be favored [51]. However, there is no consensus on which matrix (whole blood or serum) is superior as a screening tool [57]. Still, many authors agree that whole blood and serum measurements cannot be compared directly [51, 292, 300]. Measurements of chromium and cobalt levels were analyzed on serum samples in all studies of this thesis, which is also recommended by The DOS [73]. All analyses were performed on the same type of matrix. We therefore consider the comparisons of chromium and cobalt between the patient groups and follow-ups of this thesis to be trustworthy. However, since Vendittoli et al. reported that analysis performed on serum samples in general were higher than those performed on whole blood [325], one should be cautious of this difference when comparing measurements of chromium and cobalt concentrations in this thesis to those reported in other studies.
All patients were screened for renal insufficiency using plasma creatinine levels and estimated glomerular filtration rate (eGFR). However, we obtained no information on any nutritional supplements or work-related or leisure-related chromium or cobalt exposure. Nor did we register if patients had CoCr implants in other places than the hip joints. These are potential sources of chromium and cobalt exposure, which could have influenced our measurements. Furthermore, fluid intake and output were not monitored, simply because it would have been impractical and a huge task to monitor patients' fluid balance. Consequently, it is unknown whether patients were dehydrated or overhydrated during the blood tests. This might also have biased the serum-ion measurements of chromium and cobalt.

Clinical outcome scores (Study I, II, III and IV)

In all studies of this thesis, standardized questionnaires were used to assess patient-reported outcome measures (PROMs). One general disadvantage of using PROMs is the ceiling effect and the flooring effect. This problem occurs when a substantial percentage (within the orthopedic community, frequently described as 15% or more of the patient cohort [112, 220, 326]), achieves the highest or the lowest scores of the questionnaire, thereby making it impossible to differentiate between patients at either end of the measure scale [220, 304]. A ceiling effect, but no floor effect, has been reported using both the HHS [326], the OHS [92], the HAGOS [166], and the VAS for pain [101]. However, we did not estimate the percentage of patients achieving the highest or the lowest scores of each questionnaire, wherefore this effect is most likely a problem causing bias in the results of each of the PROMs.

The HHS differs from the OHS, the HAGOS, and the VAS for pain measurement because it is a clinician-based outcome questionnaire scored by a healthcare professional, whereas the patients themselves fill out the other three questionnaires. The physical examination at baseline in Study I and II was performed by one examiner (MHH), and the examinations performed after surgery, at 3 weeks and at 1 and approximately 5 years in Study III and IV were performed by three orthopedic surgeons. Ideally, at all follow-ups in Study I and II, the HHS should have been performed by one orthopedic surgeon. However, the interrater reliability of the HHS has been reported as good to excellent [169, 301]. Furthermore, the test-retest reliability for physiotherapists and physicians has been reported to be excellent [301], which adds strengths to the reported HHS.

All of the studies of this thesis were limited by the fact that the HHS examiners were not blinded to patients' type or brand of hip arthroplasty (Study I and II) or to the surgical approach used for implantation (Study III and IV). We chose to use the HHS in all of the studies, since it is a widespread method for assessing hip function, and therefore made it possible to compare our results with those of multiple other studies.

Assessment of patient physical activity (Study II)

Measurements of patient activity and function can be achieved in various ways; by PROMs like the UCLA activity-level rating scale [339], the Tegner score [308], and the Activity Rating Scale [207], by telephone surveys [61], and by step counters [168]. For clinical research, a more detailed description of gait or function can be obtained using lab-based gait analyses and with tools like force plates, video motion-capture, electromyography (EMG), by performance-based tests such as the 6-Minute Walk test (6MWT) or the Timed Up-and-Go test (TUG), and by 3D accelerometers.

We chose to monitor patient activity in Study II using 3D accelerometers since they provide objective and detailed descriptions of patients' everyday activities during longer follow-ups [230, 285]. A more precise and highly detailed biomechanical description of patient movement (joint moments and joint angles) could have been achieved using lab-based motion capture gait analyses. However, such method is time-consuming, costly, and does not allow for long-time monitoring of patients' daily activity.

Using PROMs for assessment of patient activity would have been an easy and low-cost approach. However, PROMs are subjective measures that have been shown to have poor

validity [309]. If step counters had been used, only the total step count per day would have been measured. Moreover, non-walking activities like cycling, stair walking, or standing would not have been recorded. Due to the disadvantages of these other, currently available methods for assessing patient activity, we found that 3D accelerometers were the best choice for Study II.

Although patients were instructed to wear the accelerometers for 14 days, they wore them for a mean of 15 (range: 10 - 21) days in reality. This wide difference in wear time occurred because some patients had to go on a holiday, to a wedding, or other events during which they did not wish to wear the accelerometer. Other patients simply continued wearing the accelerometer until the battery light went off. One could argue that all patients should have worn the accelerometers for 14 consecutive days during the 1-year follow-up to obtain the most precise measure of the patients' PA level. However, it has been shown that 3-5 days of activity monitoring is sufficient to reflect an individual's usual or habitual PA level [312, 314]. Since patients in this study wore the accelerometers much longer, we do not expect the occasional missing day to bias our results. Patients with bilateral hip arthroplasties did not wear a 3D accelerometer at each leg. Instead, we assumed that an equal amount of activity had been performed with each leg, since activity of the lower extremities is nearly always performed bilaterally. This could theoretically have influenced our results; however, we expect that a potential difference between the legs would have been very small and insignificant.

Plain radiographs (Study I, II, III and IV)

All radiographs were evaluated in consensus between two observers; one experienced orthopedic surgeon (SSJ) and one PhD student (MHH). One limitation was that we did not investigate the inter- or intra-observer reliability of these evaluations.

Measurements of cup position (Study III and IV)

In Study III, we read the anteversion and inclination angels of the ReCap acetabular cup from the model-based RSA software after complete pose estimation of the implant model. This method has not been validated. However, since the model-based RSA software uses the exact 3D cup model and allows for a submillimeter-precise fit of the cup contour including the four rim indentations on the stereo-radiographs, we believe that the cup position measured by model-based RSA is both a suitable and reliable method for measuring anteversion and inclination angles, and potentially better than using standard LA and AP supine hip radiographs. Furthermore, measurements of both anteversion and inclination angles read from the model-based RSA software in Study III were quite similar (matching within a few degrees) to those measured in Study IV, where the PolyWare software was used.

RSA (Study III)

Measurements of implant fixation and migration

Loosening of hip arthroplasties can be suspected on conventional radiographs when progression of radiolucent lines is observed around the implants and visible implant migration or change of component position with respect to the bony landmarks is seen over time. However, bony landmarks are not sufficiently distinctive and are therefore difficult to measure in a reproducible manner.

One study determined the accuracy of stem and cup migration analysis obtained by conventional radiographs using digitized and manual measurements and compared the results with those assessed by RSA. The accuracy of the digitized and manual measurements was 3.9-12.3 mm (mean + 2 SD) for femoral stems and 4.4-6.5 mm (mean + 2 SD) for acetabular cups [205]. Over the years, many attempts have been made to improve the accuracy of implant migration measured on conventional radiographs, for example by standardizing the patient's position, adding further bony landmarks, and using software performing measurements in a reproducible and objective manner [114]. The Einzel Bild Roentgen Analysis (EBRA) method combines these three factors for calculating implant migrations and thereby improves the accuracy for acetabular cups to 1.0 mm for longitudinal and 0.8 mm for transverse migrations [172]. However, when assessing implant migrations within the first 6 months after surgery or when comparing differences in migration patterns between small patient groups, even this accuracy is not sufficient. Compared to the RSA method, the EBRA method measures only 2D migration, meaning that it is able to detect migrations of translations along the x-axis and y-axis, but not along the z-axis, and no measurements of rotations can be assessed. For stems and cups, the migration direction of implants that fail is typically associated with x-axis or y-axis migration, which EBRA would sufficiently detect. However, for detailed description of migration patterns of new implant designs, implant coatings, and types of bone cement, this is a substantial limitation. Furthermore, the higher accuracy and precision of the RSA method makes it is possible to conduct studies with small patient groups [63, 145, 318]. Since the purpose of Study III was to compare implant migration between two small patients groups, randomized to surgery with the ReCap resurfacing hip by two different surgical approaches, the above-mentioned advantages of the RSA method made it the most suitable method. However, the RSA and the EBRA method have different strengths and weaknesses that should be taken into consideration when planning studies on implant migration.

The use of marker-based and model-based RSA

Using the RSA method, two main techniques may be deployed for measuring implant migration: the marker-based and the model-based techniques. The precision of marker-based RSA for measurements of implant migration of the Recap resurfacing system is superior to that of model-based RSA. However, the precision of model-based RSA is reported to be acceptable for use in a clinical setting [197].

We used model-based RSA for all analyses of implant migration. Yet, due to the geometrical configuration of the acetabular cups and femoral stems, we struggled to achieve a high rotational precision for the cups (x-axis: 1.65°, y-axis 1.27°, z-axis: 1.98°). We may have

obtained a better precision using marker-based RSA. However, one study comparing the clinical precision (double-examination of eight patients) of marker-based RSA versus model-based RSA reported a precision of 0.2 mm for TT and 1° for TR marker-based RSA compared with 0.5 mm for TT and 1° for TR with model-based RSA [197]. The precision of marker-based RSA was reported to be superior to that of TT, but no statistically significant difference between the methods was found for TR [197].

Even though the use of marker-based RSA would have provided a slightly better precision in Study III, this method is limited by other problems such as occluded implant markers, broken implant marker-towers, and over-projections of the implant [159, 161]. Especially difficulties visualizing the tantalum markers on pin of the ReCap resurfacing femoral component have been reported as problematic. This led to the exclusion of RSA analyses in a previous study and thereby introduced a risk of type two error [197]. This problem was avoided by using model-based RSA at the expense of a slightly poorer precision.

DXA scans (Study III)

No software was available for creating the ROIs used to evaluate the BMD measurements around the ReCap resurfacing femoral component. The ROIs therefore had to be created manually and applied on the DXA scans. Hence, there was a risk of introducing human error. With the Lunar Prodigy Advance 2005 DXA scanner (General Electric, Chicago, IL, USA) a template of ROIs is created and applied on the postoperative scan and subsequently copied to follow-up scans. This makes it much easier to place the ROIs similarly on follow-up scans. Although patients were placed in standardized positions on the examination table with their feet fixed to a device, there is a possibility that some difference in leg rotation may have occurred between follow-ups. Since BMD measurements around MoM RHA have been shown to be particularly sensitive to leg rotations due to the small zones of the femoral ROIs [233, 257], this might have created some noise in the BMD measurements.

Generalizability

Study I

The pseudotumor prevalence found in Study I was evaluated in a study population with specific brands of MoM THAs, MoM RHAs, and MoP THAs. Since multiple factors (including implant and patient factors) potentially influence pseudotumor formation, our results may not be similar to those obtained in other studies investigating different study populations and other MoM THA, MoM RHAs and MoP THA brands.

Study II

Various factors have been shown to affect metal-ion measurements of chromium and cobalt in patients with MoM THA/RHAs. We verified a correlation between patients' daily PA level and metal-ion measurements of chromium at all follow-ups. However, we were not able to adjust statistically for all possible confounders (due to the size of the study population), and we cannot reject the possibility that other factors may have played a role in the generation of metal-ions, e.g. radial clearance, manufacturing process, type of coating, shell thickness, and use of adapter sleeve. Therefore, further investigation of the correlation between patients' PA level and metal-ion measurements is advisable in other brands of MoM THAs/RHAs.

Study III

Although we used the same implant and surgeons, the two different surgical approaches used for implantation resulted in different primary fixation patterns. This underlines that many different factors (including non-implant-related ones) may influence implant fixation; and even though we found good secondary fixation in both groups, this may not necessarily be the case in other study populations of the ReCap resurfacing system inserted via different surgical approaches or fixed by different types of cements than those used in our study. Furthermore, the implant migration patterns found in this study may not be representative of other brands of MoM RHAs.

Study IV

To our knowledge, this is the first study to investigate the influence of the surgical approach used on the location of pseudotumors and muscle atrophy. We found a clear relationship between these parameters, but the study sample was small since the original study was an RSA RCT dimensioned for a small sample size. Therefore, the findings can be generalized only to patients with a mid-term follow-up of the ReCap implant.

8. Conclusion

Study I

Periprosthetic pseudotumors were commonly seen in MoM THA, MoM RHA, and MoP THA. Similar pseudotumor prevalences were seen irrespective of the bearing type used. The prevalence of mixed or solid pseudotumors was higher in MoP THAs than in MoM THAs and MoM RHAs. Moreover, significantly higher metal-ion levels of cobalt and lower clinical outcome scores of HHS and OHS were found in hips with mixed or solid pseudotumors than in hips without pseudotumor or with a cystic pseudotumor. Currently, the use of MoM hip articulations is limited, and MoP THA is the main bearing type implanted globally. Because of the current guidelines for MoM hip arthroplasty, follow-up clinicians will continue to see both MoM and MoP hip arthroplasties for follow-up for many years to come, and the importance of the present findings therefore concern both patient groups. A new finding in this context is the conclusion that clinicians examining patients with unexplained pain related to a MoP THA should keep in mind the risk of a mixed or solid pseudotumor.

Study II

The daily PA level of MoM THA/RHA patients correlated with metal-ion concentrations of chromium but not with metal-ion concentrations of cobalt or fluctuations of pseudotumor size. A similar correlation was not observed in MoP THA patients. According to the Anderson Grading system, changes in pseudotumor classification during the first year of follow-up occurred in 38% of MoM THA/RHA patients and in 28% of MoP THA patients. The outcomes of this study may be of significance when developing new evidence-based follow-up guidelines for MoM THA/RHA patients.

Study III

The AntLat surgical approach did not demonstrate the expected superiority of implant fixation of the ReCap resurfacing components, BMD measurements of the femoral neck, or clinical outcome scores. We found higher cup migrations of TT and TR at 3 months and inferior BMD measurements at the medial side of the femoral stem at 1 and 2 years in the AntLat group than in the Post group. However, implant migrations at 1 and 2 years were similar in the two groups, indicating good secondary fixation. Moreover, the difference found in BMD measurements were small and might not be of clinical significance. Still, we cannot recommend the AntLat approach over the Post approach for future insertions of the ReCap resurfacing system.

Study IV

The anatomical location of pseudotumors followed the surgical route used for implantation of the ReCap resurfacing system; pseudotumors in the AntLat group were located antero-laterally to the hip joint, and pseudotumors in the Post group were located postero-laterally to the hip joint. Some degree of muscle atrophy was present in all patients, and the AntLat group had significantly higher grades of muscle atrophy of the caudal part of the gluteus medius and minimus, whereas the Post group had significantly higher grades of muscle atrophy of the small external rotators. These findings add new knowledge to the existing literature on the location of pseudotumors and muscle atrophy after insertion of the ReCap resurfacing system using two different surgical approaches. Furthermore, this information may help clinicians to distinguish between “normal postoperative appearance” and “MoM disease” on MRI.

9. Future research

Study I

The most ideal study regime would have been one where patients were examined with US scans after the final MARS MRI scan had been performed in Study II. Furthermore, in patients with a cystic, mixed, or solid pseudotumor, fluid aspirations or biopsy for histological evaluation with aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) scores should have been performed. The combination of histological matching with the MARS MRI findings would have provided a more detailed characterization of the pseudotumor types found in patients with MoM and MoP bearing surfaces. Furthermore, histological examination would possibly have made it possible to distinguish between subtypes of pseudotumors found in relation to different bearing types.
In an ongoing revision study of MoM THAs/RHAs and MoP THAs, we obtained pseudocapsule biopsies and synovial fluid samples from the hip of a few patient undergoing revision surgery. This material is currently stored at –80°C in a freezer at our department, and we look forward to investigating it. Furthermore, the prevalence of pseudotumor in ceramic articulations (MoC and CoC) has not yet been described.

Study II

Pseudotumors are dynamic and might change in size/type between two imaging examinations. We could not verify that patients' daily PA level was related to changes in pseudotumor size/type. Therefore it remains uncertain if specific factors lead to these changes, and at which stage asymptomatic pseudotumors become symptomatic and destructive. Further research of these essential topics would therefore be most interesting. Additionally, there is currently no consensus on which patients could benefit from revision surgery and what the timing should be. Future research should focus on generating new and evidence-based guidelines for revision of MoM arthroplasty and hip arthroplasty when pseudotumors are present.

Study III

Patients included in Study III attended a 5-year follow-up examination where RSA was measured and clinical outcome scores of HHS and OHS were obtained. However, we have not yet evaluated these data. RSA guidelines recommend extension of short-term RSA studies to long-term RSA studies to firmly establish the relationship between early migration and future implant loosening. We therefore plan to invite this patient group to participate in a 10-year RSA and possibly MRI follow-up of their ReCap RHA.
Furthermore, our RSA results showed that the surgical approach affected cup migration patterns. This demonstrates the importance of "a stepwise introduction" of new devices. It is therefore highly recommendable to conduct small-scale RSA studies of all new articulations, cements, coatings, and surgical approaches before they are released.

Study IV

As described above, patients investigated in Study III will be invited for a 10-year RSA follow-up of their ReCap hip arthroplasty. Furthermore, they will be followed according to the MoM guidelines issued by The DOS. In case of any revision surgeries, we will obtain biopsies from the pseudocapsule for histological examinations with ALVAL scores and synovial fluid samples for metal-ion measurement of chromium and cobalt.

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Appendices

Appendix 1

European multidisciplinary consensus statement on the use and monitoring of metal-on-metal bearings for total hip replacement and hip resurfacing [113].

ABSTRACT

The European Commission asked the SCENIHR for a scientific opinion to assess the safety of Metal-on-Metal joint replacements with a particular focus on hip implants.

There are two commonly used types of total hip arthroplasty (THA) (i) "stemmed" implants consisting of a ball head (either small-head diameter < 36 mm or large-head diameter ≥ 36 mm), which replaces the entire femoral head, connected to a stem embedded in the femur as well as a cup embedded in the acetabulum. If both head and cup are metal, the implant is called "metal-on-metal" (MoM) total hip arthoplasty; (ii) "hip resurfacing arthroplasty" (HRA) in which the femoral head is resurfaced without a stem and a cup embedded in the acetabulum; both components in HRA consist of metal alloys and are always large diameter.

All types of MoM hip arthroplasties release metals in terms of particles, ions and/or metallo-organic compounds. The deposition of these substances in body fluids and tissue may lead to local and/or systemic adverse health effects. MoM implants with large diameters (large-head MoM THA and HRA) show the highest incidence of local reactions. For systemic health effects, no association with the type of implant or diameter has been established. Local as well as systemic adverse effects can also occur with other types of metallic implants (e.g. plates, screws).

Local tissue reactions: The local responses comprise a broad clinical spectrum ranging from small asymptomatic tissue lesions to severe destruction of bone and soft tissues and include metallosis, aseptic lymphocytic vasculitis associated lesions, pseudotumours and adverse reactions to metal debris. These local responses can occur at any time after surgery (short, medium and long term).

Systemic adverse responses: The toxicity of several metals present in implants has been evaluated in experimental and epidemiological studies. Extrapolation of these data to evaluation of metal particles, ions, and metallo-organic compounds released at the site of the implant and distributed into lymph nodes, bone marrow and internal organs is currently limited because the degradation products are not adequately characterised. There are some specific concerns related to the possible systemic exposure to cobalt and/or chromium after MoM-hip arthroplasty, such as systemic organ toxicity, carcinogenicity and teratogenicity.

There have been a few studies of carcinogenicity but with no consistent evidence of an overall increase in cancer associated with MoM HRA although there has been occasional reported elevation of hematopoetic malignancy, prostate cancer and melanoma rates.

Transplacental passage of metal ions has been demonstrated although without any teratogenic effect up to now.

The SCENIHR concludes that critical values for systemic effects are not yet established for patients after MoM implantation because of the lack of data and it is thus not possible to provide indications on limit values for the metals in any forms.

The SCENIHR decided to adopt the strategy as outlined in the European Consensus Statement, which includes recommendations on technical issues (e.g. metal ion determination for screening purposes should be performed in whole blood), determination of critical threshold ranges (e.g. for Co a range of 2 to 7 µg/L Co whole blood) and systematic follow-up for all patients and all implants due to the risks of MoM bearings.

Overall, the choice of the type of implant should be based on a detailed case-by-case evaluation taking into account risks and benefits relating to the characteristics of each patient such as age, gender, physical activity, occupation etc.

The experience with MoM implants to date indicates that introduction of new or technically modified implants on the market should be made step-by-step. It is stressed that suitable preclinical and clinical studies are particularly important and that MoM implants requires close and comprehensive post-market surveillance. Further research is needed including appropriate toxicological studies using comparable routes of exposure to humans, prospective human studies with adequate exposure and outcome data and post-mortem studies. National registries of MoM HRA patients are recommended with follow-up for local, systemic and long-term effects

Appendix 2

The United State Food and Drug Administration [84].

Follow-Up for Asymptomatic Patients

Clinical Evaluation

If a patient with a metal-on-metal (MoM) hip implant is asymptomatic and has a well functioning hip, follow-up should occur periodically (typically 1 to 2 years).

- Be aware the following patients may experience increased wear of the implant and/or adverse reaction to metal debris and require closer monitoring. They include:
  - Patients with bilateral implants
  - Patients with resurfacing systems with small femoral heads (44mm or smaller)
  - Female patients
  - Patients receiving high doses of corticosteroids
  - Patients with evidence of renal insufficiency
  - Patients with suppressed immune systems
  - Patients with suboptimal alignment of device components
  - Patients with suspected metal sensitivity (e.g. cobalt, chromium, nickel)
  - Patients who are severely overweight
  - Patients with high levels of physical activity
- Patient follow-up visits should include:
  - Physical exam with functional assessment;
  - Checking for asymptomatic local swelling or masses; and
  - Assessment for possible systemic adverse events in cardiovascular, nervous, endocrine (especially thyroid) and renal systems.

Additional Testing for Asymptomatic Patients

If the orthopaedic surgeon feels the hip is functioning properly and the patient is asymptomatic, the FDA does not believe there is a clear need to routinely check metal ion levels in the blood or perform soft tissue imaging.

- Findings of lesions on soft tissue imaging, or of elevated blood metal ion levels in the absence of symptoms have been reported in a limited number of research studies for some MoM hip implant patients. These studies are difficult to interpret because:
  - The exact incidence or prevalence of asymptomatic lesions and their natural history is not known.
  - The correlation between elevated blood metal ion levels and development of future local or systemic system adverse reactions is not well established.
- If the orthopaedic surgeon determines it is in the best interest of the patient to conduct soft tissue imaging, please review FDA's recommendations.
- If the orthopaedic surgeon determines it is in the best interest of the patient to measure metal ion levels, please review FDA's recommendations.

Follow-Up for Symptomatic Patients
Clinical Evaluation

- If a patient experiences local symptoms (i.e. pain or swelling at or near the hip, a change in walking ability, or a noise from the hip joint) more than three months after metal-on-metal (MoM) hip implant surgery, conduct a thorough evaluation.
- Follow-up of symptomatic patients with MoM hip implants should occur at least every six months.
- Guide your clinical evaluation by the symptoms and physical findings, including an assessment for well-known emergent complications including joint infection, implant loosening, peri-prosthetic facture and dislocation.
- Recognize that localized lesions associated with reactions to metal debris may also present with pain or a variety signs and symptoms including:
  - Local nerve palsy
  - Palpable mass
  - Local swelling
  - Joint dislocation or subluxation

Additional Testing for Symptomatic Patients

- In some patients with symptoms, plain radiograph findings (e.g. osteolysis, femoral neck narrowing, component suboptimal positioning, fracture), in conjunction with other non-imaging information, are sufficient to indicate a need for revision surgery.
- In other symptomatic patients, cross-sectional imaging should be considered to diagnose and assess soft tissue findings surrounding an implant.
- Patients with MoM hip implants who develop any symptoms or physical findings that indicate their device may not be functioning properly, should be considered for metal ion testing. It is important to note that at the current time, the FDA believes there is not enough evidence in the U.S. to demonstrate a correlation between a metal ion level and the presence of localized lesions, clinical outcomes and/or the need for revision surgery.

Appendix 3

The Hip Society: algorithmic approach to diagnosis and management of metal-on-metal arthroplasty [193].

Figure 1 An algorithm outlining the steps recommended for evaluating a patient who presents in follow-up after hip arthroplasty with an asymptomatic metal-on-metal articulation.

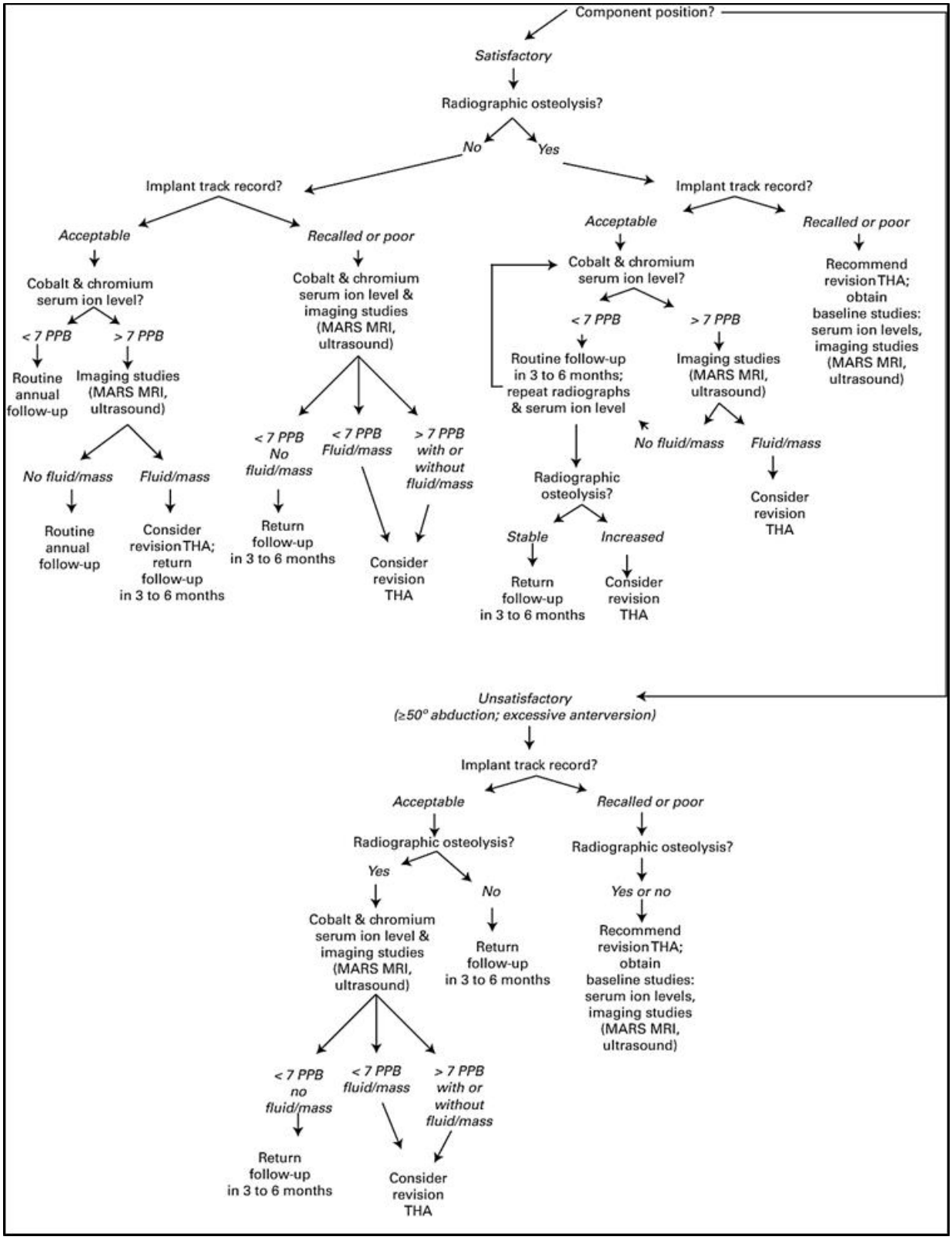
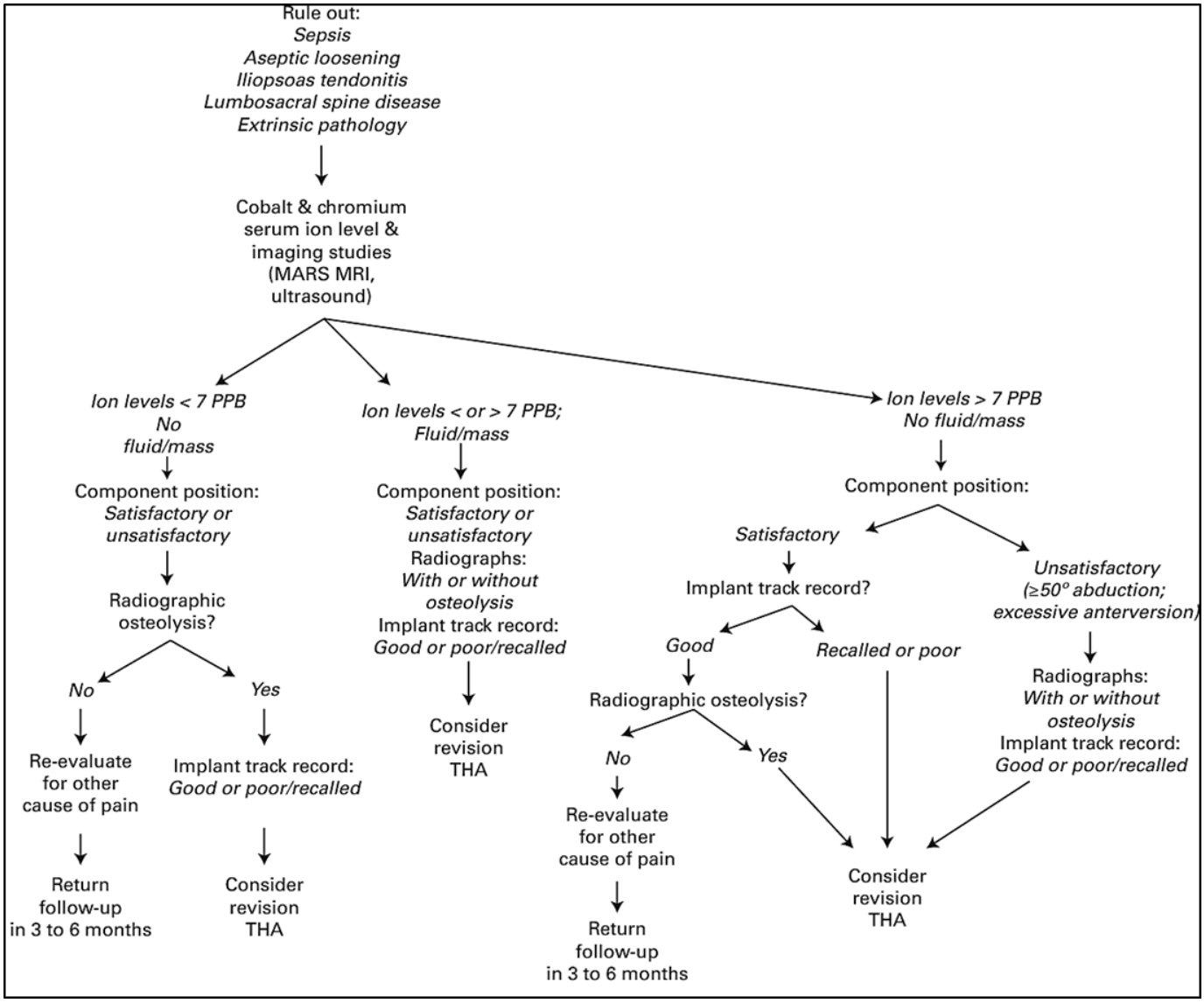


Figure 2 An algorithm outlining the steps recommended for evaluating a patient who presents in follow-up after hip arthroplasty with a symptomatic metal-on-metal articulation.



Appendix 4

Risk Stratification Algorithm for Management of Patients with Metal-on-Metal Hip Arthroplasty
Consensus Statement of the American Association of Hip and Knee Surgeons,
the American Academy of Orthopedic Surgeons, and The Hip Society [187].

TABLE II MoM 'Low' Risk Group

'Low' Risk Group Stratification	
Patient factors	Patient with low activity level
Symptoms	Asymptomatic (including no systemic or mechanical symptoms)
Clinical examination	No change in gait (i.e., no limp, no abductor weakness)
	No swelling
Implant type	Small-diameter femoral head (<36 mm) modular MoM THA; hip resurfacing in males <50 with osteoarthritis
Radiographs (2 views ± serial for comparison when available)	Optimal acetabular cup orientation (40° ± 10° inclination for hip resurfacing)
	No implant osteolysis/loosening
Infection work-up (ESR, CRP, ± hip aspiration)	Within normal limits
Metal ion level test (if available)	Low (<3 ppb)
Cross-sectional imaging (if available): these studies include MARS MRI; ultrasound or CT when MRI contraindicated or MARS protocol not available	Within normal limits
Treatment recommendation	Annual follow-up

TABLE III MoM 'Moderate' Risk Group

'Moderate' Risk Group Stratification	
Patient factors	Male or female
	Dysplasia (for hip resurfacing)
	Patient with moderate activity level
Symptoms	Symptomatic
	Mild local hip symptoms (e.g., pain, mechanical symptoms)
	No systemic symptoms
Clinical examination	Change in gait (i.e., limp)
	No abductor weakness
	No swelling
Implant type	Large-diameter femoral head (≥36 mm) modular or nonmodular MoM THA
	Recalled MoM implant
	Hip resurfacing with risk factors (female with dysplasia)
	Modular neck device
Radiographs (2 views ± serial for comparison when available)	Optimal acetabular cup orientation
	No implant osteolysis/loosening
Infection work-up (ESR, CRP, ± hip aspiration)	Within normal limits
Metal ion level test	Moderately elevated (3-10 ppb)
Cross-sectional imaging (MARS MRI; ultrasound or CT when MRI contraindicated or MARS protocol not available)	Presence of abnormal tissue reactions *without* involvement of surrounding muscles and/or bone
	Simple cystic lesions or small cystic lesions without thickened wall
Treatment recommendation	Follow-up in 6 months
Revision surgery	Consider revision surgery if symptoms progress, imaging abnormality progresses, and/or there are *rising* metal ion levels over 6 months

TABLE IV MoM 'High' Risk Group

'High' Risk Group Stratification	
Patient factors	Female with dysplasia (for hip resurfacing)
	Patient with high activity level
Symptoms	Symptomatic
	Severe local hip and/or mechanical symptoms
	Systemic symptoms
Clinical examination	Change in gait (i.e., limp)
	Abductor weakness
	Swelling
Implant type	Large-diameter femoral head (≥36 mm) modular or nonmodular MoM THA
	Recalled MoM implant
Radiographs (2 views ± serial for comparison when available)	Suboptimal acetabular cup orientation
	Implant osteolysis/loosening
Infection work-up (ESR, CRP, ± hip aspiration)	Within normal limits
Metal ion level test	High (>10 ppb)
Cross-sectional imaging (MARS MRI; ultrasound or CT when MRI contraindicated or MARS protocol not available)	Presence of abnormal tissue reactions *with* involvement of surrounding muscles and/or bone
	Solid lesions
	Cystic lesions with thickened wall
	Mixed solid and cystic lesions
Treatment recommendation	Consider revision surgery

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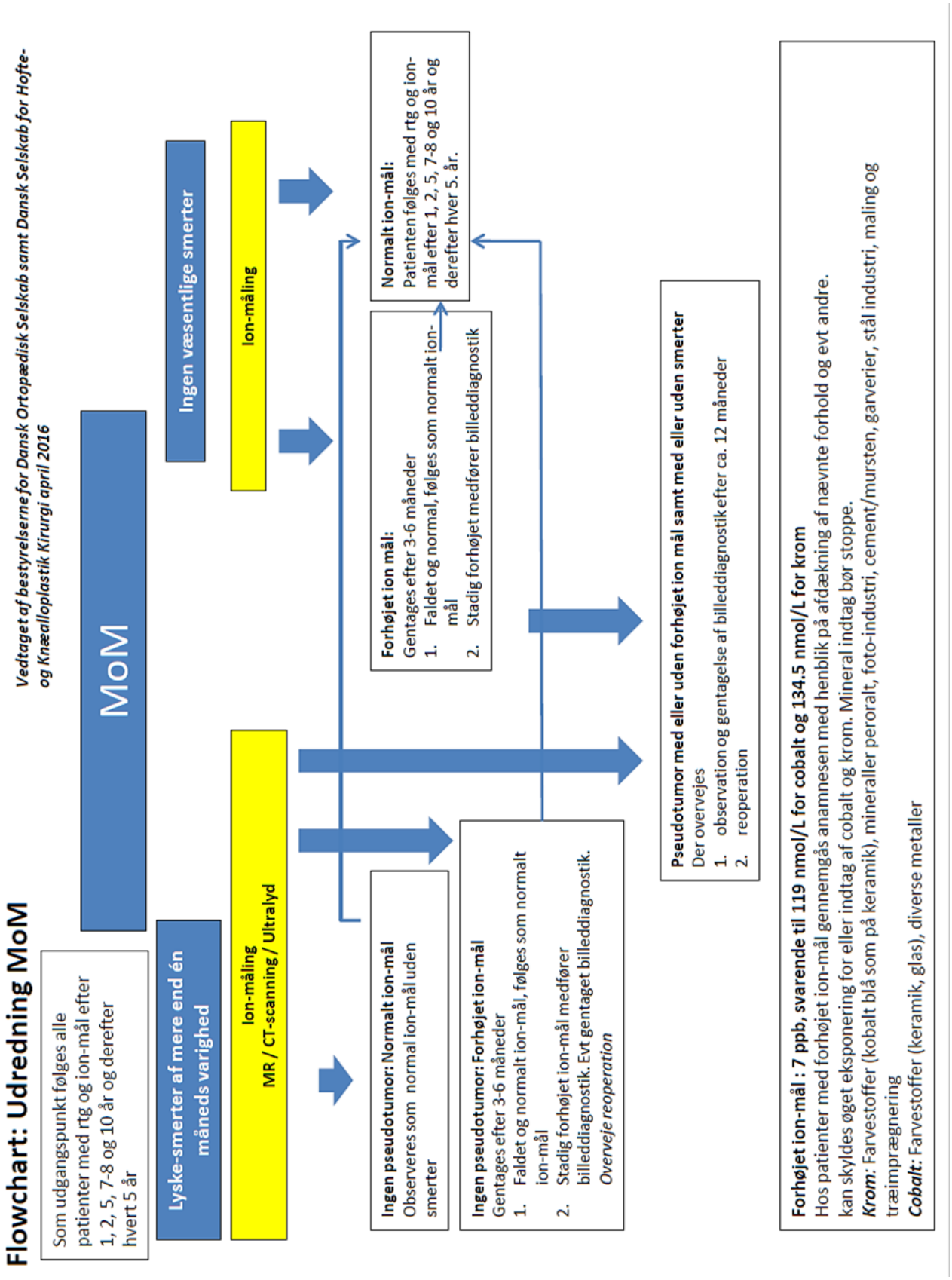
Appendix

Management recommendations for patients with metal-on-metal hip replacement implants

	MoM hip resurfacing (no stem)		Stemmed MoM total hip replacements – femoral head diameter <36mm		Stemmed MoM total hip replacements – femoral head diameter ≥36mm		DePuy ASR™ hip replacements (all types)	
	Symptomatic patients	**Asymptomatic patients**	**Symptomatic patients**	**Asymptomatic patients**	**Symptomatic patients**	**Asymptomatic patients**	**Symptomatic Patients**	**Asymptomatic patients**
Patient follow-up	Annually for the life of the implant	According to local protocols	Annually for the life of the implant	According to local protocols	Annually for the life of the implant	Annually for the life of the implant	Annually for the life of the implant	Annually for the life of the implant
Imaging: MARS MRI or ultrasound	Recommended in all cases	**No** - unless concern exists for cohort or patient becomes symptomatic	Recommended in all cases	**No** - unless concern exists for cohort or patient becomes symptomatic	Recommended in all cases	Recommended if blood metal ion levels rising	Recommended in all cases	Recommended in all cases
1st blood metal ion level test	**Yes**	**No** - unless concern exists for cohort or patient becomes symptomatic	**Yes**	**No** - unless concern exists for cohort or patient becomes symptomatic	**Yes**	**Yes**	**Yes**	**Yes**
Results of 1st blood metal ion level test	*Blood metal ion level >7ppb indicates potential for soft tissue reaction*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction*	*If blood metal ion level >7ppb then second blood test required 3 months later*	*Blood metal ion level >7ppb indicates potential for soft tissue reaction*	*If blood metal ion level >7ppb then second blood test required 3 months later*
2nd blood metal ion level test	**Yes** - 3 months after 1st blood test if result was >7ppb		**Yes** - 3 months after 1st blood test if result was >7ppb		**Yes** - 3 months after 1st blood test if result was >7ppb	**Yes** - 3 months after 1st blood test if result was >7ppb	**Yes** - 3 months after 1st blood test if result was >7ppb	**Yes** - 3 months after 1st blood test if result was >7ppb
Results of 2nd blood metal ion level test	*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*	*If blood metal ion levels rising - further investigation required including imaging*	*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*	*Blood metal ion level rising indicates potential for soft tissue reaction*
Consider need for revision	If imaging is abnormal and/or blood metal ion levels rising		If imaging is abnormal and/or blood metal ion levels rising		If imaging is abnormal and/or blood metal ion levels rising	If imaging is abnormal and/or blood metal ion levels rising	If imaging is abnormal and/or blood metal ion levels rising	If imaging is abnormal and/or blood metal ion levels rising

Appendix 6

The Danish Orthopedic Society [74].



Appendix 7

Units used for metal-ion measurements

Different units have been used for reporting the metal-ion measurements

Micrograms per liter (µg/l) corresponds directly to nanograms per milliliter (ng/ml) since µg/L = 1000 ng/1000 mL=ng/mL

Micrograms per liter (µg/l) also corresponds directly to parts per billion (ppb), which describes mass fraction, because one liter of blood/serum weighs approximately 1000 grams;

1 µg/L = 10^{-6} g / 1000 g = 10^{-9} = 1 ppb.

Nanomoles per liter (nmol/l) is based on the atomic weight of chromium (52.00 g/mol) and cobalt (58.93 g/mol), and can be calculated by multiplying for example units of µg/L by 19.23 (chromium) and 16.97 (cobalt). Nmol/l is used is the screening program issued by the Danish Orthopedic Society [74].

Papers I-IV

STUDY I

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Complications - Other

Higher Prevalence of Mixed or Solid Pseudotumors in Metal-on-Polyethylene Total Hip Arthroplasty Compared With Metal-on-Metal Total Hip Arthroplasty and Resurfacing Hip Arthroplasty

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ABSTRACT

Background: Pseudotumors are a common finding in metal-on-metal (MoM) total hip arthroplasty (THA) and resurfacing hip arthroplasty (RHA). However, information on pseudotumors in metal-on-polyethylene (MoP) THA is limited.
Methods: One hundred eleven patients with 148 hip articulations—30 MoM THA, 47 MoM RHA, and 71 MoP THA—participated in a cross-sectional study at mean 7.1 (range: 0.2-21.5) years postoperatively. Patients were evaluated with metal artifact reducing sequence magnetic resonance imaging, measurements of metal ions, clinical scores of Harris Hip Score, Oxford Hip Score, the Copenhagen Hip and Groin Outcome Score, and conventional radiographs.
Results: Pseudotumors were present in 13 of 30 (43%) MoM THA, 13 of 47 (28%) MoM RHA, and 29 of 71 (41%) MoP THA patients, which was a similar prevalence ($P = .10$). The prevalence of mixed or solid pseudotumors was significantly higher in patients with MoP THA (n = 10) compared to MoM THA (n = 3) and MoM THA (n = 0), ($P = .01$). Hips with a mixed or solid pseudotumor had significantly poorer scores of Harris Hip Score ($P = .01$) and OHS ($P = .002$) and higher metal ion levels of cobalt ($P = .0009$) compared to hips without a pseudotumor or with a cystic pseudotumor.
Conclusion: Pseudotumors have primarily been associated with MoM hip articulations, but we found a similar pseudotumor prevalence in MoP THA, which is the most common bearing worldwide. Mixed or solid pseudotumors were more often seen in MoP THA compared with MoM hip articulations, and patients with a mixed or solid pseudotumor had poorer clinical scores and higher metal ion levels than patients without a pseudotumor or with a cystic pseudotumor.

Background

In the recent years, concerns have been raised about unexpected and undesirable side effects associated with metal-on-metal (MoM) total hip arthroplasty (THA) and resurfacing hip arthroplasty (RHA). This has led to official safety alerts and market withdrawal of some MoM hip arthroplasty designs [1,2] and publication of different screening programs including clinical examination, plain radiographs, measurements of chromium and cobalt levels, cross-sectional imaging such as ultrasound, computer tomography, and magnetic resonance imaging (MRI) [3–5]. Center of attention has been the detection of adverse cystic, mixed, and solid soft-tissue reactions in relation to the hip joint termed "pseudotumors." Pseudotumors have been described in patients with high acetabular cup inclination angels [6], metal wear debris [7], high systemic levels of chromium and cobalt [6,8], and pain [9,10]. However, pseudotumors have also been found in asymptomatic patients with low systemic levels of chromium and cobalt and well-positioned acetabular cups [11–14]. Most

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Table 1
Descriptive Baseline Characteristics of Patients With MoM THA, MoM RHA, and MoP THA.

Articulation	MoM THA	MoM RHA	MoP THA	*P* Value
Number of patients	30	47	71	-
Sex (male/female)	22/8	29/18	30/41	.01[b]
Age at follow-up, mean (range)	55 (30-70)	58 (39-73)	66 (45-77)	.00[a]
Years since operation, mean (range)	7.3 (5.3-8.3)	5.6 (2.4-9.4)	8.1 (0.2-21.5)	.00[a]
Implant side, right/left	15/15	30/17	33/38	.17[b]
Inclination cup angle (°), mean (range)	44.4 (32.4-57.1)	42.9 (30.4-52.2)	43.9 (28.9-61.2)	.57[b]
Anteversion cup angle (°), mean (range)	22.1 (8.6-36.6)	16.9 (4.9-36.9)	23.9 (3.3-44.3)	.00[b]

MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.
[a] Kruskal-Wallis rank test.
[b] Analysis of variance.

pseudotumors have been described as cystic, whereas mixed or solid pseudotumors are less common [9,15,16]. In MoM THA, the pseudotumors have been reported with a prevalence ranging from 9% to 59% [8,16,17], and in MoM RHA, between 4% and 28% [10,18,19]. Some smaller studies and case reports have found pseudotumors in patients with other bearing types than MoM hip arthroplasties, such as MoP and ceramic-on-polyethylene (CoP) [20–24]. However, information on this topic is limited and insufficiently explored on larger study populations, and potentially identical cystic and solid soft-tissue reactions could be found on cross-sectional images with a similar prevalence. A deeper knowledge on this subject would be valuable when discussing the clinical significance of pseudotumors, when examining MoP THA patients with unexplained pain, and when designing future screening programs and recommendations for revision surgery of patients who undergo MoM hip arthroplasties. The primary aim of this cross-sectional case-control study was to evaluate the pseudotumor prevalence and the type detected by metal artifact reducing sequence (MARS) MRI in patients with MoM THA, MoM RHA, and MoP THA. The secondary aim was to compare measurements of chromium and cobalt serum metal ion levels, clinical outcome scores, and conventional radiographs between the 3 bearing types and between patients with and without a pseudotumor.

Patients and Methods

Between May 19, 2014 and July 17, 2014, 111 patients (50 females, 61 males) with a total of 148 THAs (67 females, 81 males) participated in a cross-sectional study at Aarhus University Hospital, Denmark, at mean 7.1 (range: 0.2-21.5) years after surgery. Patients were identified and recruited from 5 former local research projects on MoM and MoP hip arthroplasties. The overall inclusion criteria of these 5 studies were primary osteoarthritis of the hip, acceptable bone mineral density on preoperative dual-energy X-ray absorptiometry scan (T-score > 1), age between 18 and 65 years, and an informed written consent to participate. The overall exclusion criteria of the 5 studies were vascular or neuromuscular disease in the operated leg, fracture sequelae, avascular necrosis of the femoral head, women planning pregnancy, alcohol abuse, and daily intake of nonsteroidal anti-inflammatory drugs, K-vitamin antagonists, or loop diuretics. A more detailed description of the inclusion and exclusion criteria in each study can be found in the following publications [25–28]. Patients were divided into 3 groups: (1) MoM THA (n = 30), (2) MoM RHA (n = 47), and (3) MoP THA (n = 71). Descriptive baseline characteristics of all patients and arthroplasties are presented in Table 1 and Figure 1.

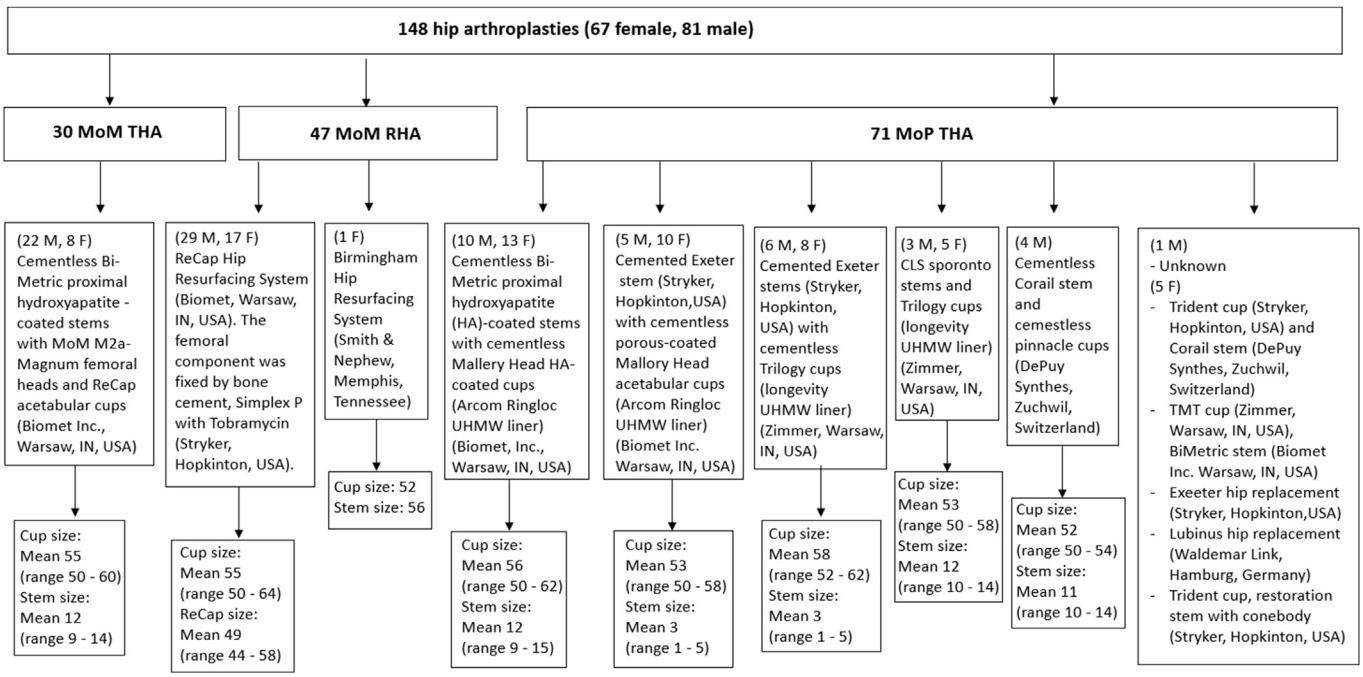

Fig. 1. Presentation of the different types and brands of hip articulations included in the study.

Table 2
Details of Magnetic Resonance Imaging Parameters Used in This Study.

Pulse Sequence Name	TE (ms)	TR (ms)	TI (ms)	ST (mm)/gap (mm)	FOV	Matrix Size	BW (Hz/Pixel)	Coil
Coronal T1W MARS	15	450-650	-	2.5/1	360 × 450	380 × 356	438.6	Sense Body 16ch
Coronal STIR MARS	40	4000-8000	130	3.5/1	400 × 454	364 × 320	434.7	Sense Body 16ch
Coronal T2W MARS	80	3000-7000	-	2.5/1	360 × 450	380 × 316	438.6	Sense Body 16ch
Axial T1W MARS	16	450-650	-	2.5/1.5	400 × 454	420 × 348	437.7	Sense Body 16ch
Axial STIR MARS	40	4000-8000	130	3.5/1.5	360 × 447	276 × 272	435.5	Sense Body 16ch

BW, bandwidth; ch, channel; FOV, field of view; MARS, metal artifact reducing sequence; ST, slice thickness (mm, millimeter); STIR, short tau inversion recovery; TE, time of echo (ms, millisecond); TI, time of inversion (ms, millisecond); TR, time of repetition (ms, millisecond); TSE, turbo spin echo; W, weighted.

All MoM and MoP THAs were inserted with a posterior surgical approach, and the MoM RHAs were inserted with either a posterior (ad modum Moore) [29] (n = 38) or an anterolateral (ad modum Watson) [29] (n = 9) surgical approach.

MARS MRI of the pelvis and proximal one-third of both femurs was performed using 2 identical 1.5 T Philips Ingenia MRI scanners (Koninklijke Philips Electronics NV, Eindhoven, the Netherlands). A protocol with 5 sequences was used (Table 2). During MRI scans, the patients were placed in standardized positions: supine, body parallel to the examination table, foot fixated with a band, and the first toes pointing toward each other. The MRI scans were assessed on a PACS workstation (Agfa Impax, Belgium, version 6.3.1.8000) and evaluated in consensus by 2 observers: 1, an experienced musculoskeletal radiologist (L.R.) and 1, a PhD student (M.H.). Both observers were blinded to patients' serum metal ions, clinical details, and radiographs. Pseudotumor findings were classified according to the Anderson grading system, which has the highest intraobserver and interobserver reliability of the currently used systems [30,31]. The Anderson grading system consists of categories A, B, and C; category A is equivalent to “normal or acceptable,” category B is equivalent to “infection,” and category C is divided into 3 subgroups: C1 indicates “mild MoM disease,” C2 indicates “moderate MoM disease,” and category C3 indicates “severe MoM disease”.

In addition to the Anderson grading system, pseudotumor type (fluid/mixed or solid), anatomical location (anterolateral or posterolateral to the greater trochanter or located in the iliopsoas bursa), and any communication to the hip joint was recorded. In contrast to the Anderson grading system, we did not classify patients with a C1 lesion and muscle atrophy or edema in any other muscles than the short external rotators as C2 because different surgical approaches have been shown to cause muscle atrophy in other muscle groups than the short external rotators [32]. Areas and lesions with high grade 2 signal on both T1 and short tau inversion recovery sequences were considered metal artifacts.

Standardized weight-bearing anteroposterior pelvic and lateral hip radiographs were obtained postoperatively and at mean 7.1 (range: 0.2-21.5) years after surgery. The following parameters were evaluated in consensus between 2 observers (S.S.J., M.H.H.): radiolucent lines >1 mm, signs of osteolysis in the DeLee Zones around the cup [33], and in the Gruen Zones in THA [34], or zones by Kishida et al in RHA [35] and heterotopic ossification [36]. Cup inclination and anteversion were measured digitally (PolyWare 3D Digital version 5.10; Draftware Developers, Conway, SC) [37,38]. Blood samples were collected according to the published guidelines [39], and to eliminate any form of metal contamination, analyses were performed using an inductively coupled plasma mass spectrometry at Vejle Hospital, Denmark.

All patients were examined according to the Harris Hip Score (HHS) (range 0-100) [40], and all patients completed the Oxford Hip Score (OHS) (range 0-48) [41] and the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire (range 0-100) [42]. Patients with bilateral hip articulations filled out 2 questionnaires (Table 3).

Statistical Analysis

All continuous variables were tested for normality (Shapiro-Wilk test). Analysis of variance was used to compare the parametric demographic variables between the 3 bearing types, and Kruskal-Wallis test was used to compare the nonparametric variables. The difference in pseudotumor prevalence, serum metal ions, and clinical outcome scores between the 3 bearing types and between patients with and without a pseudotumor was analyzed with the use of multiple regression, adjusting for risk factors of sex, age, and time since arthroplasty. Given the small number of patients in some subgroup analyses, Fisher exact test was used to compare some parameters. *P* values less than 0.05 were considered statistically significant for the hypothesis tests. All analyses

Table 3
Scores of the Harris Hip Score (HHS), the Oxford Hip Score (OHS), the Copenhagen Hip and Groin Outcome Score (HAGOS), and the Physical Activity Scale (PAS), and Measurements of Chromium and Cobalt Metal Ions Years Postoperative.

Articulation	MoM THA	MoM RHA	MoP THA	*P* Value[a]
HHS (30/47/71)	98.3 (89-100)	97.6 (76-100)	95.9 (76-100)	.08
OHS (29/47/66)	46.2 (36-48)	44.9 (31-48)	43.6 (10-48)	.39
HAGOS (27/45/68)				
Symptoms	92.9 (71-100)	90.1 (32-100)	85.1 (3.6-100)	.20
Pain	95.2 (75-100)	94.5 (65-100)	86.8 (0-100)	.06
Function in daily living	96.3 (65-100)	91.2 (20-100)	86.5 (0-100)	.18
Sport and recreation	85.9 (47-100)	83.8 (16-100)	64.5 (0-100)	.04
Physical activities	87 (25-100)	73.3 (0-100)	64.5 (0-100)	.05
Hip-related quality of life	85.6 (35-100)	83.3 (10-100)	78.5 (0-100)	.19
Chromium (μg/L)	3.01 (0.59-9.74)	2.26 (0.59-9.74)	0.98 (0.59-6.90)	.00
Cobalt (μg/L)	2.02 (0.59-5.45)	1.53 (0.59-5.96)	1.14 (0.59-5.90)	.03

Values are expressed as mean (range).
MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.
[a] Multiple regression (adjusting for risk factors of sex, age, and time since arthroplasty).

Table 4
Results of the MARS MRI Evaluations According to the Anderson Classification.

Articulation	MoM THA	MoM RHA	MoP THA	*P* Value
Total number of patients	30	47	71	-
Grade A "normal or acceptable"	17	34	42	.11[a]
Grade B "infection"	0	0	0	-
Grade C1 "mild MoM disease"	7	7	15	.38[a]
Fluid	6	7	12	.64[a]
Mixed or solid	1	0	3	.42[b]
Grade C2 "moderate MoM disease"	6	6	12	.28[a]
Fluid	4	6	7	.36[a]
Mixed or solid	2	0	5	.16[b]
Grade C3 "severe MoM disease"	0	0	2	.70[b]
Fluid	0	0	0	-
Mixed or solid	0	0	2	.70[b]
Total number of pseudotumors	13	13	29	.10[a]
Total number of fluid pseudotumors	10	13	19	.40[a]
Total number of mixed or solid pseudotumors	3	0	10	.01[b]

In addition to the Anderson classification, pseudotumors were split into fluid or mixed/solid appearance.
MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.
[a] Multiple regression (adjusting for risk factors of sex, age, and time since the arthroplasty).
[b] Fisher exact test.

were performed using Stata software, version 13 (StataCorp LP, College Station, TX).

Results

MARS MRI evaluations showed that pseudotumors or "MoM disease" were present in 13 of 30 (43%) MoM THA, in 13 of 47 (28%) MoM RHA, and in 29 of 71 hips (41%) MoP THA. In total, pseudotumors were seen in 55 of 148 (37%) hip articulations. Mixed or solid pseudotumors were found in 3 MoM THA, in 0 MoM RHA, and in 10 MoP THA, and this difference was statistically significant ($P = .01$). Results of the MRI evaluations according to the Anderson grading system are shown in Table 4, and a detailed description on the pseudotumors observed in each group are shown in Table 5 and Figures 2-6.

Table 5
Detailed Presentation of Fluid-Filled and Mixed or Solid Pseudotumors in Patients With MoM THA, MoM RHA, and MoP THA.

Articulation	MoM THA	MoM RHA	MoP THA
Total number of hips	30	47	71
Total number of fluid pseudotumors	10	13	19
Sex (male/female)	8/2	11/2	9/10
Location (AL, PL, ILB)	0/10/0	2/11/0	0/8/11
Communication (yes/no or not applicable)	4/6	8/5	5/14
Width, mean (range) (mm)	40.5 (10-77)	46 (12-100)	46 (16-82)
Depth, mean (range) (mm)	19.5 (4-56)	31 (5-72)	19 (3-60)
Height, mean (range) (mm)	18 (5-34)	17 (4-33)	19 (5-41)
Total number of mixed or solid pseudotumors	3	0	10
Sex (male/female)	2/1	-	5/5
Location (AL, PL, ILB)	0/1/2	-	0/5/5
Communication (yes/no or not applicable)	2/1	-	5/5
Width, mean (range) (mm)	68 (44-101)	-	76 (41-202)
Depth, mean (range) (mm)	44 (37-48)	-	51 (16-120)
Height, mean (range) (mm)	24 (18-32)	-	33 (13-111)

Location: the anatomical location of the pseudotumor: AL, anterolateral of the greater trochanter, PL, posterolateral of the greater trochanter, and ILB, located in the Iliopsoas bursa.
MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.

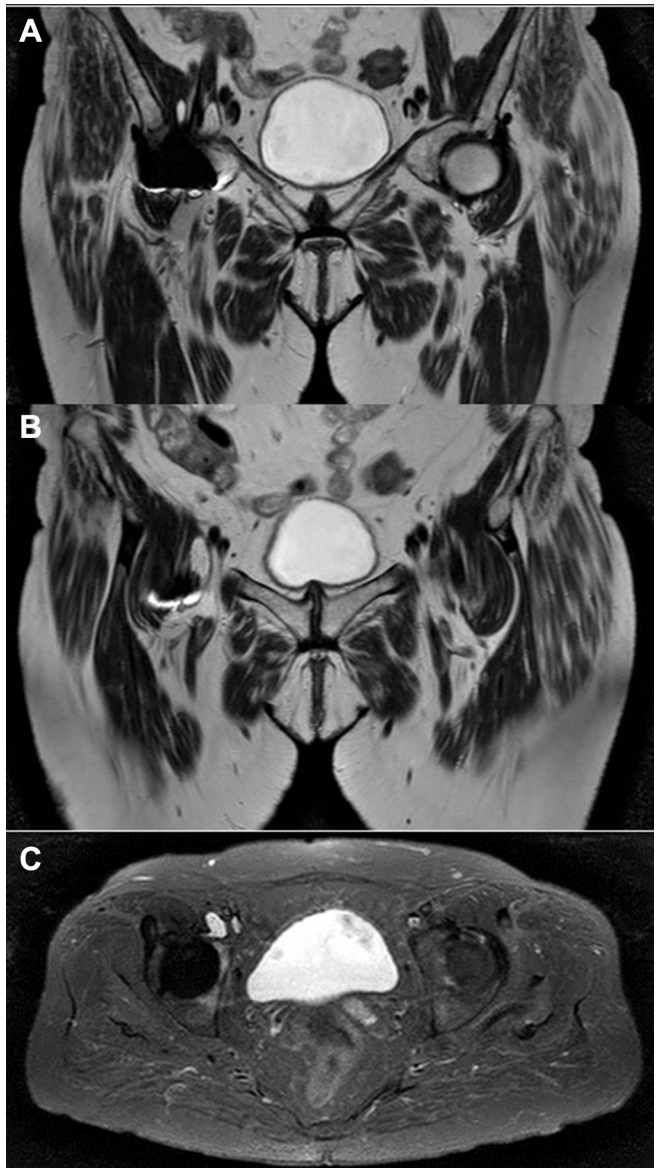

Fig. 2. Coronal (A and B) and axial (C) MARS MRIs of a 68-year-old female with a right side MoP THA (Mallory Head, BiMetric Stem) and a pseudotumor located in the iliopsoas bursa. Her serum metal ion levels of chromium and cobalt were 2.7 μg/L and 4.1 μg/L, respectively.

Based on evaluation of the conventional radiographs in the entire study population, osteolysis was seen around the cup in 0 MoM THA, in 3 MoM RHA (all in DeLee Zone I), and in 7 MoP THA (6 in DeLee Zone I and 3 in DeLee Zone I and II). Radiolucent lines around the cup were found in 2 MoM THAs (in DeLee Zone I), in 0 MoM RHA, and in 8 MoP THA (3 in DeLee Zone I and 3 in DeLee Zone I and II). For the stems, no osteolyses were seen in MoM THA or MoM RHA, but 7 MoP THA had osteolyses (4 in Gruen Zone I and 3 in Gruen Zone I and VII). Radiolucent lines around the stem were observed in 0 MoM THA, in 7 MoM RHA (all distal around the tip of the stem), and in 2 MoP THA (1 in Gruen Zone I and 1 in Gruen Zone VII).

Chromium and cobalt serum metal ion levels and clinical outcome scores of HAGOS "sport and recreation" were statistically significantly different between the 3 bearing types ($P = .00$, $P = .03$,

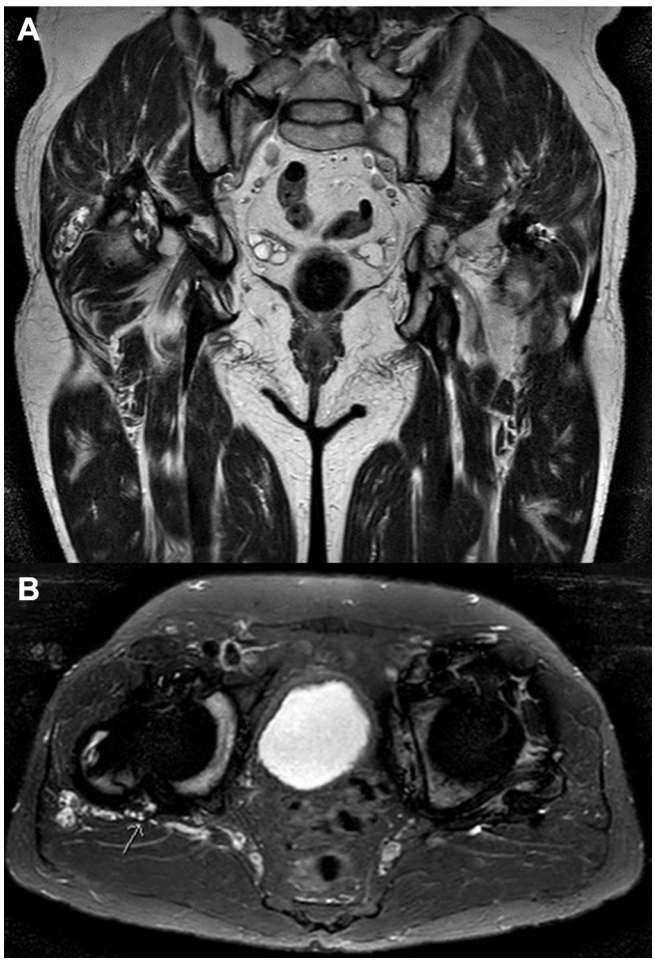

Fig. 3. Coronal (A) and axial (B) MARS MRIs of a 64-year-old male with bilateral MoP THA (right side: Mallory Head, Exeeter Stem, and left side: Pinnacle cup, Corail stem). The pseudotumor on the right side is a mixed type and on the left side is a cystic type.

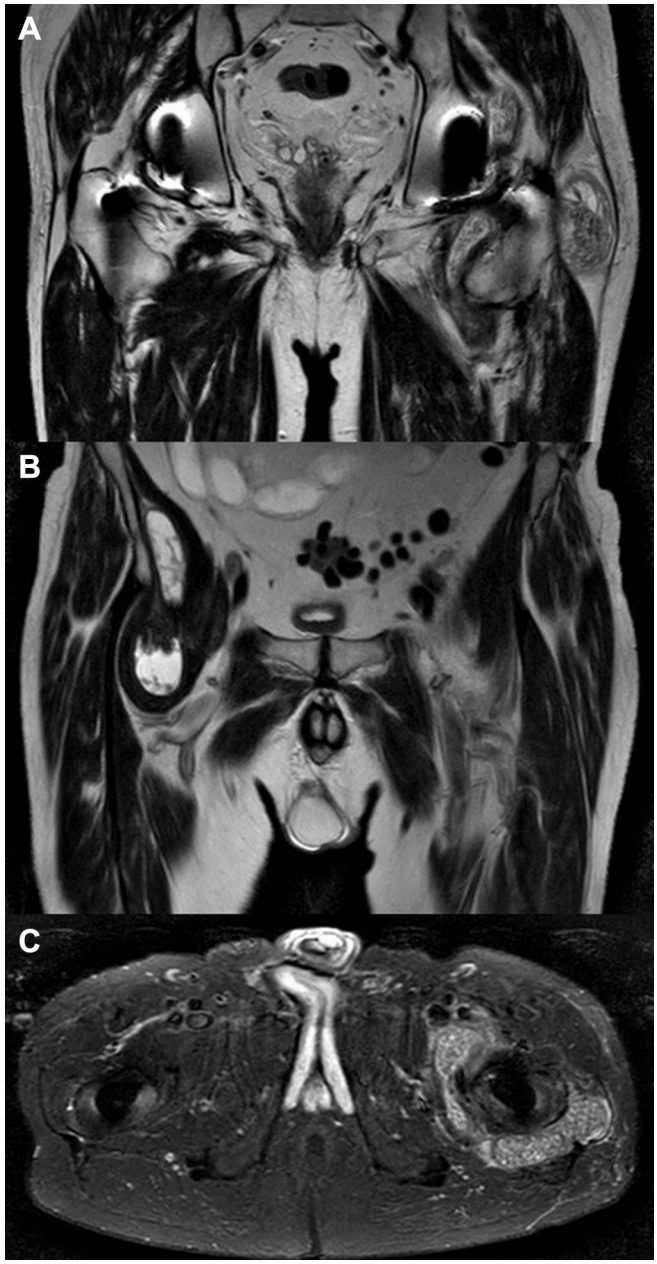

Fig. 4. Coronal (A and B) and axial (C) MARS MRIs of a 71-year-old male with bilateral MoP THA (right + left side: Mallory Head, BiMetric stem). Both pseudotumors are of mixed type.

and $P = .04$; (Table 3), but otherwise no differences in clinical outcome scores were found between the 3 groups ($P \geq .05$) (Table 3).

Hips with a pseudotumor had similar serum metal ion levels of chromium and cobalt and clinical outcome scores of HHS, OHS, and HAGOS as hips without a pseudotumor ($P \geq .21$). But, hips with a mixed or solid pseudotumor had significantly higher serum metal ion levels of cobalt; mean 2.45 (range: 0.59-5.60) μg/L vs mean 1.34 (range: 0.59-5.9) μg/L in hips without a mixed or solid pseudotumor ($P = .00$). Serum metal ion levels of chromium were similar; mean 2.24 (0.59-9.74) μg/L in hips with a mixed or solid pseudotumor and mean 1.75 (range: 0.59-9.74) in hips without a mixed or solid pseudotumor ($P = .09$). Significantly poorer clinical outcome scores of HHS of mean 93.6 (range: 76-100) and OHS of mean 38 (range: 10-48) were found in hips with a mixed or solid pseudotumor compared to HHS of mean 97 (range 78-100) and OHS of mean 45 (30-48) in hips without a mixed or solid pseudotumor ($P = .01$ and $P = .00$).

Discussion

To our knowledge, this is the first study to screen a larger population of MoM THA, MoM RHA, and MoP THA with MARS MRI to investigate pseudotumor prevalence with different types of hip articulations. Interestingly, our results showed that pseudotumors were found not only in hips with MoM hip articulations but also in hips with MoP THA—and even with a similar pseudotumor prevalence. Furthermore, the number of mixed or solid pseudotumors was significantly higher in hips with MoP THA compared to hips with MoM hip articulations. This is important information for the clinician who should be aware that unexplained pain after MoP THA might be related to a mixed or solid pseudotumor.

We found that cystic pseudotumors were more common (43% in MoM THA, 28% in MoM RHA, and 41% in MoP THA) compared to mixed or solid pseudotumors (10% in MoM THA, 0% in MoM RHA, and 14% in MoP THA). The prevalence of cystic pseudotumors in our study is in accordance with that in the study Nishii et al who investigated 64 MoM hip articulations (MoM THA + MoM RHA) and

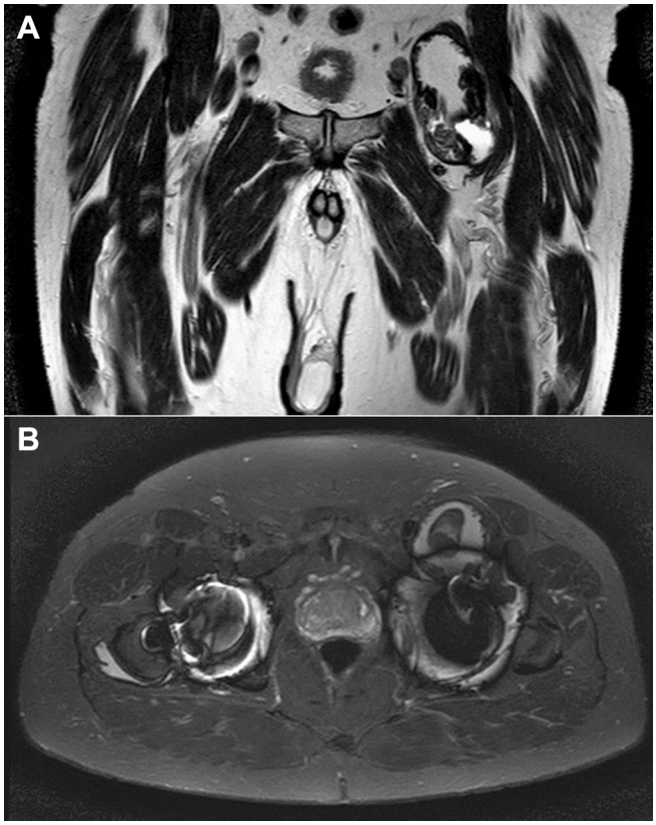

Fig. 5. Coronal (A) and axial (B) MARS MRIs of a 71-year-old male with bilateral MoP THA (right + left side: Trilogy cup, BiMetric stem). Both pseudotumors are of mixed type. His serum metal ion levels of chromium and cobalt were 3.9 μg/L and 5.9 μg/L, respectively.

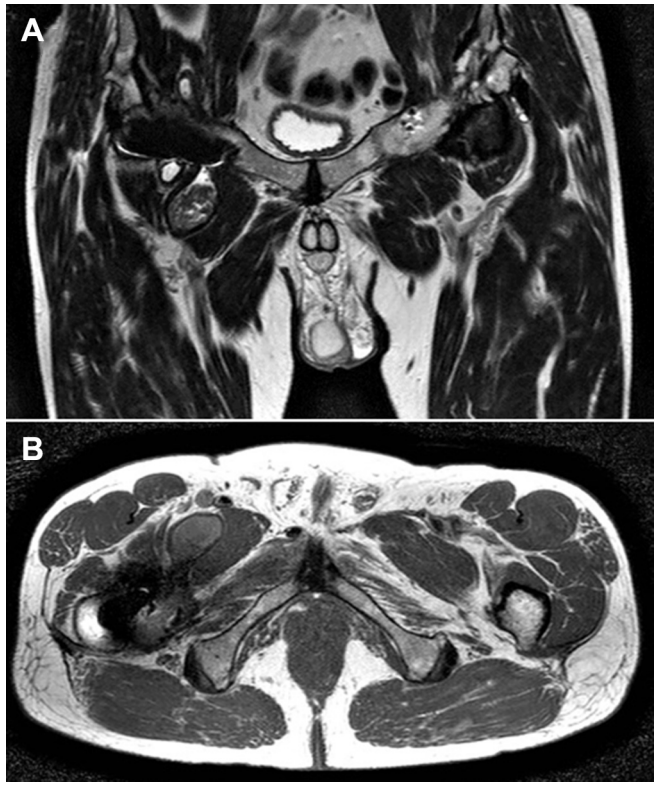

Fig. 6. Coronal (A) and axial (B) MARS MRIs of a 54-year-old male with right side MoM THA (M2a-Magnum, BiMetric Stem) and a mixed pseudotumor located in the iliopsoas bursa. His serum metal ion levels of chromium and cobalt were 1.4 μg/L and 2.8 μg/L, respectively.

67 highly crosslinked polyethylene THA with MRI and ultrasound at mean 7.3 years postoperatively and found cystic pseudotumors in 33% MoM hip articulations and in 37% highly crosslinked polyethylene THA, but only a few mixed or solid pseudotumors were seen: 3% in MoM hip articulations and 0% in highly crosslinked polyethylene THA [15]. At mean 4.6 years postoperatively, Bisseling et al evaluated the pseudotumor prevalence in 25 MoM THA, 35 MoM RHA, and 33 CoP THA and found pseudotumors in 4% MoM THA, 17% MoM RHA, and 18% CoP THA, with solid pseudotumors exclusively seen in MoM RHA [20]. It is difficult to give an exact explanation for the different prevalence of cystic, mixed, or solid pseudotumors found in these studies compared with our study. It is possible that patients, surgery, and implant-related factors might play a role. Although, several attempts have been made to define the "true" pseudotumor prevalence, no consensus has been reached, and it seems that patients, surgery, and implant-related factors might play a role. Various definitions of pseudotumors and pseudotumor grading systems have been published [9,11,13,31,43], which makes it difficult to compare results between different studies directly. We used the Anderson grading system as it has proven to be highly reliable compared to the classifications by Hart/Matthies et al 2012 and Hauptfleisch et al [30]. We found that advantages of the Anderson grading system were the inclusion of a grade A "normal or acceptable," the detailed description of each pseudotumor grade, and that the grading system is based on objective measures such as pseudotumor size rather than MRI signal appearance, which hardly can be objectively assessed by the radiologist.

Mean serum metal ion levels of chromium and cobalt were significantly different between the 3 bearing types; the highest levels were found in MoM THA, lower levels in MoM RHA, and the lowest levels were found in MoP THA. Elevated serum metal ion levels in MoM THA compared to MoM RHA have previously been reported [44,45], and it appears that corrosion at the junction between the femoral neck and the adapter sleeve plays a significant role in the generation of metal ion wear debris [46–48]. A similar mechanism has been described in MoP THA leading to elevated metal ion levels and soft-tissue reactions with pseudotumors that are identical on MR images to those seen in MoM hip articulations [22,49–51].

In accordance with the previous studies, we found that mixed or solid pseudotumors were less common (9%) compared to cystic pseudotumors (28%) and that the mixed or solid pseudotumors were more often located in the iliopsoas bursa, whereas the cystic pseudotumors were typically seen posterolateral to the hip joint [9,15,16,52,53]. The clinical significance and relevance of pseudotumors remain unclear, and because some fluid collection seems to be normal after any THA procedure, it is currently debated whether or not all periprosthetic lesions should be identified as "real" pseudotumors because a large number of cystic pseudotumors have been found among asymptomatic patients. Hart et al [9] suggested that less clinical importance should be given to cystic pseudotumors but that concerns instead should be focused on solid pseudotumors. We found significantly poorer clinical outcome scores measured with the HHS and OHS and higher serum metal ion levels of cobalt in hips diagnosed with a mixed or solid pseudotumor (3 MoM THA and 10 MoP THA), which supports the suggestion by Hart et al. Likewise, former studies on both MoM THA and MoP THA have reported associations between pain and solid pseudotumors [8,43,49,54] and higher serum metal ion levels of cobalt in symptomatic patients [45,49,55]. Owing to this, and regardless of the bearing type, the clinician should consider image

diagnostic evaluation for mixed or solid pseudotumors and measurement of serum metal ion levels.

We acknowledge the limitations of our study. First, the 3 groups were unmatched and, by coincidence, significantly different in age, gender, and time since operation. However, because we adjusted for these variables statistically, this could hardly have biased our results.

Second, no histological matching of aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) scores with the imaging findings was performed because we did not do biopsy of the lesions. The combination of MARS MRI and histology would probably have given a more precise description of the pseudotumor type and might have indicated the causality between pseudotumor and bearing types. However, taking a biopsy involves risk of infection, which could lead to revision surgery.

Third, MARS MRI scans, blood samples, and clinical outcome scores were collected at one single timepoint. Studies with additional follow-ups have demonstrated that pseudotumors are dynamic [56], that initially asymptomatic pseudotumors often become symptomatic [57], and that metal ion levels of chromium and cobalt fluctuate [58]; hence, our results might just represent a snapshot of the wider picture and does not provide information on patients who succumbed to future revision surgery.

In conclusion, pseudotumors were present in 13 of 30 (43%) MoM THA, 13 of 47 (27%) MoM RHA, and 29 of 71 (41%) MoP THA, which shows a statistically similar prevalence. Surprisingly, the prevalence of mixed or solid pseudotumors was significantly higher in patients with MoP THA hips with a mixed or solid pseudotumor and the patients had significantly poorer clinical outcome scores of HHS and OHS and higher serum metal ion levels of cobalt compared to hips without a pseudotumor or with a cystic pseudotumor. The use of MoM hip articulations is currently limited, but since MoP THA is the most commonly implanted THA bearing worldwide, the clinician who investigates patients with unexplained pain after MoP THA should remember the possibility of a mixed or solid pseudotumor.

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STUDY II

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Original Article

Physical Activity Is Associated With the Level of Chromium but Not With Changes in Pseudotumor Size in Patients With Metal-on-Metal Hip Arthroplasty

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ABSTRACT

Background: Metal-on-metal (MoM) total hip arthroplasty (THA) and resurfacing hip arthroplasty (RHA) were previously considered an excellent option for young and physically active patients. However, the relationship between MoM THA/RHA patients' daily physical activity (PA), metal ion measurements of chromium and cobalt, and pseudotumor dynamic is insufficiently explored.
Methods: One hundred eleven patients with 148 hip articulations, 77 MoM THA/RHA and 71 MoP THA, participated in a prospective cohort study, with 5 cross-sectional analyses during a 1-year follow-up. Baseline follow-up was at mean 7.1 (range: 0.2-21.5) years postoperative. At baseline and every 3 months thereafter, patients' daily PA was monitored during a 2-week period using a triaxial accelerometer, and next metal artifact reducing sequence magnetic resonance imaging scans, metal ion measurements of chromium and cobalt, and the Copenhagen Hip and Groin Outcome Score questionnaire were completed.
Results: We found a statistically significant relationship between daily PA and metal ion measurements of chromium at all follow-ups in MoM THA/RHA patients ($P \leq .03$) but not in MoP THA patients ($P > .35$). Patients' daily PA was not related to changes in pseudotumor size at any follow-up ($P > .30$). Ten of 26 (38%) pseudotumors in MoM THA/RHA and 8 of 29 (28%) pseudotumors in MoP THA changed classification according to the Anderson grading. No pseudotumors transformed in appearance or changed anatomical location.
Conclusion: The daily PA of MoM THA/RHA patients is associated with metal ion measurements of chromium but not with changes in pseudotumor size. This is new and important knowledge, which may be useful for hip surgeons in recommendation and monitoration of the consequences of PA in active patients with MoM THA/RHA.

The term pseudotumor was originally used to describe noninfectious, nonmalignant, cystic, solid, or mixed periprosthetic soft-tissue masses associated with metal-on-metal (MoM) total hip arthroplasty (THA) and resurfacing hip arthroplasty (RHA) [1]. Pseudotumors have been observed in patients with increased metal wear debris [2], leading to high systemic levels of chromium and cobalt [3,4]. However, they have also been found in patients with low systemic levels of chromium and cobalt [5,6]. Recently, pseudotumors were also identified in patients with metal-on-polyethylene (MoP) and ceramic-on-polyethylene hip arthroplasty bearings [7–11]. In MoP THA polyethylene wear particles and subsequent osteolysis have been associated with patients' level of physical activity (PA) rather than with the time in situ [12,13]. Although a similar association have been hypothesized in MoM THA/RHA [14,15], the influence of PA on metal wear particles is

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insufficiently explored, and the few available publications have controversial results. Khan et al [16] reported an increase in cobalt (13%) and chromium (11%) levels in 15 patients with MoM hip articulations after a 1-hour treadmill run, and some hip simulator studies measured increased wear rates during imitated jogging motions [17,18]. In contrast, Heisel et al [19] found no difference in chromium and cobalt levels in 7 patients who participated in a high activity week and a low activity week. Short-term longitudinal studies on MoM THA/RHA have shown changes in pseudotumor size/type between 2 cross-sectional images [20–24], and metal ion levels of chromium and cobalt have also been reported to fluctuate [25,26]. Until now, factors leading to these alterations over time have only been sparsely investigated, and whether similar dynamics occurs in MoP THA is unclear. A deeper understanding of the relationship between patient activity, metal ion measurements, and pseudotumor dynamics would be valuable for clinicians when advising active patients with MoM THA/RHA about the effects of PA on metal ion measurements and pseudotumor dynamics. Thus, the primary aim of this longitudinal study was to investigate (1) the relationship between patients' daily PA and metal ion measurements of chromium and cobalt, (2) the relationship between patients' daily PA and changes in pseudotumor size, and (3) changes in pseudotumor type over time.

Materials and Methods

Between May 19, 2014 and July 17, 2014, 111 patients (50 females, 61 males) with a total of 148 THAs (67 females, 81 males) participated in a prospective cohort study at Aarhus University Hospital, Denmark, with baseline follow-up at mean 7.1 (range: 0.2-21.5) years after surgery. Patients were identified and recruited from 5 former local research projects on MoM and MoP hip arthroplasties. The overall inclusion criteria of these 5 studies were primary osteoarthritis of the hip, acceptable bone mineral density on preoperative dual-energy x-ray absorptiometry scan (T-score > 1), age between 18 and 65 years, and an informed written consent to participate. The overall exclusion criteria of the 5 studies were vascular or neuromuscular disease in the operated leg, fracture sequelae, avascular necrosis of the femoral head, women planning pregnancy, alcohol abuse and daily intake of nonsteroidal anti-inflammatory drugs, K-vitamin antagonists, or loop diuretics. A more detailed description of the inclusion and exclusion criteria in each study can be found in the following publications [27–30]. Patients were divided into 2 groups: (1) MoM hip articulations (n = 77) (MoM THA [n = 30] and MoM RHA [n = 47]) and (2) MoP THA (n = 71). Descriptive characteristics of all patients and arthroplasties are presented in Table 1 and Figure 1.

At baseline, and for every 3 months thereafter, patients' daily PA was monitored during a 2-week period using a triaxial accelerometer, and next metal artifact reducing sequence (MARS) magnetic resonance imaging (MRI) scans, metal ion measurements of chromium and cobalt, and the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire were completed. Conventional radiographs and questionnaires of Harris Hip Score and Oxford Hip Score were obtained at baseline.

All MoM and MoP THAs were inserted with a posterior surgical approach, the MoM RHAs were inserted with either a posterior (ad modum Moore) [31] (n = 38) or an anterolateral (ad modum Watson) [31] (n = 9) surgical approach. All patients gave a written informed consent to participate in this study, and all examinations were performed in accordance with the Helsinki Declaration II. The study was approved by the Central Denmark Region Committee on Biomedical Research Ethics (03.17.2014; jr. nr.: 1-10-72-65-14) and by the Danish Data Protection Agency (02.17.2014; jr. nr.: 2007-58-0010, Trial nr.: 1-16-02-87-14).

Table 1
Descriptive Baseline Characteristics, Outcome Scores of Questionnaires, Activity, and Chromium and Cobalt Measurements at All Follow-Ups in Patients With Metal-on-Metal (MoM) Total Hip Arthroplasty (THA)/Resurfacing Hip Arthroplasty (RHA) and Metal-on-Polyethylene (MoP) THA.

Articulation	MoM THA/RHA	MoP THA	*P* Value
Patients and implants			
Number of patients	77	71	-
Sex (male/female)	51/26	30/21	.01[a]
Age at follow-up	59.1 (51.3-64.4)	68.3 (60.9-69.9)	.00[b]
Years since operation	7.1 (4.6-7.6)	8.9 (4.7-10.7)	.00[b]
Implant side, right/left	45/32	32/39	.10[a]
Inclination cup angle (°)	43.5 (42.2-44.8)	43.8 (42.2-45.5)	.74[a]
Anteversion cup angle (°)	18.7 (17.0-20.5)	23.9 (21.4-26.5)	.00[a]
Questionnaires			
HHS at baseline	100 (96-100)	98 (94-100)	.03[b]
OHS at baseline	47 (45-48)	46 (43-48)	.23[b]
HAGOS baseline[c]	95 (77.5-100)	85 (72.5-100)	.14[b]
HAGOS 3 mo[c]	95 (67.5-100)	90 (70-100)	.61[b]
HAGOS 6 mo[c]	92.5 (75-100)	90 (80-100)	.90[b]
HAGOS 9 mo[c]	95 (75-100)	90 (77.5-100)	.78[b]
HAGOS 12 mo[c]	90 (75-100)	85 (75-100)	.37[b]
Physical activity level[d] (%)			
3 mo	12.66 (11.62-13.69)	13.43 (12.13-14.72)	.35[a]
6 mo	11.82 (10.81-12.83)	12.33 (10.50-14.17)	.61[a]
9 mo	11.12 (10.19-12.05)	10.94 (9.35-12.53)	.84[a]
12 mo	13.15 (12.20-14.09)	13.34 (11.66-15.03)	.83[a]

HAGOS, Copenhagen Hip and Groin Outcome Score; HHS, Harris Hip Score; OHS, Oxford Hip Score.
[a] Analysis of variance. Values are given as mean (95% confidence interval).
[b] Two-sample Wilcoxon rank-sum (Mann-Whitney) test. Values are given as median (interquartile range).
[c] Clinical outcome scores of HAGOS subscale "hip-related quality of life".
[d] Physical activity level includes the mean time spent walking, bicycling, and high-impact activities (%) during total daily wear time.

MARS MRI of the pelvis and proximal one-third of both femurs was performed using 2 identical 1.5 T Philips Ingenia MRI scanners (Koninklijke Philips Electronics NV, Eindhoven, the Netherlands). A protocol with 5 sequences was used (Table 2). During MRI scans, patients were placed in standardized positions; supine with the body parallel with the examination table, internally rotated hips and feet fixated with a band. The MRI scans were assessed on a PACS workstation (Agfa Impax, Belgium, version 6.3.1.8000) and evaluated in consensus by 2 observers; one experienced musculoskeletal radiologist (LR) and one PhD student (MHH). Both observers were blinded to patients' metal ion measurements, clinical details, and radiographs.

Pseudotumor findings were classified according to the Anderson grading system, which has the highest intraobserver and interobserver reliability of the currently used systems [32,33]. The Anderson grading system consists of category A, B, and C; category A is equivalent to "normal or acceptable", category B is equivalent to "infection", and category C is divided into 3 subgroups; C1 indicates "mild MoM disease", C2 indicates "moderate MoM disease", and category C3 indicates "severe MoM disease".

In addition to the Anderson grading system, the pseudotumor type (fluid/mixed or solid) and anatomical location (anterior-lateral or posterior-lateral to the greater trochanter or located to the iliopsoas bursa) were noted. In contrast to the Anderson grading system, patients with a C1 lesion and muscle atrophy or edema in any other muscles than the short external rotators were not classified as C2 because different surgical approaches have been shown to cause muscle atrophy in other muscle groups than the short external rotators [34].

A commercially available, accelerometer (Axivity, Newcastle upon Tyne, England) which determines the acceleration of body parts in 3 planes was used to measure and classify PA in the patients. The accelerometer was set to monitor at 100 Hz and ±8 g.

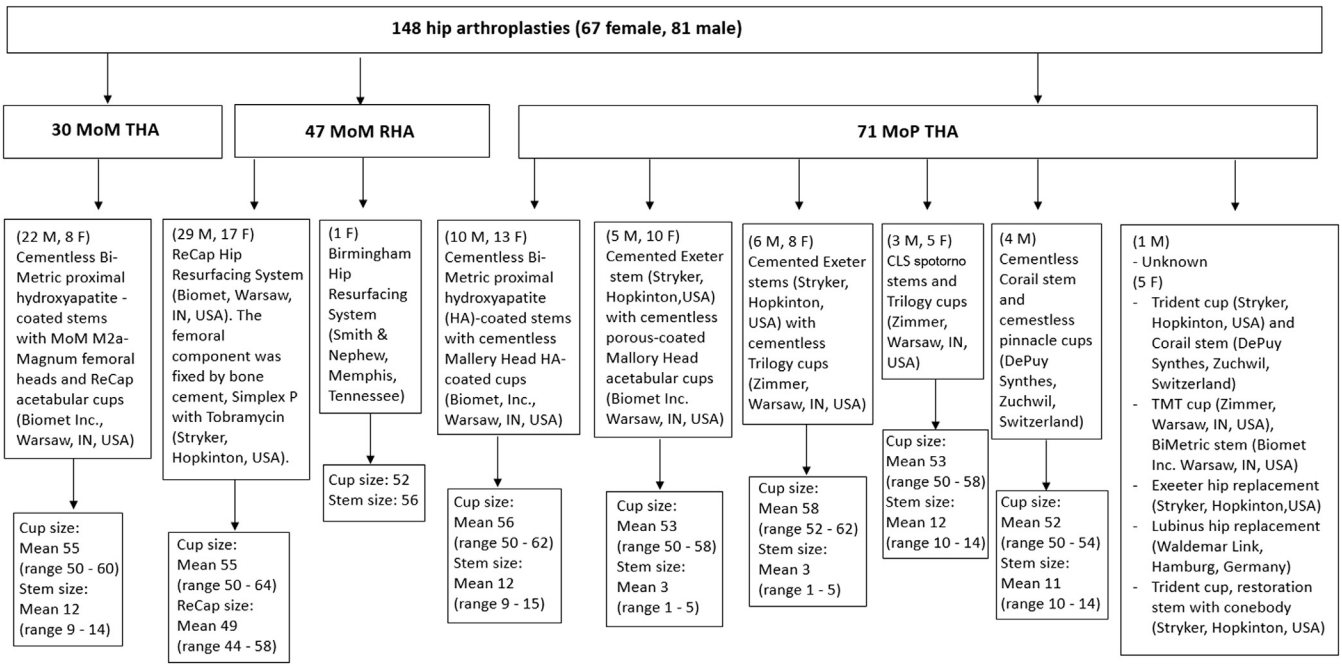

Fig. 1. Presentation of the different types and brands of hip articulations included in the study at baseline.

The patients were instructed to mount the accelerometer on the lateral side on the right thigh with fixomull tape (3M) and instructed to wear it during wake hours. Three-five days of activity monitoring have been proven sufficient to reflect an individual's usual or habitual level of PA [35,36], and accelerometers in the present study were worn for mean 15 (range: 10-21) days, with a minimum of 8 hours wear time per day. One person analyzed all accelerometer-based activity data. The raw acceleration signal was analyzed using the inclinometer function of the accelerometer and algorithm-based peak detection methods in Matlab (MATLAB R2010a, the Mathworks Inc., Natick, MA), based on previously published principles [37,38]. Briefly, calibration of the accelerometer's orientation was performed within a period of level walking, which was manually selected. Within this walking period, the average magnitudes of the 3 acceleration vectors and the gait cycle frequency (GCF; Hz) were derived to allow further differentiation

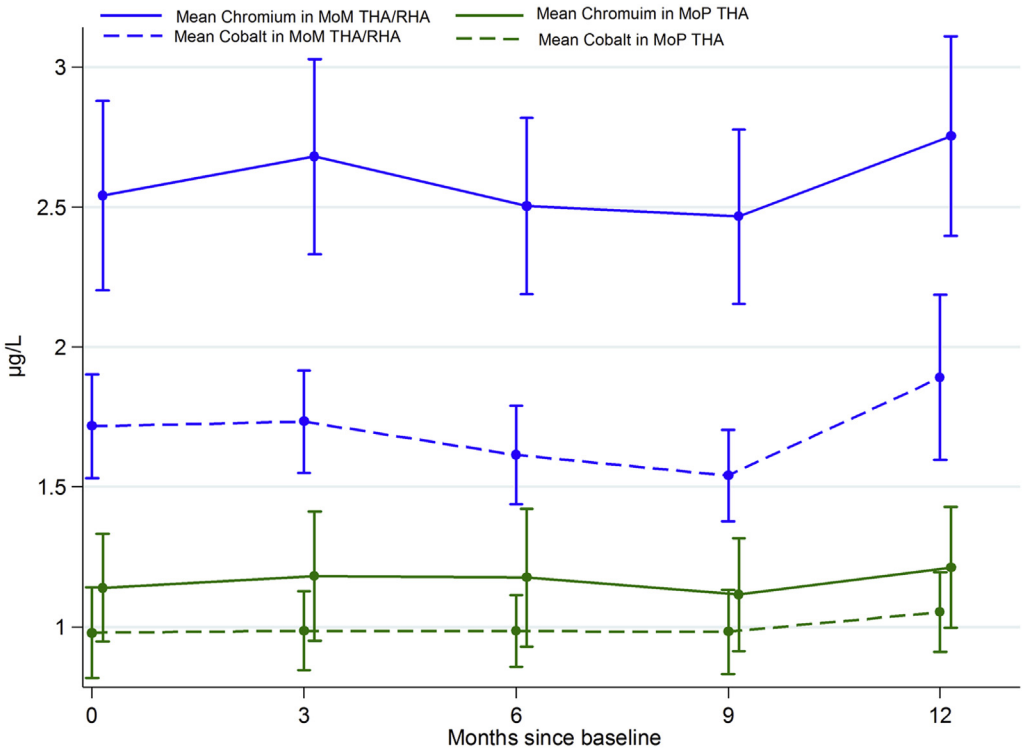

Fig. 2. Figure showing the mean serum metal ion levels of chromium and cobalt in MoM THA/RHA patients and MoP THA patient at baseline, 3, 6, 9, and 12 months of follow-up.

Table 2
Details of Magnetic Resonance Imaging Parameters Used in This Study.

Pulse Sequence Name	TE (ms)	TR (ms)	TI (ms)	ST (mm)/Gab (mm)	FOV	Matrix Size	BW (Hz/Pixel)	Coil
Coronal T1W MARS	15	450-650	-	2.5/1	360 × 450	380 × 356	438.6	Sense Body 16ch
Coronal STIR MARS	40	4000-8000	130	3.5/1	400 × 454	364 × 320	434.7	Sense Body 16ch
Coronal T2W MARS	80	3000-7000	-	2.5/1	360 × 450	380 × 316	438.6	Sense Body 16ch
Axial T1W MARS	16	450-650	-	2.5/1.5	400 × 454	420 × 348	437.7	Sense Body 16ch
Axial STIR MARS	40	4000-8000	130	3.5/1.5	360 × 447	276 × 272	435.5	Sense Body 16ch

BW, bandwidth; FOV, field of view; ST, slice thickness (mm, millimeter); STIR, short tau inversion recovery; TE, time of echo (ms, millisecond); TR, time of repetition (ms, millisecond); TSE, turbo spin echo; TI, time of inversion (ms, millisecond); W, weighted.

between activities. Differentiation between standing periods and sitting periods was based on the direction of the gravitation vector. Walking was differentiated from other upright activities (all classified as standing) by application of heuristic rules to the GCF. A walking period was classified when at least 5 consecutive heel strike peaks are detected, with 0.6 Hz and 5 min walking bouts. More detailed information of the accelerometer and its clinical application have been described in a previous study [39].

Standardized weight-bearing anteroposterior pelvic and lateral hip radiographs were obtained at baseline. The following parameters were evaluated in consensus between 2 observers (S.S.J., M.H.H.): radiolucent lines >1 mm, signs of osteolysis in the DeLee Zones around the cup [40], and in the Gruen Zones in THA [41], or zones by Kishida Y et al [42] in RHA, and heterotopic ossification [43]. Cup inclination and anteversion were measured digitally (PolyWare 3D Digital version 5.10; Draftware Developers, Conway, SC) [44,45].

Blood samples were collected according to published guidelines [46]. To eliminate any form of metal contamination, analyses were completed using an inductively coupled plasma mass spectrometry at Vejle Regional Hospital, Denmark. All patients had normal renal function as determined by serum creatinine levels and estimated glomerular filtration rate. All patients were examined according to the Harris Hip Score (range 0-100) (Harris, 1969), and all patients completed the Oxford Hip Score (range 0-48) [47] and the HAGOS questionnaire (range 0-100) [48]. Patients with bilateral hip articulations filled out 2 questionnaires.

Statistical Analysis

Data were checked for normality by Q plot and histograms. Analysis of variance was used to compare the parametric demographic variables between the 2 groups and the 2-sample Wilcoxon rank-sum test (Mann-Whitney) was used to compare the nonparametric variables. Multiple regression analysis showed no difference between MoM THA and RHA regarding the influence of activity level, cadence, and sex on the levels of chromium and cobalt at any follow-up ($P > .54$). We, therefore, chose to gather MoM THA and MoM RHA patients in one group and thereby achieving more statistical power in the analysis.

Multiple regression analysis was performed to assess the effect of patients' daily PA on metal ion measurements of chromium and cobalt and on pseudotumor size at all follow-ups. We adjusted for sex, inclination angels, and time since surgery because these variables have been shown to affect serum metal ion levels of chromium and cobalt and pseudotumor prevalence [49–52]. P values less than .05 were considered statistically significant for the

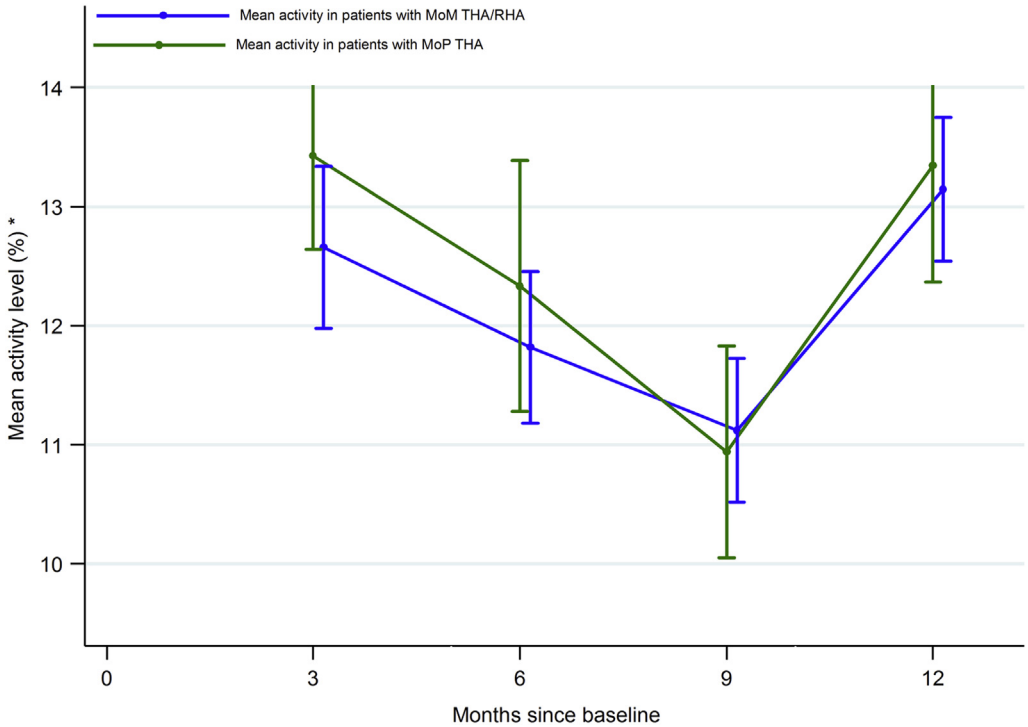

Fig. 3. Figure showing the mean daily physical activity level (*defined as combined walking, bicycling, and high-impact activity in % of total daily wear time) in MoM THA/RHA patients and MoP THA patient at the 3, 6, 9, and 12 months of follow-up.

Table 3
Multiple Regression Analysis on the Effect of All Activity (Defined as the Sum of Walking, Cycling, and High-Activity Measurements) on Measurements of Chromium and Cobalt in Patients With MoM THA/RHA and MoP THA at 3, 6, 9, 12, and 24 Mo.

Articulation	MoM THA/RHA				MoP THA			
	Adj. R^2	β	95% CI	*P* Value	Adj. R^2	β	95% CI	*P* Value
Activity and chromium								
3 mo (66/56)	0.25	0.13	0.01 to 0.24	.03	−0.05	−0.02	−1.08 to 0.03	.35
6 mo (61/48)	0.28	0.17	0.0 to 0.28	.006	−0.08	0.01	−0.40 to 0.04	.96
9 mo (65/49)	0.29	0.18	0.0 to 0.29	.003	−0.08	0.01	−0.50 to 0.06	.83
12 mo (63/51)	0.23	0.17	0.0 to 0.30	.01	−0.06	0.01	−0.03 to 0.06	.53
Activity and cobalt								
3 mo (66/56)	0.12	0.05	−0.01 to 0.12	.12	0.15	−0.03	−0.11 to 0.41	.39
6 mo (61/48)	0.16	0.07	−0.01 to 0.14	.04	0.11	0.01	−0.06 to 0.08	.81
9 mo (65/49)	0.16	0.06	−0.01 to 0.13	.08	0.09	0.02	−0.05 to 0.08	.62
12 mo (63/51)	0.11	0.06	−0.02 to 0.15	.18	0.14	0.02	−0.05 to 0.08	.55

We adjusted for sex, inclination angle, and time since surgery in the multiple regression model.
CI, confidence interval; MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.

hypotheses tests. All analyses were performed using Stata software version 13 (StataCorp LP, College Station, TX).

Results

Mean activity levels in the MoM THA/RHA group and the MoP THA group were comparable at all time points ($P > .47$) (Table 1, Fig. 3). Results of the multiple regression analysis showed a statistical significant relationship between patients' daily PA and metal ion measurements of chromium at all follow-ups in MoM THA/RHA patients but not in MoP THA patients ($P > .35$) (Table 3, Figs. 2 and 3). The relationship between patients' daily PA and metal ion measurements of cobalt was not statistically significant in MoM THA/RHA patients ($P \geq .05$) or in MoP THA patients ($P > .39$) (Table 3) neither was the relationship between patients' daily PA and changes in pseudotumor size ($P > .30$) (Table 4). Baseline MARS MRI evaluations showed that pseudotumors or "MoM disease" were present in 26 of 77 (34%) MoM THA/RHA and in 29 of 71 (41%) MoP THA. In total, pseudotumors were seen in 55 of 148 (37%) hip articulations at baseline. Results of the MRI evaluations of all patients at the 5 follow-ups according to the Anderson classification are presented in Table 5. During the 5 MARS MRI scans, which were all performed within a year, 10 of 26 (38%) pseudotumors in MoM THA/RHA and 8 of 29 (28%) pseudotumors in MoP THA changed classification according to the Anderson grading (Table 6). No pseudotumors transformed appearance (cystic, solid, or mixed type), and no pseudotumors changed anatomical location during the follow-up. Evaluation of the conventional radiographs showed osteolyses around the cup in 0 MoM THA, 3 MoM RHA (all in DeLee Zone I), and 7 MoP THA (6 in DeLee Zone I and 3 in DeLee Zone I and II). Radiolucent lines around the cup were found in 2 MoM THAs (in DeLee Zone I), 0 MoM RHA, and 8 MoP THAs (3 in DeLee Zone I, and 3 in DeLee Zone I and II). For the stems, no osteolyses were seen in MoM THA or MoM RHA, but 7 MoP THA had osteolyses (4 in Gruen Zone I, and 3 in Gruen Zone I and VII). Radiolucent lines around the stem were observed in 0 MoM THA, 7 MoM RHA (all distal around the tip of the stem), and 2 MoP THA (1 in Gruen I and 1 in Gruen Zone VII).

Discussion

To our knowledge, this is the first prospective cohort study to investigate a large population of MoM THA/RHA and MoP THA with accelerometer-based activity monitoring, MARS MRI scans, and serum metal ion measurements with multiple systematic follow-ups during 1 year. We found a statistically significant relationship between patients' daily PA levels and metal ion measurements of chromium at all 4 follow-ups in MoM THA/RHA patients but not in MoP THA patients. We could not verify a relationship between patients' daily PA levels and changes in pseudotumor size; however, we found that 10 of 26 (38%) pseudotumors in MoM THA/RHA and 8 of 29 (28%) pseudotumors in MoP THA changed classification according to the Anderson grading during the 1-year follow-up. This is important information for the hip surgeon when advising active patients with MoM THA/RHA about the risk of PA on metal ion measurements and pseudotumor dynamics. Furthermore, knowledge on how pseudotumors behave over time is valuable when generating new evidence-based follow-up screening protocols and establishing indications for operative interventions of patients with MoM THA/RHA.

Previous clinical studies on the effect of patient's activity on the generation of metal ions of chromium and cobalt have revealed conflicting results. Gleizes et al [53] found a 10% rise in cobalt levels in 2 patients with Metasul 28-mm bearings after completing 800 m of walking. Contrasting, De Haan et al could not verify metal ion changes in a triathlete with Birmingham hip resurfacing before,

Table 4
Multiple Regression Analysis on the Effect of all Activity (Defined as the Sum of Walking, Cycling, and High-Activity Measurements) on the Pseudotumor Volume (cm^3) in Patients With MoM THA/RHA and MoP THA at 3, 6, 9, 12, and 24 Mo.

Articulation	MoM THA/RHA				MoP THA			
	Adj. R^2	β	95% CI	*P* Value	Adj. R^2	β	95% CI	*P* Value
Activity and pseudotumor volume (cm^3)								
3 mo (64/55)	0.02	0.02	−0.04 to 0.08	.46	0.01	0.01	−0.03 to 0.04	.70
6 mo (60/49)	0.05	0.02	−0.23 to 0.07	.39	0.01	0.01	−0.04 to 0.07	.61
9 mo (65/49)	0.02	−0.01	−0.06 to 0.04	.81	−0.05	0.01	−0.04 to 0.06	.64
12 mo (63/51)	0.06	−0.02	−0.05 to 0.01	.30	0.05	0.01	−0.04 to 0.06	.73

We adjusted for sex, inclination angle, and time since surgery in the multiple regression model.
CI, confidence interval; MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.

Table 5
Results of the MARS MRI Evaluations According to the Anderson Classification.

Articulation	Baseline		3 mo		6 mo		9 mo		12 mo	
	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA	MoM THA/RHA	MoP THA
Total number of hips	77	71	69	63	68	56	68	52	65	56
Pseudotumors	26	29	22	25	23	24	22	23	23	25
Grade A “normal or acceptable”	51	42	47	38	45	32	46	29	42	31
Grade B “infection”	-	-	-	-	-	-	-	-	-	-
Grade C1 “mild MoM disease”	15	15	13	14	14	14	12	14	15	15
Fluid	14	12	12	12	13	11	11	12	13	12
Mixed or solid	1	3	1	2	1	3	1	2	2	3
Grade C2 “moderate MoM disease”	11	12	9	9	9	10	10	9	8	10
Fluid	9	7	8	4	8	5	9	4	8	5
Mixed or solid	2	5	1	5	1	5	1	5	0	5
Grade C3 “severe MoM disease”	0	2	0	2	0	0	0	0	0	0
Fluid	0	0	0	0	0	0	0	0	0	0
Mixed or solid	0	2	0	2	0	0	0	0	0	0

Additional to the Anderson classification, pseudotumor appearance (fluid or mixed/solid) was recorded.
MARS, metal artifact reducing sequence; MoM, metal-on-metal; MoP, metal-on-polyethylene; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty; MRI, magnetic resonance imaging.

during, and after the race. However, De Haan et al [14] reported that urinary chromium levels was elevated after the race, demonstrating that additional chromium ions might have been generated during the run (urinary cobalt was not measured). It is difficult to compare our results directly to those of the aforementioned 4 studies because the study design, population, and setup are different. These previous studies all investigated correlations between acute changes in activity level and metal ion measurements at short-term follow-ups, whereas we investigated the relationship between patients' daily PA levels and metal ion measurements with multiple follow-ups during 1 year in a patient group with midterm follow-up of hip arthroplasty. The acute changes in activity levels with high-intensity exercise performed in the previous studies might have led to reduced body water at the time of blood sampling and thereby introduced bias in the metal-ion measurements. Furthermore, a proportion of body chromium is intracellular, and high-intensity exercise could lead to cellular damage of skeletal muscle fibers and red blood cells and contribute to an increase in chromium [54]. We limited these 2 potential sources of error by monitoring the daily PA of our study population. The previous studies were also limited by small study populations (15, 2, 7, and 1 patient), whereas a strength of this study was the large number of patients investigated. One other study with a large study population of 214 RHAs reported no correlation between outcome scores of the self-reported University of California, Los Angeles activity questionnaire and metal ion measurements [55]. However, assessment of patient activity by questionnaires has shown poor validity [56], and scores may reflect patients' expectation to the MoM RHA design, rather than the actual activity level. By using 3D accelerometers for activity monitoring, we obtained objective and detailed descriptions of the everyday activity.

Short-term studies with 2 cross-sectional imaging techniques have shown that pseudotumors are dynamic and may change in size/type over time [20–24]. We could not verify that patient's daily PA levels affected the pseudotumors size, but because initially asymptomatic pseudotumors may become symptomatic with increasing

Table 6
Descriptive Data of Patients With Pseudotumors, Which Changed Anderson Classification During the Study Period.

Articulation	Gender	Age (y)	Location[a]	MRI Signal[b]	HHS	MRI 1, Baseline[c]	MRI 2, 3 mo[c]	MRI 3, 6 mo[c]	MRI 4[c], 9 mo[c]	MRI 5, 12 mo[c]
MoM THA/RHA										
1. M2a-Magnum/Bimetric stem	Female	64	PL	Mixed	100	C2	C2	C2	C2	C1
2. ReCap Resurfacing	Female	60	PL	High	100	A	C1	C1	C1	C1
3. ReCap Resurfacing	Male	49	PL	High	96	A	A	A	A	C1
4. ReCap Resurfacing	Male	39	PL	High	100	C1	C2	C1	C1	C1
5. ReCap Resurfacing	Female	54	PL	High	95	A	A	C1	C1	C1
6. ReCap Resurfacing	Female	55	PL	High	100	C1	C1	C1	C2	C2
7. M2a-Magnum/Bimetric stem	Male	54	PL	High	100	C1	C1	A	A	A
8. M2a-Magnum/Bimetric stem	Male	62	PL	High	100	C1	A	C1	C1	C1
9. M2a-Magnum/Bimetric stem	Male	52	PL	High	89	C2	C1	C1	C2	C2
10. M2a-Magnum/Bimetric stem	Male	50	PL	High	100	C2	C1	C2	C1	C1
MoP THA										
1. Pinnacle cup, corail stem	Male	65	PL	High	100	C1	A	C1	C1	C1
2. Mallory head/Exeter stem	Female	69	PL	High	100	A	A	A	A	C1
3. Lubinus hip arthroplasty	Female	69	ILB	High	91	C1	C1	C1	C1	C2
4. Trilogy cup, CLS Spotorno	Male	48	PL	High	90	C2	C1	A	A	A
5. Trilogy cup/Bimetric stem	Female	68	PL	High	98	C1	A	-	-	-
6. Mallory head/Exeter stem	Male	72	ILB	High	94	C2	C1	C2	C1	C1
7. Mallory head/Exeter stem	Male	69	PL	High	84	A	A	A	C1	C1
8. Mallory head/Bimetric stem	Female	60	PL	High	100	A	A	C1	C1	A

HHS, Harris Hip Score; MoM, metal-on-metal; MoP, metal-on-polyethylene; MRI, magnetic resonance imaging; RHA, resurfacing hip arthroplasty; THA, total hip arthroplasty.
[a] The anatomical location of the pseudotumor: PL, posterior-lateral of the greater trochanter and ILB, located to the iliopsoas bursa.
[b] High MRI signal intensity is associated with fluid content, and low signal intensity is associated with solid content.
[c] Grading according to the Anderson classification and chromium and cobalt levels (chromium/cobalt) (μg/L) at the time of follow-up.

pseudotumor volume and eventually require revision surgery [57], we encourage future studies to focus on investigation of factors predisposing to these alterations. During the 5 MARS MRI scans performed within a year, 38% pseudotumors in MoM THA/RHA and 28% pseudotumors in MoP THA changed classification according to the Anderson grading. This might seem like a large proportion of the pseudotumors. However, no pseudotumors changed into C3, which indicates “severe MoM disease” where urgent revision have been advised [33], and no cystic type pseudotumors changed into mixed or solid type, which have been associated with pain in both MoM and MoP THA [3,58–60] and with poor outcomes of revision surgery [61]. Furthermore, changes in pseudotumor classification occurred in both MoM THA/RHA and MoP THA, which suggest that this is a normal postoperative happening after hip arthroplasty. Different monitoration guidelines have been published for patients with MoM hip arthroplasties [62,63], but still there is no algorithm for how often cross-sectional imaging should be repeated. Anderson et al suggest that patients with pseudotumors graded as C1 should be followed clinically with serial MRI, patients with C2 pseudotumors should be revised electively, and patients with C3 pseudotumors should be revised urgently. However, van der Weegen et al [64] propose a more conservative approach in patients with pseudotumors graded as Anderson C2, who are asymptomatic and have normal metal ion levels and Hart et al [65] suggested that less clinical importance should be given to cystic pseudotumors and more should be focused on solid pseudotumors. We support the suggestions by van der Weegen et al and Hart et al because our study demonstrated that cystic pseudotumors classified as C1 and C2 may show some fluctuation within intervals of just 3 months, without related bone or soft-tissue damage visible on MRI, in asymptomatic patients. Some fluid collection might be normal following any THA procedure and whether or not all cystic collections should be classified as “real pseudotumors” is still debated because a high number of cystic pseudotumors have been identified in asymptomatic patients.

We acknowledge the limitations of our study. First, the 2 groups were unmatched, and a significant difference in age, gender, and time since operation occurred. To minimize the influence of these variables, we adjusted for them statistically. Furthermore, the absence of major differences in activity levels and clinical outcome scores of HAGOS “hip-related quality of life” between groups suggests that alleviating matching did not have a great influence. Second, we did not monitor fluid intake and output, simply because it would have been a huge work and impractical to monitor the fluid balance, and thus, patients might have been dehydrated or overhydrated at the time point of blood sampling, which could affect the serum ion measurements of chromium and cobalt. Third, no histological matching of aseptic lymphocyte-dominated vasculitis-associated lesion scores with the imaging findings were performed because we did not take biopsies of the lesions. The combination of MARS MRI and histology would probably have provided more information on the different pseudotumor types, and perhaps revealed a difference between the pseudotumors found in patients with MoM THA/RHA and those in patients with MoP THA. However, taking a biopsy involves a risk of prosthetic infection, which could lead to revision surgery.

In conclusion, the daily PA levels of MoM THA/RHA patients are associated with metal ion measurements of chromium but not with changes in pseudotumor size. This is new and important knowledge, which may be useful for hip surgeons in recommendation and monitoration of the consequences of PA in active patients with MoM THA/RHA. Changes in pseudotumor classification according to the Anderson grading were observed in 38% MoM THA/RHA and 28% MoP THA. This information may be valuable when generating new evidence-based follow-up screening protocols for MoM THA/RHA patients.

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STUDY III

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Primary Arthroplasty

Equal Primary Fixation of Resurfacing Stem, but Inferior Cup Fixation With Anterolateral vs Posterior Surgical Approach. A 2-Year Blinded Randomized Radiostereometric and Dual-energy X-Ray Absorptiometry Study of Metal-on-Metal Hip Resurfacing Arthroplasty

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ABSTRACT

Background: The anterolateral (AntLat) surgical approach may spare the blood supply to the femoral head and improve the accuracy of cup positioning in metal-on-metal hip resurfacing arthroplasty. Thereby, potentially lessen complications such as avascular head necrosis, femoral neck narrowing and fracture, improve implant fixation, and lessen periprosthetic bone mineral density (BMD) loss.
Methods: Between November 2008 and January 2012, a randomized clinical trial was performed at Aarhus University Hospital. A total of 49 patients (28 males) were allocated to metal-on-metal hip resurfacing arthroplasty by the AntLat (n = 25) or the posterior (Post; n = 24) surgical approach. Patients were followed with radiostereometric analysis, measurements of periprosthetic BMD, clinical outcome scores of Harris hip score and visual analogue scale, serum metal ions, and conventional radiographs.
Results: At 3 months, cups in the AntLat group had higher total translations of mean 1.00 ± 0.70 mm vs mean 0.64 ± 0.45 mm in the post group ($P = .04$), and higher total rotations of mean 2.44° ± 1.36° vs mean 1.39° ± 1.17° in the Post group ($P = .002$). All migrations of cup and stem were similar at 1 and 2 years postoperative ($P > .07$). At 1 year, periprosthetic BMD since postoperative at the medial side of the stem was reduced to mean 98.45% ± 8.57% in the AntLat group, and increased to mean 105.57% ± 11.07% in the Post group ($P = .02$), but measurements were comparable at 2 years ($P = .05$).
Conclusion: Cups inserted by the AntLat approach migrated more until 3 months postoperative. This illustrates a less good primary cup fixation with the AntLat approach; however, all cups were well-fixed after 3 months' follow-up indicating a good secondary fixation.

In metal-on-metal hip resurfacing arthroplasty (MoM HRA), causes of failure such as periprosthetic femoral fractures, avascular necrosis of the femoral head, and component loosening have been identified [1–5]. Previous studies have speculated that changes in the vascularity of the femoral head and the resulting osteonecrosis may contribute to these failure modes [6,7]. The surgical exposure of the hip during MoM HRA procedures can be achieved through a variety of surgical approaches, whereof the anterolateral (AntLat) approach and the posterior (Post) approach are the most widely used and well documented. Potential advantages and disadvantages have been described in both approaches. The AntLat approach preserves the blood supply to the femoral head [8], and has results in a more accurate and consistence cup positioning in total hip arthroplasty (THA) [9]. However, it also leads to an increased risk of postoperative limp because of a risk of interference with the abductor muscles and the superior gluteal nerve [10,11], and an inevitable “learning curve” have been described for this procedure

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[12]. The Post approach have been considered the easiest to perform; however, this procedure sacrifices the medial circumflex artery thus compromising the blood supply to the femoral head, which contributes to osteonecrosis, fracture risk, and implant loosening [13,14].

Femoral neck fractures after HRA surgery can be visualized in conventional radiographs. Avascular head necrosis is not visible because of the resurfacing cap, but may be revealed as small implant migrations. Radiostereometric analyses (RSA) can detect implant loosening with a threshold of translation up to 10 times better than conventional radiography [15–17]. Ideally, a phased introduction including small-scale randomized radiostereometric studies of all new implant designs, cements, or surgical procedures should be performed [15,18–20]. Thus, the goal of this small-scale randomized clinical trial was to investigate if the AntLat approach provided superior outcomes for both cup and femoral components compared with the Post approach. We evaluated 3 hypotheses: (1) the AntLat approach provides superior cup and femoral component fixation compared with the Post approach, (2) the AntLat approach increases the periprosthetic bone mineral density (BMD) around the femur component compared with the Post approach, and (3) patients operated by the AntLat approach have better outcome scores of Harris hip score (HHS) and lower visual analog scale (VAS) for pain compared with patients operated by the Post approach.

Material and Methods

Design and Patients

Between November 2008 and January 2012, a randomized clinical trial was performed at Aarhus University Hospital, where 49 patients (28 males) received the ReCap Hip Resurfacing System (Biomet Inc, Warsaw, IN).

Inclusion criteria were primary or secondary (because of mild or moderate dysplasia) osteoarthritis of the hip, acceptable BMD on preoperative dual-energy x-ray absorptiometry (DXA) scan (T-score > −1), and age between 30 and 60 years. Exclusion criteria were vascular or neuromuscular disease in the operated leg, fracture sequelae, avascular necrosis of the femoral head, women planning pregnancy, alcohol abuse and daily intake of nonsteroidal anti-inflammatory drugs, K-vitamin antagonists, or loop diuretics. Patients were allocated to surgery with MoM HRA by either the Post surgical approach (n = 24) or the AntLat surgical approach (n = 25). Patients were blinded regarding the surgical approach used for implantation. Baseline demographics of all patients are presented in Table 1.

All examinations were designed and carried out in compliance with the Helsinki II declaration, laws on personal data protection, and laws on patient's rights. All patients gave informed consent before entering the study. The study was approved by the Central Denmark Region Committee on Biomedical Research (Journal no. M-20070082; issue date August 29, 2007) and by the Danish Data Protection Agency (Protocol no. 2007-41-1559; issue date December 5, 2007). The project was registered with www.clinicaltrials.gov (Clinical Trials Study ID number; 20070082).

Prosthesis, Surgery and Rehabilitation

All patients received a ReCap Hip Resurfacing System (Biomet, Warsaw, IN) consisting of a cemented cobalt chrome femoral component and a cementless titanium non–hydroxyapatite-coated closed pore porous-coated acetabular component, with a cobalt chrome core fixed by press fit. The femoral component was fixed by bone cement, Simplex P with Tobramycin (Stryker, Hopkinton). Two experienced orthopedic hip surgeons undertook the operations using standard equipment provided by the manufacturer. Patients were assigned to surgery with MoM HRA by either the AntLat surgical approach (ad modum Watson) or the Post surgical approach (ad modum Moore) [21]. The MoM ReCap Resurfacing System was used at our institution between January 2006 and January 2012. During this period, 110 patients were operated with the MoM ReCap Resurfacing System. Of these, 37 patients were operated with the AntLat approach (whereof 25 was included in this study) and the remaining 73 were operated by the Post approach (whereof 24 was included in this study). Postoperative, the hospital's physiotherapists gave identical instructions to all patients in a home-based training program, which allowed full weight bearing. During the first 6 weeks, patients were advised limited adduction, but thereafter no further restrictions were given (Fig. 1).

Radiostereometric Analysis

For RSA measurements, 8-10 tantalum markers (1 mm) were inserted into the greater and lesser trochanteric region, and 6-8 tantalum markers were inserted in the periacetabular bone during surgery. The RSA setup at our institution has been described in a previous paper [22]. Stereoradiographs were obtained within the first postoperative week and at the 3 months, 1- and 2-year follow-up. Implant migration was assessed on all follow-up stereoradiographs using the postoperative stereoradiograph as the reference. Stereoradiographs were analyzed using 3-dimensional computer-aided design surface model/marker models [23]. All RSA analyses of implant migrations were performed by 2 experienced RSA technicians. Translations (implant movement along the axes) were expressed as x-translations (medial/lateral direction), y-translations (proximal/distal direction), and z-translations (anterior/posterior direction). Rotations were expressed as rotations about

Table 1
Descriptive Baseline Characteristics of the Patients, Implants, and Surgery.

	Posterior Approach	Anterolateral Approach	*P* Value[a]
Number of patients	24	25	-
Sex (male/women)	15/9	13/12	.47
Age at operation, y; mean (range)	47 (32-60)	53 (44-61)	.01
Implant side, right/left	13/9	12/8	.48
Femoral head size, mm; mean (range)	50 (50-60)	48 (48-64)	.49
Inclination cup angle, °	39.4 (32.6-47.6)	41.6 (21-50.7)	.07
Anteversion cup angle, °	9.7 (3.6-21.8)	14.1 (3.4-24.8)	.008
Stem position (neutral/valgus/varus)	15/9/0	21/4/0	.09
Stem position (neutral/anterior/posterior)	23/1/0	24/1/0	.97
Surgery length, min; mean (range)	106.5 (75-140)	103.3 (75-120)	.45
Blood loss during surgery, mL; mean (range)	297.7 (150-600)	344.5 (100-700)	.12

[a] Satterthwaite *t* test.

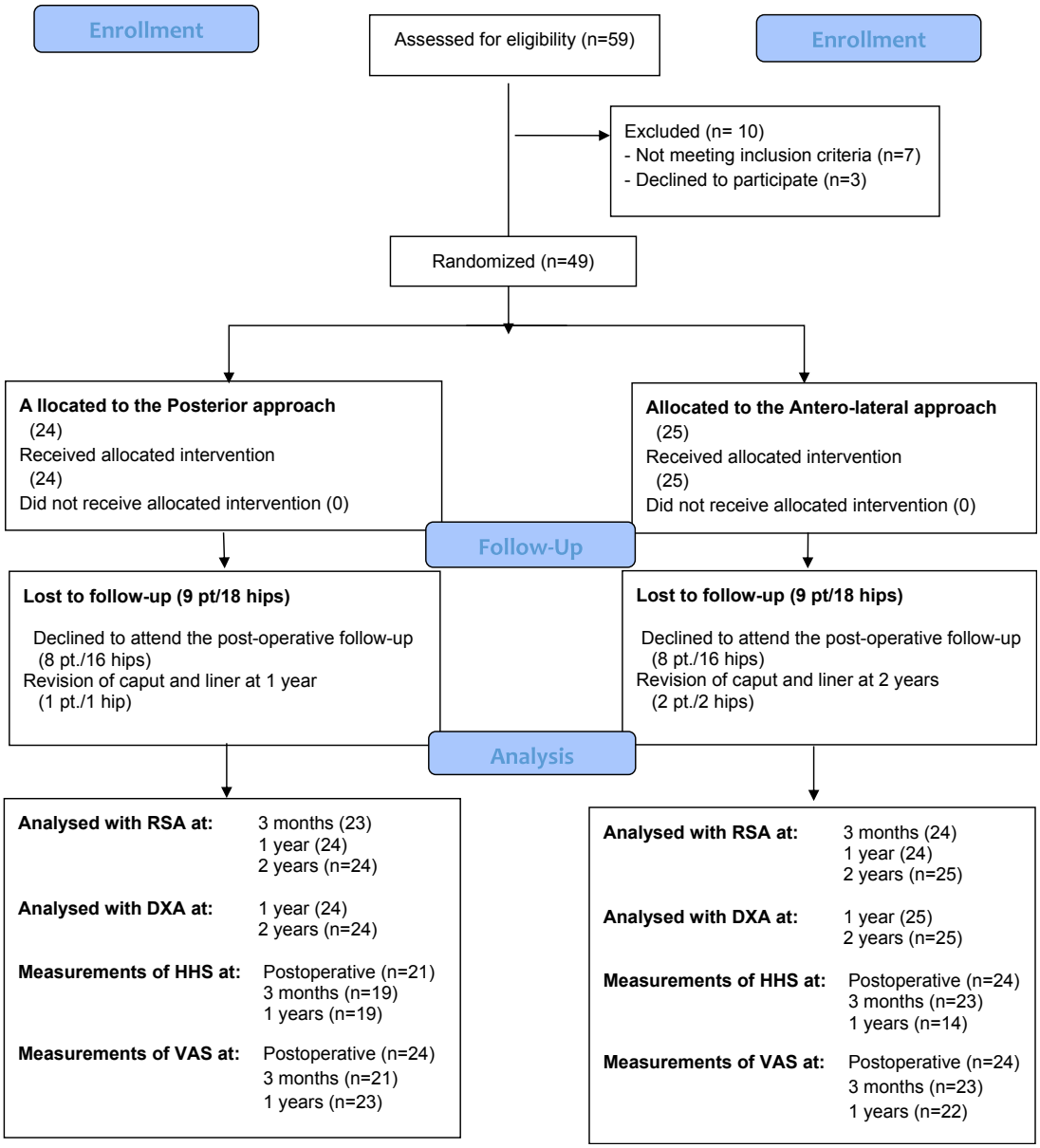

Fig. 1. CONSORT flow diagram showing the inclusion/exclusion process and follow-up until 2 years follow-up. DXA, dual-energy x-ray absorptiometry; HHS, Harris hip score; RSA, radiostereometric analyses; VAS, visual analogue scale.

the x-axis (anterior/posterior tilt), y-axis (retroversion/anteversions), and z-axis (valgus/varus tilt) (Figs. 2 and 3). The total translation (TT) and the total rotation (TR) were calculated by use of the Pythagorean theorem ($\sqrt{(x^2 + y^2 + z^2)}$). The distribution of the implant and femoral bone markers can be assessed using the condition number, and an upper limit of $\leq$150 has been suggested [24]. Mean condition number of the markers in the femur and acetabulum was 17.69 ± 5.04 and 56.22 ± 15.82, respectively. The rigid body error represents the stability of the markers. Mean rigid body error in the analysis of the markers in the femur and acetabulum was 0.14 ± 0.05 and 0.19 ± 0.07, respectively. The rigid body match threshold was set to 0.50 mm (software default).

The precision of the RSA analyses was assessed by "double examinations" of all patients, which was performed according to the guidelines [24,25]. The standard deviation of the difference between the two examinations (SD dif.) reflects the precision of the RSA results. The coefficient of repeatability (±1.96 × SD dif.) reflects the lower limit within which it is possible to detect prosthetic migration on the individual basis of the system [25,26] (Table 2).

Dual-Energy X-Ray Absorptiometry Scans

Postoperatively (within 1 week after surgery), at 1 and 2 years after surgery, quantitative measurements of the periprosthetic BMD (g/cm^2) was acquired by DXA scans by a Lunar Prodigy Advance 2005 DXA scanner (General Electric, Chicago, IL), and analyses were performed using the enCORE version 11.40 software. Calibration was performed daily with two different phantoms according to the manufactures guidelines, to verify the reliability of the system.

The patients were placed in standardized positions: supine, body parallel with the examination table, and the big toes pointing straight up and fixation of the feet to a device. The postoperative DXA scan served as baseline for the subsequent scans as recommended by Kröger et al [27]. BMD of the femoral neck was analyzed

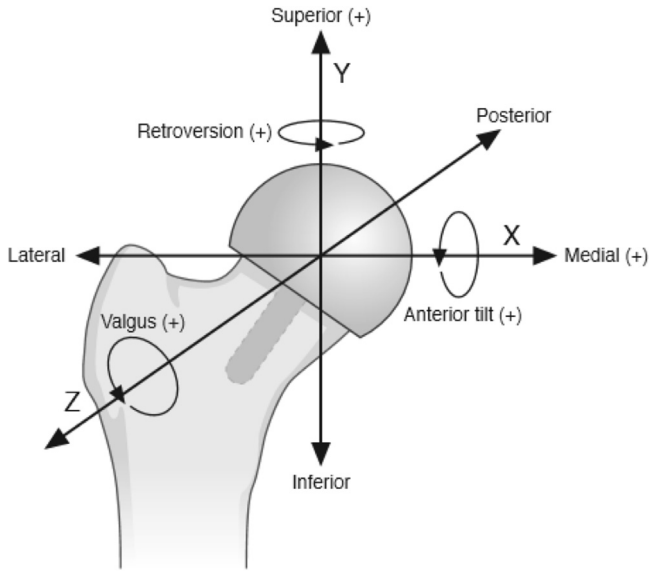

Fig. 2. Illustration of directions of translations and rotations for the ReCap resurfacing femoral component.

in 2 models: (1) in a 2-region of interest (ROI) model with a subregion medial (Med) and lateral (Lat) to the pin of the femoral articulation as suggested by Penny et al [28] and (2) in a 6-ROI model with 3 regions medial (M1-3) and 3 regions lateral (L1-3) to the pin of the femoral component as suggested by Kishida et al [29] (Fig. 4). No specialized software was available for creating the femoral neck regions, and consequently customized ROIs were created in a template, that was applied at the baseline scan with ROIs evenly distributed on either side of the implant stem, and subsequently the ROIs were copied to the follow-up scans (Fig. 4).

Clinical Outcome Measures and Complications

Clinical outcome measures were assessed by the HHS [30] (range 0-100) and the VAS for pain (range 0-100) [31] at

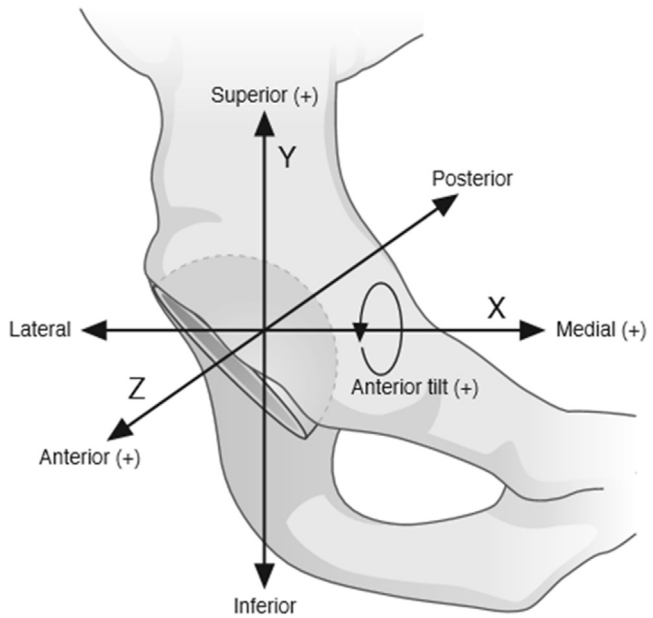

Fig. 3. Illustration of directions of translations and rotations for the ReCap acetabular component.

Table 2
Measurement of Error of the RSA for Double-Examination Stereo Radiographs for Translations and Rotations.

Axis	Translation, mm				Rotation, °			
	x	y	z	TT[a]	x	y	z	TR[b]
Femoral component								
Mean dif.	0.02	0.02	−0.06	0.01	0.04	−0.01	−0.05	−0.02
SD dif.	0.14	0.12	0.40	0.31	0.39	0.28	0.33	0.33
CR (±1.96 × SD dif.)	0.27	0.24	0.78	0.61	0.76	0.55	0.65	0.65
Cup								
Mean dif.	0.05	0.03	−0.01	−0.11	−0.21	0.19	−0.09	−0.05
SD dif.	0.50	0.15	0.44	0.44	0.84	0.65	1.01	0.89
CR (±1.96 × SD dif.)	0.98	0.29	0.86	0.86	1.65	1.27	1.98	1.74

Mean dif. represents the systematic error of the system. SD dif. Is the random variation within the method comparing the double examinations. CR (±1. 96 × SD dif.) reflects the precision on the individual basis of the system.
3-D, three-dimensional; CR, coefficient of repeatability; RSA, radiostereometric analyses; SD, standard deviation; TR, total rotation; TT, total translation.
[a] The TT was calculated using the 3-D Pythagorean theorem ($TT = \sqrt{(x^2 + y^2 + z^2)}$).
[b] The TR was calculated using the 3-D Pythagorean theorem ($TR = \sqrt{(x^2 + y^2 + z^2)}$).

postoperative, 3 months and 1 year after surgery. Complications since operation was obtained until 2 years postoperative.

Conventional Radiography, Implant Position and Serum Metal Ion Measurements

Standardized weight-bearing anteroposterior pelvic and lateral hip radiographs were obtained postoperative and at 3 (1-5.2) years after surgery. The following parameters were evaluated in consensus between 2 observers: narrowing of the femoral neck using the method described by Hing et al [32], radiolucent lines >1 mm, signs of osteolysis around the cup [33] and stem [34], heterotopic ossification (classified according to Brooker et al [35]),

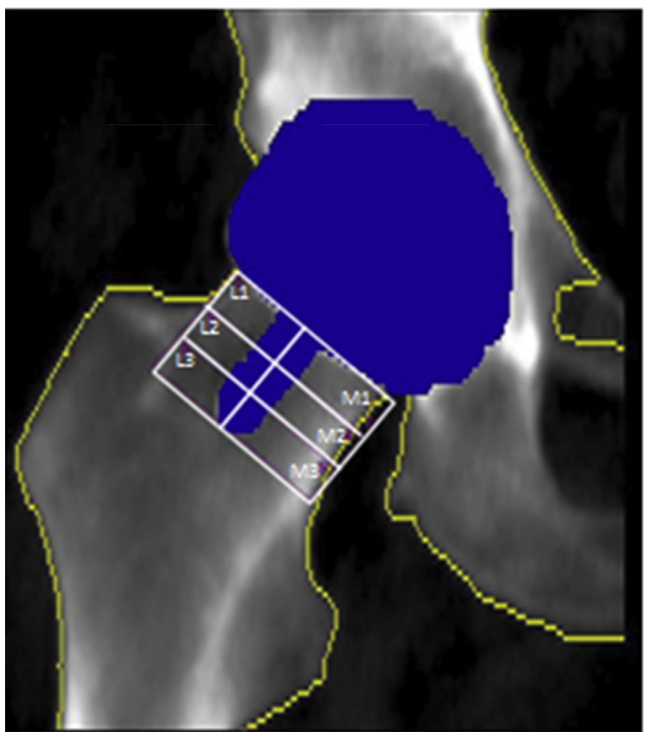

Fig. 4. Six-region of interest (ROI) model with 3 regions lateral (L1-3) and 3 regions medial (M1-3) to the pin of the femoral component.

Table 3
Scores of the HHS and VAS for pain, and chromium and cobalt values.

Outcomes	Posterior Approach	Anterolateral Approach	*P* Value[a]
HHS			
Postoperative (21/24)	59.8 (10.6)	60.1 (14.6)	.70
3 mo (19/23)	86 (12.8)	90.1 (10.31)	.24
1 y (19/14)	91 (9.9)	89.2 (14.2)	.89
VAS			
Postoperative (24/24)	51.8 (18.6)	51.8 (19.2)	.97
3 mo (21/23)	11.3 (15.6)	10.7 (17.8)	.80
1 y (23/22)	10.6 (11.9)	6.9 (14.38)	.09
Chromium, μg/L			
3 (1-5.2) y (24/25)	2.20 (0.59-10.5)	1.87 (0.64-4.50)	.91
Cobalt, μg/L			
3 (1-5.2) y (24/25)	1.59 (0.59-7.26)	1.37 (0.59-4.96)	.74

Values of HHS and VAS are mean (SD). Values of chromium and cobalt are mean (range).
HHS, Harris hip score; SD, standard deviation; VAS, visual analogue scale.
[a] Two-sample Wilcoxon rank-sum (Mann-Whitney) test.

and stem location of neutral, valgus or varus position (relative to the center line of the femoral neck). Measurements of cup inclination and anteversion were read from the Model-based RSA software (RSAcore, Leiden, The Netherlands) using the positions of the fitted models on the 2-year stereoradiographs. Blood samples were collected according to published guidelines [36–38] at mean 2.4 (0.31-3.8) years postoperative. Measurements of cup positions were not checked with intraoperative radiographs or a C Arm. Serum samples were examined by inductively coupled plasma mass spectrometry at XXX Hospital, Denmark.

Statistics and Sample Size

All continuous variables were tested for normality (Shapiro-Wilk test). When data were not normally distributed, nonparametric tests (Mann-Whitney *U* test and Wilcoxon rank-sum test) were used. When data were normally distributed, Satterthwaite *t* test was used. Calculation of the correlation coefficient (r) of independent variables was made using the Spearman correlation analysis when the data were not normally distributed, and Pearson correlation analysis when the data were normally distributed. A *P* value below .05 was considered statistically significant. All analyses were performed using STATA 13 (StataCorp LP, College Station, TX).

The predefined primary end point was implant migration at 2 years, and secondary outcomes were measurements of periprosthetic BMD, clinical outcome scores of HHS and VAS for pain. Sample size was calculated using RSA data. Based on an estimated clinically significant difference of 0.6 mm and a standard deviation of 0.7 mm between groups [39], a prestudy sample size calculation required 22 patients in each group to achieve 80% power at a 0.05 significance level. Because of potential drop outs, we planned to include 25 patients in each group, but because the Danish Orthopedic Society advised against further the use of any MoM hip articulations prior completed study inclusion, only 24 patients were included in the Post group.

The 2 research workers who performed the RSA analyses and the DXA analyses were blinded from knowing the surgical approach used for MoM HRA implantation.

Results

Radiostereometric Analysis

At 3 months, migrations of the acetabular cup had higher TT in the AntLat group of mean 1.00 ± 0.70 mm vs mean 0.64 ± 0.45 mm in the Post group ($P = .04$). But, no difference in TT was observed at 1 or 2 years ($P > .07$), and no difference was observed when analyzing the individual translations on the x, y, and z axes ($P > .39$) (Table 3). The individual migration patterns of TT revealed 7 cups (5 AntLat and 2 Post) with migration above the precision limit (0.86 mm) of TT (range 0.99-1.85 mm) between 3 months and 2 years.

Table 4
Migrations of the ReCap Femoral Component as Mean (SD) Along and Around the 3 Axes Measured With RSA at 3 mo, 1 y, and After Surgery.

Axis	Posterior Approach	Anterolateral Approach	*P* Value[a]
Translations, mm			
Medial/lateral (x-axis)			
3 mo	−0.02 (0.26)	−0.04 (0.25)	.95
1 y	0.08 (0.56)	−0.08 (0.16)	.12
2 y	0.04 (0.56)	−0.07 (0.22)	.39
Proximal/distal (y-axis)			
3 mo	−0.02 (0.26)	0.02 (0.13)	.71
1 y	−0.14 (0.73)	0.00 (0.18)	.78
2 y	−0.16 (0.77)	−0.09 (0.24)	.37
Anterior/posterior (z-axis)			
3 mo	−0.18 (0.58)	−0.02 (0.42)	.24
1 y	−0.35 (0.68)	0.02 (0.41)	.08
2 y	−0.25 (0.69)	0.14 (0.54)	.09
TT[b]			
3 mo	0.56 (0.42)	0.43 (0.26)	.35
1 y	0.78 (0.91)	0.44 (0.18)	.27
2 y	0.79 (0.91)	0.49 (0.42)	.14
Rotations, °			
Anterior/posterior tilt (x-axis)			
3 mo	0.19 (0.45)	−0.07 (0.42)	.11
1 y	0.14 (0.59)	0.02 (0.33)	.39
2 y	−0.12 (0.67)	0.08 (0.41)	.62
Anteversion/retroversion (y-axis)			
3 mo	0.01 (0.31)	−0.09 (0.31)	.25
1 y	−0.03 (0.46)	−0.05 (0.29)	.85
2 y	−0.02 (0.45)	0.00 (0.34)	.87
Valgus/varus tilt (z-axis)			
3 mo	−0.16 (0.50)	0.05 (0.38)	.23
1 y	−0.43 (1.74)	0.07 (0.35)	.27
2 y	−0.45 (1.78)	0.06 (0.39)	.25
TR[c]			
3 mo	0.63 (0.45)	0.56 (0.33)	.79
1 y	1.02 (1.65)	0.50 (0.26)	.17
2 y	1.04 (1.71)	0.52 (0.41)	.38

Examinations were performed on total (posterior approach/AntLat approach); 23/24 patients at 3 mo, 24/24 patients at 1 y, and 24/25 patients at 2 y. Values are mean (SD).
3-D, three-dimensional; AntLat, anterolateral; SD, standard deviation; TR, total rotation; TT, total translation.
[a] Paired Wilcoxon signed-rank test.
[b] The TT was calculated using the 3-D Pythagorean theorem ($TT = \sqrt{(x^2 + y^2 + z^2)}$).
[c] The TR was calculated using the 3-D Pythagorean theorem ($TR = \sqrt{(x^2 + y^2 + z^2)}$).

At 3 months, the acetabular cup also had higher TR in the AntLat group of mean 2.44° ± 1.36° vs mean 1.39° ± 1.17° in the Post group ($P = .002$). No difference in TR was observed at 1 or 2 years ($P > .13$), and no difference was observed when analyzing the individual rotations on the x, y, and z-axes ($P > .27$) (Table 4, Figs. 2 and 3). The individual migration patterns of TR showed 10 cups (7 AntLat and 3 Post) with migration above the precision limit (1.74°) of TR (range 1.87°-2.86°) between 3 months and 2 years.

For the femoral component, all translations and rotations were comparable between groups at any time point measured ($P > .11$; Table 5). Eight femoral components (2 AntLat and 6 Post) had individual migrations above the precision limit (0.65°) of TR (range 0.86°-1.95°), and 7 femoral components (2 AntLat and 5 Post) had individual migrations above the precision limit (0.61 mm) of TT (range 0.72-1.82 mm) between 3 months and 2 years.

Table 5
Migrations of the ReCap Acetabular Component as Mean (SD) Along and About the 3 Orthogonal Axes Measured With RSA at 3 mo, 1 and 2 y After Surgery.

Axis	Posterior Approach	Anterolateral Approach	*P* Value[a]
Translations, mm			
Medial/lateral (x-axis)			
3 mo	0.17 (0.40)	0.18 (0.55)	.99
1 y	0.21 (0.55)	0.28 (0.46)	.39
2 y	0.16 (0.63)	0.15 (0.72)	.92
Proximal/distal (y-axis)			
3 mo	0.36 (0.31)	0.37 (0.34)	.90
1 y	0.40 (0.31)	0.48 (0.37)	.55
2 y	0.40 (0.33)	0.55 (0.59)	.56
AntLat/posterior (z-axis)			
3 mo	0.09 (0.45)	0.21 (0.95)	.58
1 y	0.36 (0.84)	0.35 (0.86)	.98
2 y	0.39 (0.86)	0.39 (1.16)	.74
TT[b]			
3 mo	0.64 (0.45)	1.00 (0.70)	.04
1 y	0.88 (0.80)	0.99 (0.72)	.35
2 y	0.98 (0.77)	1.37 (0.87)	.07
Rotations, °			
Anterior/posterior tilt (x-axis)			
3 mo	−0.16 (1.05)	0.12 (0.63)	.59
1 y	0.24 (2.52)	0.09 (1.59)	.73
2 y	0.32 (2.64)	0.08 (1.80)	.70
Anteversion/retroversion (y-axis)			
3 mo	−0.03 (0.87)	−0.33 (1.43)	.75
1 y	−0.32 (1.95)	−0.26 (1.51)	.98
2 y	−0.45 (0.45)	−0.33 (1.70)	.85
Valgus/varus tilt (z-axis)			
3 mo	0.01 (1.22)	−0.40 (1.74)	.30
1 y	−0.34 (1.21)	−0.58 (1.57)	.43
2 y	0.01 (1.59)	−0.73 (1.81)	.27
TR[c]			
3 mo	1.39 (1.17)	2.44 (1.36)	.002
1 y	2.21 (2.61)	2.32 (1.43)	.13
2 y	2.92 (2.55)	2.68 (1.61)	.80

Examinations were performed on total (posterior approach/AntLat approach); 23/24 patients at 3 mo, 24/24 patients at 1 y, and 24/25 patients at 2 y. Values are mean (SD).
3-D, three-dimensional; AntLat, anterolateral; RSA; SD, standard deviation; TR, total rotation; TT, total translation.
[a] Paired Wilcoxon signed-rank test.
[b] The TT was calculated using the 3-D Pythagorean theorem ($TT = \sqrt{(x^2 + y^2 + z^2)}$).
[c] The TR was calculated using the 3-D Pythagorean theorem ($TR = \sqrt{(x^2 + y^2 + z^2)}$).

Dual-Energy X-Ray Absorptiometry Scans

Patients operated by the AntLat approach gained periprosthetic BMD since postoperative in L1, L2, L3, and M3, but had a reduction in periprosthetic BMD since postoperative in M1 and M2 at 1 and 2 years (Fig. 2). Patients operated by the Post approach had gained periprosthetic BMD in all ROIs at 1 and 2 years postoperative (Fig. 4, Table 6). At 1 year, periprosthetic BMD since postoperative at the medial side of the stem was reduced to mean 98.45% ± 8.57% in the AntLat group, and increased to mean 105.57% ± 11.07% in the Post group ($P = .02$), but measurements were comparable at 2 years ($P = .05$).

We found a significant difference between groups in M1; at 1 year, periprosthetic BMD in the AntLat group was reduced to mean 98.58% ± 8.75% and increased to mean 106.35% ± 10.19% in the Post group ($P = .01$). Similar measurements were obtained at 2 years where periprosthetic BMD in the AntLat group was decreased to mean 99.47% ± 9.05% and increased to mean 107.16% ± 11.18% in the Post group ($P = .01$; Table 6).

At 1 year, periprosthetic BMD in the entire medial ROI was significantly different between groups; the AntLat group had a reduction of mean 98.45% ± 8.57% and the Post group had an increase of mean 105.57% ± 11.07% ($P = .02$; Table 6).

Table 6
Bone Mineral Density in the 8 ROIs as Percentage of Baseline (Postoperative) Values up to 2 y After Surgery.

ROI	Posterior Approach	Anterolateral Approach	*P* Value[a]
L1			
1 y	132.21 (49.83)	112.16 (26.66)	.08
2 y	134.57 (37.96)	118.59 (37.83)	.15
L2			
1 y	111.46 (37.75)	103.25 (21.73)	.35
2 y	107.35 (28.33)	109.57 (23.47)	.77
L3			
1 y	107.22 (29.99)	100.36 (20.95)	.36
2 y	101.55 (20.01)	101.29 (22.88)	.97
M1			
1 y	106.35 (10.19)	98.58 (8.75)	.01
2 y	107.16 (11.18)	99.47 (9.05)	.01
M2			
1 y	101.23 (10.22)	96.97 (8.10)	.11
2 y	102.08 (11.29)	97.34 (9.14)	.11
M3			
1 y	110.15 (22.09)	100.62 (14.87)	.06
2 y	109.60 (20.58)	103.18 (14.48)	.21
Lat			
1 y	116.32 (37.84)	104.58 (18.91)	.17
2 y	113.58 (27.51)	108.73 (23.29)	.50
Med			
1 y	105.57 (11.07)	98.45 (8.57)	.02
2 y	105.60 (10.77)	99.83 (9.10)	.05

Examinations were performed on total (posterior approach/anterolateral approach); 24/25 patients at 1 y and 24/25 patients at 2 y. Values are mean (SD).
ROI, region of interest; SD, standard deviation.
[a] Satterthwaite *t* test.

Clinical Outcome Measures and Complications

There was no difference in the clinical outcome scores of HHS or VAS of pain at postoperative, 3 months or 1 year ($P > .09$; Table 3).

No components had been revised at the 2-year follow-up. But, until now 3 female patients have undergone revision surgery; 2 operated by the AntLat approach at 2.6 and 4.1 years postoperative, and 1 operated by the Post approach at 2.7 years postoperative. The female operated by the AntLat approach was revised at 2.6 years after surgery, had severe groin pain and levels of chromium of 2.5 μg/L and cobalt of 18.23 μg/L. Computed tomography scan revealed a 9 × 2.4 − 5.5 cm mass (pseudotumor) from the top of trochanter major and distally. During revision, the surgeon observed metallosis around the hip joint, and the histological examination of the pseudocapsule showed high aseptic lymphocyte-dominant vasculitis-associated lesion scores of 8-9. At 3 months postoperative, serum metal ion concentrations of chromium and cobalt was 1.12 μg/L and 1.22 μg/L, respectively, and the patient reported a decrease in pain. The other two females who had revision surgery of their MoM HRA experienced groin pain, but they had low serum metal ion levels, and both magnetic resonance imaging and ultrasonography scans were normal. After revision into metal-on-polyethylene THAs, both patients were without pain.

Conventional Radiography, Implant Position and Serum Metal Ion Measurements

Comparison of the postoperative and the 3 (1-5.2) year conventional radiographs showed neck narrowing in the AntLat group of mean 12% ± 0.80% and in the Post group of mean 9.0% ± 0.50% ($P = .21$). In total, 3 radiolucent lines were observed in DeLee zones I and II in 3 different cups (1 in the AntLat group and 2 in the Post group), and 6 radiolucent lines were found around the stem (2 in the AntLat group and 4 in the Post group), 4 were found lateral to the stem, and 2 were found medial to the stem. Thirty-six stems

were orientated in neutral position (21 in the AntLat group and 15 in the Post group), 13 were orientated in valgus position (4 in the AntLat group and 9 in the Post group), and none were orientated in varus position (Table 1). Stems in valgus position did not have higher TT or TR migration ($P > .27$) or lower periprosthetic BMD measurement at the medial or lateral side of the pin as compared with patients with stems in neutral position ($P > .30$). The cup inclination angles in the AntLat group was mean 41.6° (range 21°-50.7°) and in the Post group was mean 39.4° (range 32.6°-47.6°) ($P = .07$). Cup anteversion angles in the AntLat group was mean 14.1° (range 3.4°-24.8°) and in the Post group was mean 9.7° (range 3.6°-21.8°) ($P = .008$) (Table 1). Serum metal ion measurements of chromium and cobalt were similar between groups at 2.4 (0.5-3.8) years postoperative (Table 3). In the entire study group, chromium levels were mean 2.03 μg/L (range 0.59-10.50 μg/L) and cobalt levels were mean 1.47 μg/L (range 0.59-7.26 μg/L).

Discussion

We hypothesized that the AntLat surgical approach as compared with the Post approach would demonstrate superiority in implant fixation of the cup and femoral components, periprosthetic BMD around the stem, and clinical outcome scores for insertion of the ReCap MoM HRA. However, 3 months RSA results of TT and TR, and 1 and 2 year measurements of periprosthetic BMD revealed inferior outcomes in the AntLat group compared with the Post group.

Radiostereometric Analysis

Many different MoM HRA brands and designs have been put on marked since the 90s, where MoM HRAs were reintroduced into clinical practice [40]. Similar advantages of resurfacing arthroplasty were expected for all implant designs including femoral bone conservation, reduced dislocation risk, improved function, reduced stress-shielding, and easier revision surgery was presumed [41].

Some important differences among implant designs are: coverage angle, bearing clearance, bearing metallurgy, socket fixation surface, and also the implant companies' recommendations for the surgical technique. For implantation of the BIRMINGHAM HIP Resurfacing (BHR; Smith & Nephew), the posterior approach is strongly recommended [42]; and for the Conserve Plus (Wright Medical Technology), the surgical instruments were designed for the posterior approach [43]. But, for implantation of the articular surface replacement (ASR) system (DePuy) and the ReCap (Biomet) resurfacing system, several surgical approaches can be used [44,45]. Generally, resurfacing femur components inserted by posterior approach have minor total migrations compared with conventional stems [46–48]. In agreement hereof, we found small migrations of the ReCap femoral component in both groups, and no significant difference in migrations between groups.

In the entire study group, the most migration of both cup and stem happened within the first year, which is similar to results of other RSA studies on different MoM HRA brands [46–48], and of conventional cemented femoral stems [49,50].

In conventional cemented stems, a clinically important measurement of stem fixation is subsidence at 2 years [50]. In all patients, we measured a 2-year subsidence of the ReCap femoral component of mean −0.13 mm. In comparison, the 2-year subsidence of the ASR femoral component was mean −0.06 mm, and of the BHR femoral component was mean −0.01 mm [46,47]. This is much lower than the suggested 2-year subsidence limit of 1.2 mm in conventional cemented stems; and to our knowledge, there is yet no suggested migration limit for resurfacing.

For the acetabular cup, we found that patients operated by the AntLat approach had higher migrations of TT and TR at 3 months, than patients operated by the Post approach. When examining the individual migration axes, it appeared that the difference in migration mainly occurred as rotation around and translation along the z-axis and rotation along the y-axis. The higher cup migration in the AntLat group indicates that a tight initial press-fit fixation was not obtained to the same degree in the AntLat group compared with the Post group. It is difficult to give an exact clarification of this, but a possible explanation might be, that the AntLat approach was newer to the surgeons, and an inevitable learning curve is associated with all new surgical procedures. However, the surgeons were very familiar with the anterior approach in relation to other hip joint surgeries (Ganz osteotomy). Also, cup implantation in MoM RHA is more difficult than in traditional THA because the femoral head has to be kept during the procedure and is not removed to expose the acetabulum. Although, cup migrations of TT and TR were larger in the AntLat group at 3 months, migrations between groups at 1 and 2 years were similar. This indicates that a good secondary fixation with bone ingrowth into the acetabular cup had happen in both groups. Furthermore, at group level cup migrations of both groups were stabile between 1 and 2 years postoperative, which indicates good implant fixation [51,52]. However, there were some cups which migrated above the precision limit of RSA, but with no apparent difference between groups. These RSA results demonstrate that using two different surgical approaches, but the exact same articulation, can lead to different migration patterns.

Dual-Energy X-Ray Absorptiometry Scans

In both groups, we found that the BMD of the femoral neck had increased the most on the lateral side. Two other studies on MoM HRAs (different brands) which used the same neck regions, have reported similar results at 2 years postoperative; one study on the ASR [53] found an increase in all 3 lateral ROIs, and another study on the BHR [29] found an increase in L1 and L3, but no change in L2.

MoM HRA was thought to eliminate proximal stress shielding and osteolysis of the femoral bone when compared with conventional THA, and some 1- and 2-year studies on different types of MoM HRA implanted by the Post approach, have found either no difference or smaller effects with the BMD increase predominantly on the medial side of the femoral stem [53–56]. Likewise, we found that patients operated by the Post approach had an increase in BMD at the medial side of the femoral stem at 1 and 2 years postoperative, but interestingly, patients operated by the AntLat approach had a decrease in BMD at the medial side of the femoral stem at 1 and 2 years after operation. Even though we found a statistical difference in periprosthetic BMD between groups, the percentage decrease from postoperative and until 2 years observed in the AntLat group was overall very small (<1%), and we are uncertain about the clinical relevance and eventual future consequences of this result. We can, however, conclude that cutting the posterior capsule with a substantial part of the blood supply does not affect the BMD negatively.

Clinical Outcome Measures and Complications

At 3 months and 1 year postoperative, the results of HHS were excellent (above 90), and VAS scores of pain were low. A former study on 280 ReCap resurfacing similarly reported excellent 1-year scores of HHS (mean score 92) [57]. At 6 years postoperative, HHS had decreased a little into mean 89.3 in nonrevised patients, and the authors concluded that the ReCap resurfacing system should be regarded as a difficult, but effective surgical procedure, chosen for a small and specific patient population [57].

Recent years, it has become known that MoM RHA has an increased rate of failure compared with traditional THA [58]. A retrospective cohort study of a total of 27.971 MoM RHAs used national joint registry data to investigate independent predictors of revision after MoM RHA [59]. Data of surgical approaches from the AntLat, direct lateral, lateral, and Hardinge approach was united into one group and compared with data of the posterior approach. The study found no significant difference between surgical approach in terms of risk of revision. Instead, they reported that smaller femoral head components, women, and operations performed by low-volume surgeons were more likely to require revision. Likewise, we found that women in this study has an increased risk of revision compared with men (3/21 women vs 0/28 men has been revised until now), which is also in agreement with results of other studies [60,61].

Conventional Radiography, Implant Position and Serum Metal Ion Measurements

Brennan et al [62] reported a higher degree of neck narrowing in patients undergoing MoM HRA through the Post approach compared with the AntLat approach. They proposed neck narrowing as a result of damage to the medial circumflex femoral vessel during surgery. This theory does not support our results, as we found a smaller amount of neck narrowing in the Post group than in the AntLat group. Our results rather support that the etiology of neck narrowing may be multifactorial [63], and among others represent stress shielding, impingement related, or an inflammatory response to wear particles and/or being secondary to a vascular insult.

Patients in the AntLat group had a higher cup anteversion at 2 years follow-up than patients in the Post group (14.1° vs 9.7°), and likewise a tendency toward higher cup inclination in the AntLat group. In MoM HRA, steep cup orientation with inclinations above 50° have been associated with edge loading, leading to higher wear rates and high serum metal ion concentrations [64–66]. Two patients (AntLat) had cup inclination above 50° (50.2° and 50.7°). However, we did not find higher serum metal ion levels of chromium and cobalt among the AntLat group compared with the Post group, neither in the 2 patients with cup inclination above 50°, which might be explained in that overall the cups were well-positioned in all patients with the steepest inclination angle being 50.7° and the largest anteversion angle being 24.8°.

Conclusion

We could not verify the hypothesized superior outcomes of the AntLat approach compared with the Post approach regarding implant fixation of cup and femoral components in ReCap HRA, periprosthetic BMD around the ReCap stem, and clinical outcome scores at 2 years postoperative. We found that acetabular cup migrations were higher in the AntLat group compared with the Post group at 3 months. This could be caused by a less good primary cup fixation by AntLat approach, which might be explained by the fact that prestudy the AntLat approach was less commonly used for THA surgery among the surgeons. Furthermore, patients in the AntLat group had lost periprosthetic BMD at the medial side of the femoral stem at 1 and 2 years, whereas patients in the Post group had gained periprosthetic BMD. Although these results do not support superiority of the AntLat approach compared with the Post approach for insertion of the ReCap resurfacing hip, the differences between groups were relatively small and might not be of clinical relevance. We will continue to follow-up these patients to investigate if the midterm and long-term results reveal more noticeable differences between groups.

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KS, MS, and NDL conducted the study design, and were involved in the follow-up examinations. MH performed the statistical analyses and wrote the initial manuscript; and KS, MS, SSJ, and NDL helped to revise it. All authors approved the final manuscript. The manuscript and the material within the manuscript have not been submitted for publication elsewhere.

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STUDY IV

TITLE PAGE

The anatomical location of cystic pseudotumors and muscle atrophy in metal-on-metal resurfacing hip arthroplasty is related to the surgical approach used for implantation. A subgroup analyses of a randomized controlled trial

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Abstract

Objective Pseudotumors and muscle atrophy have been associated with metal-on-metal (MoM) resurfacing hip arthroplasty (RHA). We aimed to investigate the influence of the anterolateral (AntLat) and the posterior (Post) surgical approach on the location, grade and prevalence of pseudotumors and muscle atrophy in patients with MoM RHA

Patients and Methods 49 patients (28 males) were randomized to MoM RHA by the AntLat (n=25) or the Post (n=24) approach at Aarhus University Hospital. Patients underwent metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) scans for investigation of location, grade and prevalence of pseudotumors and muscle atrophy. Furthermore, plain radiographs and measurements of serum metal-ions were evaluated and clinical outcome scores of Harris Hip Score (HHS) and Oxford Hip Score (OHS) were assessed to compare outcomes of the two surgical approaches.

Results MRI detected pseudotumors were seen in 7 of 18 patients (39%) in the AntLat group, and in 12 of 22 patients (55%) in the Post group (p=0.33). Pseudotumors were located antero-laterally to the hip joint in the AntLat group, and postero-lateral to the hip joint in the Post group. Higher grades of muscle atrophy of the caudal part of the gluteus medius and minimus (p<0.004) were seen in the AntLat group, and higher grades of muscle atrophy of the small external rotators were seen in the Post group (p<0.001). The AntLat group had higher anteversion angels of mean 15.3° (range: 6.1–7.5)° versus mean 11.5° (range: 4.9–22.5)° in the Post group (p=0.02). Serum metal-ions and outcome scores of HHS and OHS were similar between groups (p>0.08)

Conclusion Muscle atrophy and pseudotumor location after MoM RHA follows the surgical approach used for implantation.

Keywords metal-on-metal resurfacing hip arthroplasty, pseudotumor, surgical approach, metal artifact reduction sequence magnetic resonance imaging scans, plain radiographs, serum metal-ions, clinical outcome scores

Introduction

Metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) is a useful tool when monitoring patients with metal-on-metal (MoM) resurfacing hip arthroplasty (RHA) or total hip arthroplasty (THA) [39]. It allows for excellent differentiation between soft- and hard-tissues, and identifies soft-tissue abnormalities such as; pseudotumors, muscle atrophy, tendon avulusion, and synovial thickening [39].

Pseudotumors and muscle atrophy are both part of the umbrella term "adverse reactions to metal debris" ARMD, which is used to cover unexpected and undesirable side effects associated with MoM hip articulations [29]. Pseudotumors in MoM hip arthroplasty have been reported with a prevalence ranging from 0.1% to 59% [1, 43], and muscle atrophy have been reported with a prevalence ranging from 22% to 90% [20, 43, 46]. These wide-ranging prevalence's are assumed to reflect variable inflammatory responses to the wear debris from the bearing surfaces, but may also illustrate different interpretations between radiologists [6].

The clinical significance of different pseudotumor grades is still debated, and since a large number of cystic pseudotumors have been found among asymptomatic patients, it has been suggested, that their location simply reflect the surgical approach used for implantation [15, 35, 43]. Furthermore, the anatomical location of muscle atrophy has been shown to differentiate between different surgical approaches in total hip arthroplasty [3]. No studies examines the combined influence of different surgical approaches on the location, grade and prevalence of pseudotumors and muscle atrophy in MoM RHA. Thus, the aim of this randomized study was to compare the location, grade and prevalence of pseudotumors and muscle atrophy in patients allocated to MoM RHA by the

anterolateral (AntLat) or the posterior (Post) surgical approach. We evaluated 3 hypotheses: (1) The location of pseudotumors reflects the route of the surgical approach, (2) the location of muscle atrophy differentiate between the AntLat and the Post approach, and (3) the grade and prevalence of pseudotumors and muscle atrophy is similar between the AntLat and Post approach.

Patients and methods

Between November 2008 and January 2012, a randomized clinical trial (RCT) was performed at Aarhus University Hospital where 49 patients (28 males) received the ReCap Hip Resurfacing System (Biomet Inc., Warsaw, IN, USA). Patients were allocated to surgery by either the AntLat approach (n=25) or the Post approach (n=24) (Figure 1) by opening sealed envelopes prior to surgery. This study was added to the original study protocol and performed as a sub-study to the principal RCT at cross-sectional 5.3 (3.2 – 7.7) years postoperative, and includes; MARS MRI scans of the hip joint, measurements of serum metal-ions (chromium and cobalt), plain radiographs and clinical outcome scores of Harris Hip Score (HHS), and the Oxford Hip Score (OHS). The original RCT study was planned and dimensioned for comparisons of implant migrations measured with radiostereometric analysis (RSA) until two years after surgery [23]. Besides the original RCT study, two other studies have been published on this study population; one that compare the gait characteristics at three and 12 months after surgery [45], and one that compare the metabolism in the femoral head and neck during and after surgery [33].

Inclusion criteria's in the original RCT study were primary or secondary (due to mild or moderate dysplasia) osteoarthritis of the hip, acceptable bone mineral density on pre-operative DXA scan (T-score >-1), and age between 30-60 years. Exclusion criteria were vascular or neuromuscular disease in the operated leg, fracture sequelae, avascular necrosis of the femoral head, women planning pregnancy, alcohol abuse and daily intake of non-steroid anti-inflammatory drugs (NSAID), K-

vitamin antagonists, or loop diuretics. Patients were blinded regarding the surgical approach used for implantation.

All examinations were designed and carried out in compliance with the Helsinki II declaration, laws on personal data protection, and laws on patient's rights. The study was reported to the local ethics committee who accepted it as a quality study of the ReCap Hip Resurfacing System (journal no. 1-45-70-1-17) and it was approved by the Danish Data Protection Agency (journal no. 2012-58-0005). The original RCT study was registered with www.clinicaltrials.gov (Clinical Trials Study ID number; 20070082).

The ReCap Hip Resurfacing System (Biomet, Warsaw, Indiana, USA) consist of a cobalt-chrome femoral component, which was fixed by bone-cement (Simplex P with Tobramycin (Stryker, Hopkinton, USA)), and a titanium non-hydroxyapatite-coated closed-pore porous-coated acetabular component, with a cobalt-chrome core, which was fixed by press fit. Two experienced orthopedic hip-surgeons undertook all operations using standard equipment provided by the manufacturer. Patients were assigned to surgery with MoM RHA by either the AntLat approach (ad modum Watson) [25] or the Post approach (ad modum Moore) [25]. The AntLat approach was performed with a skin incision along the anterolateral aspect of the hip. Thereafter, the anterior third of the gluteus medius and gluteus minimus muscle insertions to the femoral bone were cut, and the anterior part of the joint capsule was opened. The Post approach was used with a skin incision facing the posterior part of the hip. The fibers of the gluteus maximus muscle were separated, and the tendons from the external rotators were cut through. Finally, the posterior part of the joint capsule was opened. All patients were mobilized within six hours after surgery and full weight bearing was allowed from day one. The patients stayed in the hospital two to three days after surgery, the hospitals physiotherapists gave identical instructions to all patients with a home-based

training program. During the first six weeks, patients were advised limited flexion, adduction and internal rotation, but thereafter no further restrictions were given.

MARS MRI of the pelvis and proximal one third of both femurs was performed using two identical 1.5 T Philips Ingenia MRI scanners (Koninklijke Philips Electronics NV, Eindhoven, Netherlands). A protocol with five sequences was used (Table I). During MRI scans, patients was placed in standardized positions; supine, body parallel with the examination table, feet's fixated with a band and big toes pointing toward each other. The MRI scans were assessed on a PACS workstation (Agfa Impax, Belgium, version 6.3.1.8000), and evaluated in consensus by two observers; one experienced musculoskeletal radiologist (LR) and one PhD student (MHH). They were both blinded regarding patients' radiographs, serum metal-ions and clinical details. Pseudotumor findings were classified according to the Anderson grading system, which has the highest intraobserver and interobserver reliability of the currently used systems [5, 47]. In addition to the Anderson grading system, pseudotumors anatomical site relative to the greater trochanter (anterior, posterior, medial, or lateral) and appearance of any communication to the hip joint were recorded. In contrast to the Anderson grading system, patients were not upgraded from C1 to C2 if they had muscle atrophy or edema in any muscles other than the short external rotators, since it has been shown that different surgical approaches may cause atrophy in other muscles than the short external rotators [3].

Muscle atrophy was assessed as a decrease in volume and appearance of fatty change relative to the contralateral side according to the classification system proposed by Pfirrmann et al. [40]. In this system muscle atrophy is graded from 0 to 4. Grade 0 indicates normal muscle, grade 1 indicates some fatty streaks, grade 2 indicates less fat than muscle tissue, grade 3 indicates equal amounts of fat and muscle tissue, and grade 4 indicates more fat than muscle tissue. Grade 0–4 was evaluated for the gluteus maximus, medius and minumus, the obturatorius internus and externus, the illiopsoas, the abductors and the piriformis muscle individually.

For obliquely running muscles, multiple planes were taken into consideration before grading. Standardized weight-bearing anterior-posterior pelvic and lateral hip radiographs were obtained. The following parameters were evaluated between two observers (SSJ, MHH): narrowing of the femoral neck using the method described by Hing et al. 2007 [21], radiolucent lines > 1 mm, signs of osteolysis around the cup [12], and RHA stem [26] and heterotopic ossification [9, 13]. Cup inclination and anteversion were measured digitally (PolyWare 3D Digital version 5.10; Draftware Developers, Conway, SC). Blood samples were collected according to the published guidelines [34] to eliminate any form of metal contamination. Blood analyses were undertaken using an inductively-coupled plasma mass spectrometry (ICP-MS) at Vejle Hospital. Clinical outcome measures were assessed by the Harris Hip Score HHS [18] (range; 0-100) and the Oxford Hip Score OHS (range; 0 - 48) .

Statistical analysis All continuous variables were tested for normality (Shapiro-Wilk test). When data were not normally distributed, non-parametric tests (Mann-Whitney U-test and Wilcoxon rank-sum test) were used. When data were normally distributed, Satterthwaite's t-test was used. Calculation of the correlation coefficient (r) of independent variables was made using the Spearman correlation analysis when the data were not normally distributed, and Pearson correlation analysis was used when the data were normally distributed. A P-value below 0.05 was considered statistically significant. All analyses were performed using STATA 13 (StataCorp LP, College Station, Texas).

Results

Baseline demographics of all patients are presented in Table II. Five patients declined to have a MARS MRI scan (four AntLat, one Post), three patients had been revised (two AntLat, one Post), and one patient had a pacemarker (AntLat) and could not be MRI scanned. Thereby leaving 40

patients with MARS MRI scans (18 AntLat, 22 Post) (Figure 1) at 5.3 (3.2 – 7.7) years follow-up. MARS MRI detected pseudotumors were seen in seven of 18 patients (39 %) in the AntLat group, and in 12 of 22 patients (55 %) in the Post group, the prevalence was statistical similar ($p = 0.33$).

21 patients (52.5 %) were classified as Anderson grade A "normal or acceptable" (ten AntLat, nine Post), no patients were classified as grade B "infection", 11 patients (27.5 %) were classified as grade C1"mild MoM disease" (four AntLat, seven Post), eight patients (20 %) as grade C2 "moderate MoM disease" (three AntLat, five Post), and no patients were classified as C3 "severe MoM disease". Descriptive data of patients with a pseusotumor are presented in table III. Two patients (graded as C2) had bone marrow edema (BME); one female (Post) had BME located at the ischial tubercle, and one male (AntLat approach) had BME located at the top of the anterior part of the greater trochanter (pt. no. 6 and 49 in Table III). Clear communication between the pseudotumor and the hip joint was evident in 11 patients (four AntLat, seven Post). The communication in patients operated by the AntLat approach was seen anterior to the hip joint, whereas the communicating path was seen posterior to the hip joint in patients operated by the Post approach (Figure 1, 3, and 4). No solid or mixed-type pseudotumor was found.

Patients in the AntLat group had significantly higher grades of muscle atrophy of the caudal part of gluteus medius and minimus ($p < 0.004$) compared to patients in the Post group. However, patients in the Post approach had significantly higher grades of muscle atrophy of the short external rotator muscles (piriformis, obturator internus and externus) ($p < 0.001$) compared to patients in the AntLat group (Table IV).

Comparison of the postoperative and the 5.3 (3.2 – 7.7) years plain radiographs revealed neck narrowing in the AntLat group of mean 11 % (range: 3 % to 27 %) and in the Post group of mean 11 % (range: 3 % to 26 %), which was similar ($p = 0.65$). In total, five radiolucent lines were found in DeLee Zone I in five different cups (one in the AntLat group and four in the Post group). 10

radiolucent lines were observed around the ReCap stem, six were found caudally around the lowest part of the stem (two AntLat, four Post), and another four were found medial to the stem (three AntLat). Cup anteversion angle of mean 15.3° (6.1 – 27.5)° in the AntLat group was significantly less compared to mean 11.5° (4.9 – 22.5)° in the Post group ($p = 0.02$) (Table II). Serum metal-ions, and outcome scores of HHS and OHS was similar between groups ($p>0.08$) (Table V).

Three female patients (two AntLat, one Post) had undergone revision surgery. One female (AntLat) approach was revised due to aggravating groin pain. Measurements of chromium and cobalt were 2.5 µg/L and 18.23 µg/L, and CT scan revealed a 90 x 24 x 55 mm pseudotumor (Figure 5). At three months postoperative measurements of chromium and cobalt were 1.12 µg/L and 1.22 µg/L, respectively, and the patient described that the pain had decreased [22]. The other two females who underwent revision surgery of their MoM ReCap resurfacing, both reported pain in the groin area. But, both of them had low levels of chromium and cobalt, and nothing abnormal was seen on MRI or ultrasonography (US) scans. After revision surgery into conventional metal-on-polyethylene THAs both patients reported a decrease in pain.

Discussion

To our knowledge, this is the first study to investigate the influence of the surgical approach on the location of pseudotumor and muscle atrophy in MoM RHA patients. Interestingly, we found that the pseudotumors were located on the surgical route used for implantation; patients operated by the AntLat approach had pseodotumors antero-laterally to the hip joint, and patients operated by the Post approach had pseudotumors postero-lateral to the hip joint. This strongly indicates that the surgical approach has significant influence on the anatomical location of pseudotumors in MoM RHA. Previous papers have proposed this theory [15, 35, 43] however; this is the first study to verify it.

Even though different treatment algorithms have been published for patients with MoM hip arthroplasties [27, 32], there is still no consensus of how to follow this patient group. Patients with asymptomatic pseudotumors currently pose a dilemma to surgeons - especially if there is no related bone or soft-tissue damage. Anderson et al. suggest, that patients graded as C1 should be followed-up clinically with serial MRI, patients graded as C2 should be revised electively, and patients graded as C3 should be revised urgently [5]. However, Van der Weegen et al. propose a more conservative approach in patients graded as Anderson C2, who are asymptomatic and have normal metal-ion levels [48]. We support this suggestion since our study shows that both C1 and C2 pseudotumors might simply reflect a normal postoperative finding related to the surgical trauma/approach. Also, short-term results of revised MoM hip arthroplasties have shown poor outcomes [16, 38], and longitudinal studies have shown only small changes in pseudotumor size/type between two cross-sectional images [4, 14, 41]. Thus, we believe that an overly aggressive surgical treatment of asymptomatic pseudotumores should be avoided.

All patients had some degree of muscle atrophy, which shows that muscle atrophy is a common finding in patients with MoM RHA. This is in line with previous reports on MoM hip articulations [6, 20, 42, 46].

The Anderson classification considers muscle atrophy in any other muscles than the short external rotators as a pathologic finding [5]. Our results shows that the anatomical location of muscle atrophy in MoM RHA differs between the AntLat approach and the Post approach. A recent paper, which compares soft tissue alterations between the posterior, the direct-lateral, the anterolateral and the anterior surgical approaches, reports results in conventional hip arthroplasty similar to ours with MoM HRA [3]. Furthermore, Mistry et al. found that 17 of 22 patients operated by the Post approach had muscle atrophy of the short external rotator muscles (particularly obturator internus and piriformis), but two patients operated by the AntLat approach had normal obturator internus

and piriformis muscles [37]. Results of these two studies supports that muscle atrophy of the short external rotators is an incidental finding in uncomplicated hip arthroplasty where a Post approach has been used, as well as muscle atrophy of gluteus medius and minimus may be an incidental finding where an AntLat approach has been used. This knowledge about "normal postoperative appearence" of muscle atrophy is important for the clinician who examines patients with MoM hip arthroplasties.

Hard-on-hard bearings have shown a low tolerance for acetabular cup positioning outside a reported "optimal zone", because cup malposition is associated with edge-loading, high metal-ion levels, and early implant failure [17]. Even though, we found that cup anteversion angles were significantly different between patients in the AntLat group and patients in the Post group (15.3° versus 11.5°), no difference was found in serum metal-ion levels, pseudotumor prevalence or outcome scores of HHS or OHS. This might be explained by the fact that most cups were well-positioned in the "safe-zone" [31] . Inclination angles range between 27.5° to 52.2° and anteversion angle range between 4.9° to 27.5°. Moreover, the combined effect of the inclination angle, arc of cover, component size, and anteversion angle may play a bigger role for edge-loading than the anteversion angle alone [11, 28]. Additionally, pseudotumors have previously been found in patients with satisfactorily positioned acetabular components [36], as well as in patients with inadequate acetabular component positions [30] which underlines that the relationship between acetabular component positioning and pseudotumors is complex.

At 5.3 (3.2 – 7.7) years postoperative, three female patients (6.12 %) had been revised. The National Joint Registry for England (NJR) reports a similar seven-year cumulative percentage probability of revision of 7.79 % for the MoM ReCap Resurfacing [2], and a recent meta-analysis showed a 2.5 times higher risk for revision of MoM RHA in females compared with men [19]. Even

though a small number of participants limits our study, our results are similar and supportive to those found in these larger studies.

Our study has some limitations that should be kept in mind when interpreting the results. First, a few patients from the original RCT study declined to participate in this additional follow-up of their MoM RHA, which might have caused some bias. Patients unwilling to participate could either be those who experienced no problems with their MoM RHA or those who did not have the extra energy to participate in further investigations. Second, we had no control group with conventional bearing types. Recently authors have reported pseudotumors and muscle atrophy in patients with other bearing surfaces like ceramic-on-polyethylene and metal-on-polyethylene THA [7, 8, 10, 24, 37, 44] and it would have been interesting to compare the effect of different surgical approaches on the location, grade and prevalence of pseudotumors and muscle atrophy in these bearing types as well.

In conclusion, pseudotumors were located on the route of the approach used for implantation; patients in the AntLat group had pseudotumors antero-laterally to the hip joint, and patients in by the Post group had pseudotumors postero-lateral to the hip joint. All patients had some degree of muscle atrophy; in patients operated by the AntLat approach muscle atrophy of the caudal part of gluteus medius and minimus was dominating, and in patients operated by the Post approach atrophy of the short external rotators was dominating. This study adds important information to the literature, about pseudotumor location and soft tissue alterations after MoM RHA using two different surgical approaches.

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Figure 1: CONSORT Flow Diagram showing the inclusion/exclusion process for the original RCT study, and follow-up for the sub-study at mean 5.3 (3.2 – 7.7) years' postoperative.

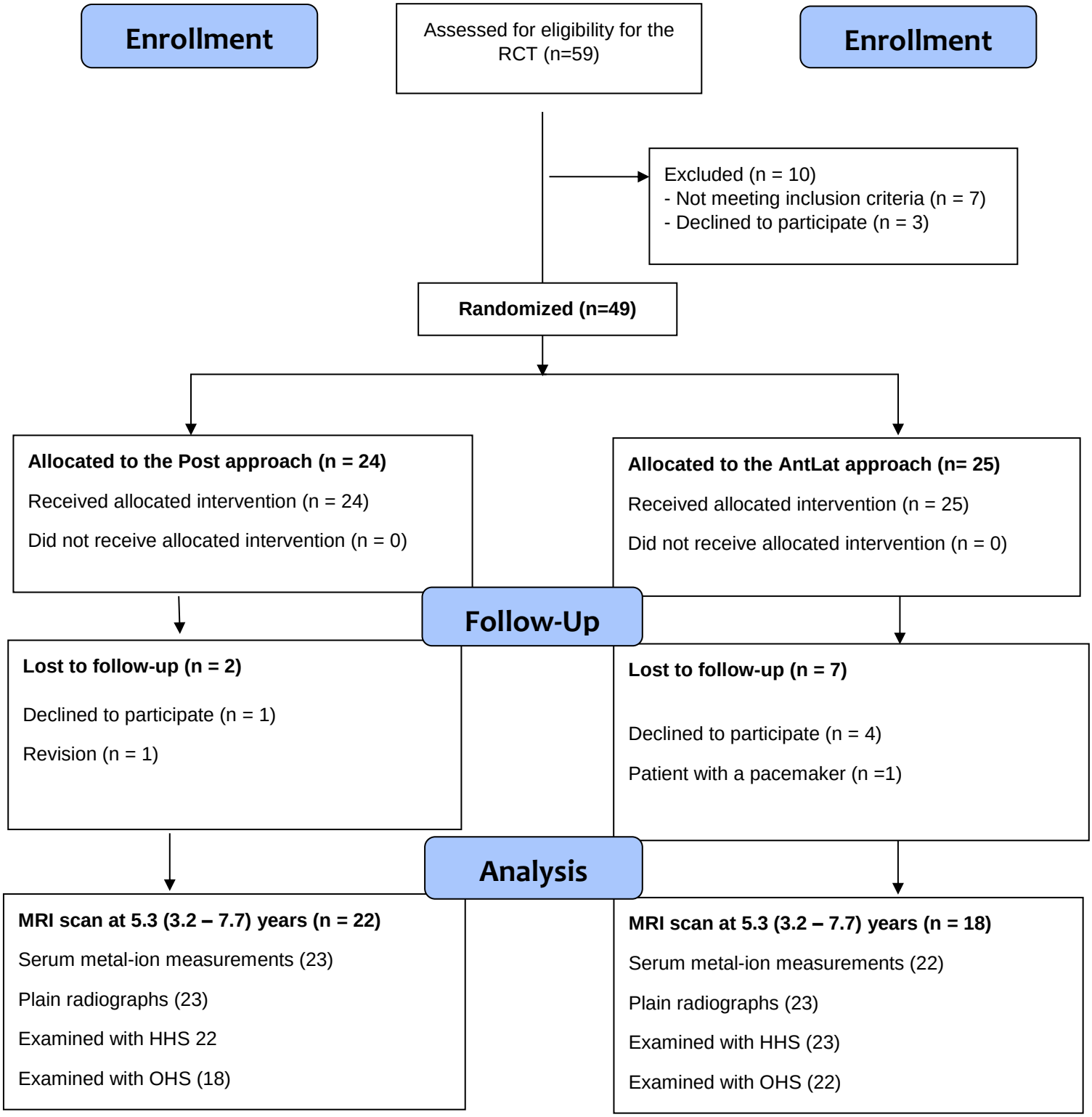

Figure 2 Coronal (A) and axial (B) MARS MRIs of a 32-year-old male with a pseudotumor located latero-dorsal to the greater trochanter, and communicating with the hip joint (pt. no. 10 in Table III).

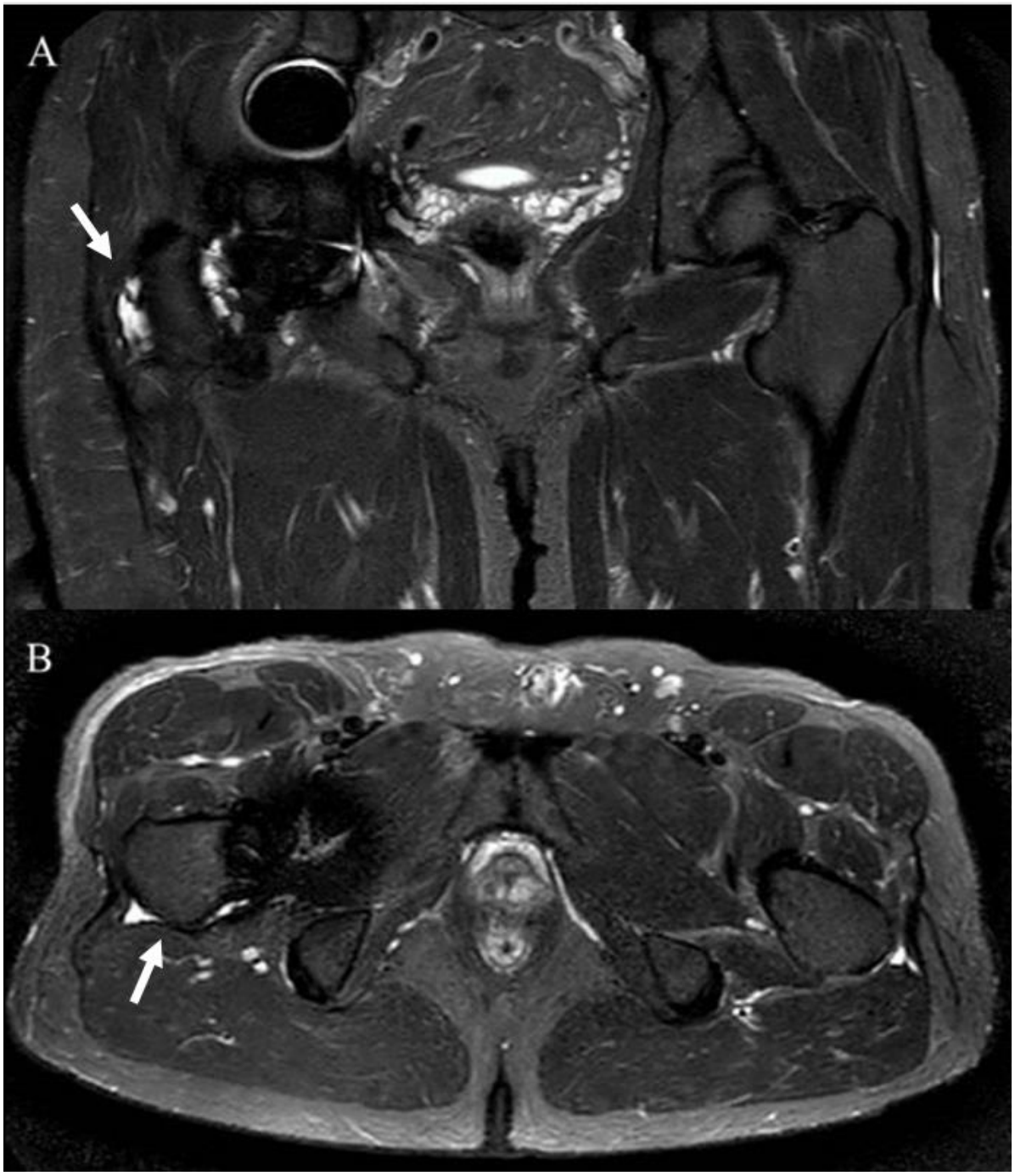

Figure 3 Coronal (A) and axial (B) MARS MRIs in a 60-year-old male with a pseudotumor located antero-laterally to the greater trochanter and communicating with the hip joint (pt. no. 25 in Table III).

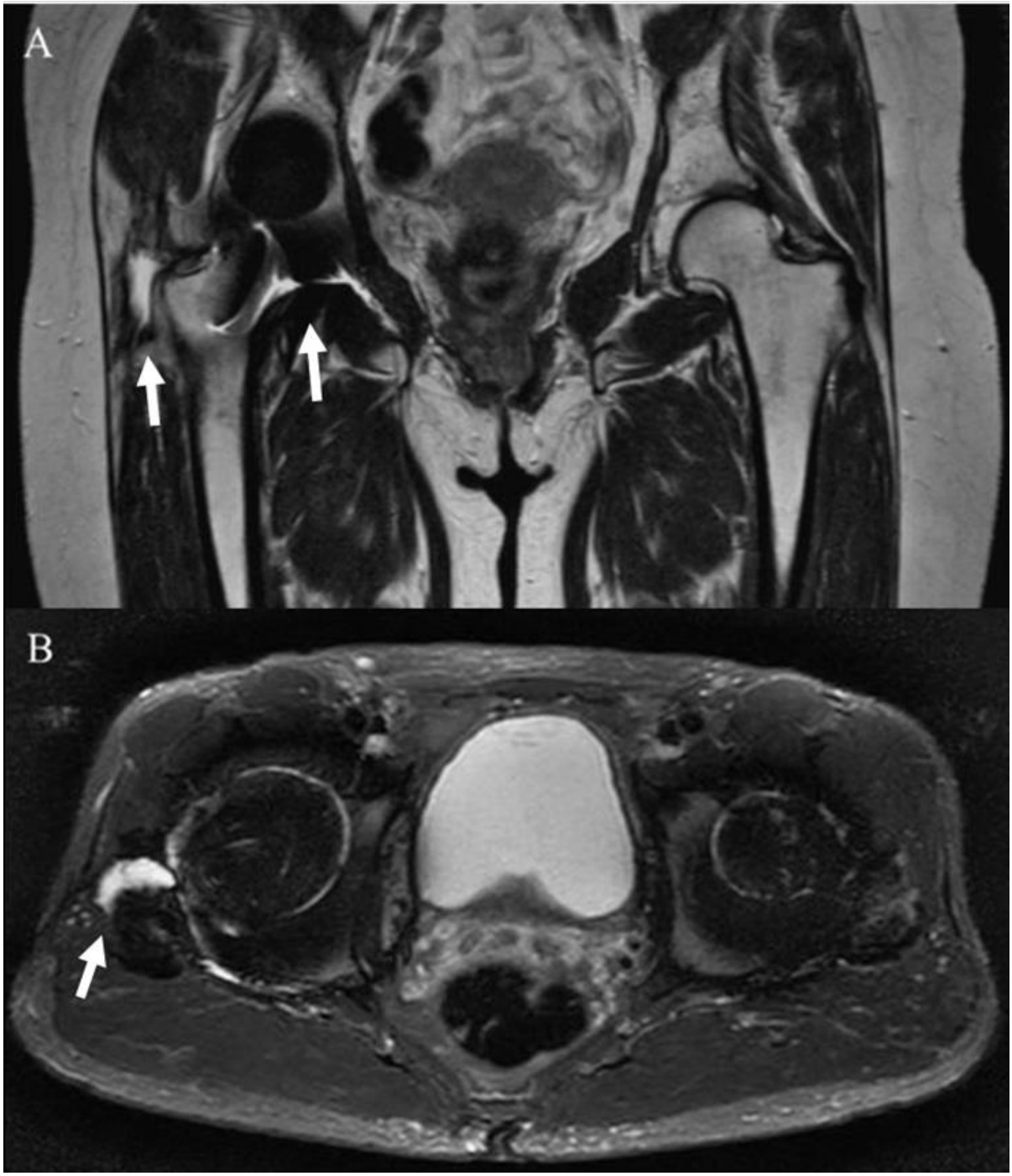

Figure 4 Coronal (A) and axial (B) MARS MRIs in a 50-year-old female with a pseudotumor located antero-laterally to the greater trochanter and communicating with the hip joint (pt. no. 17 in Table III).

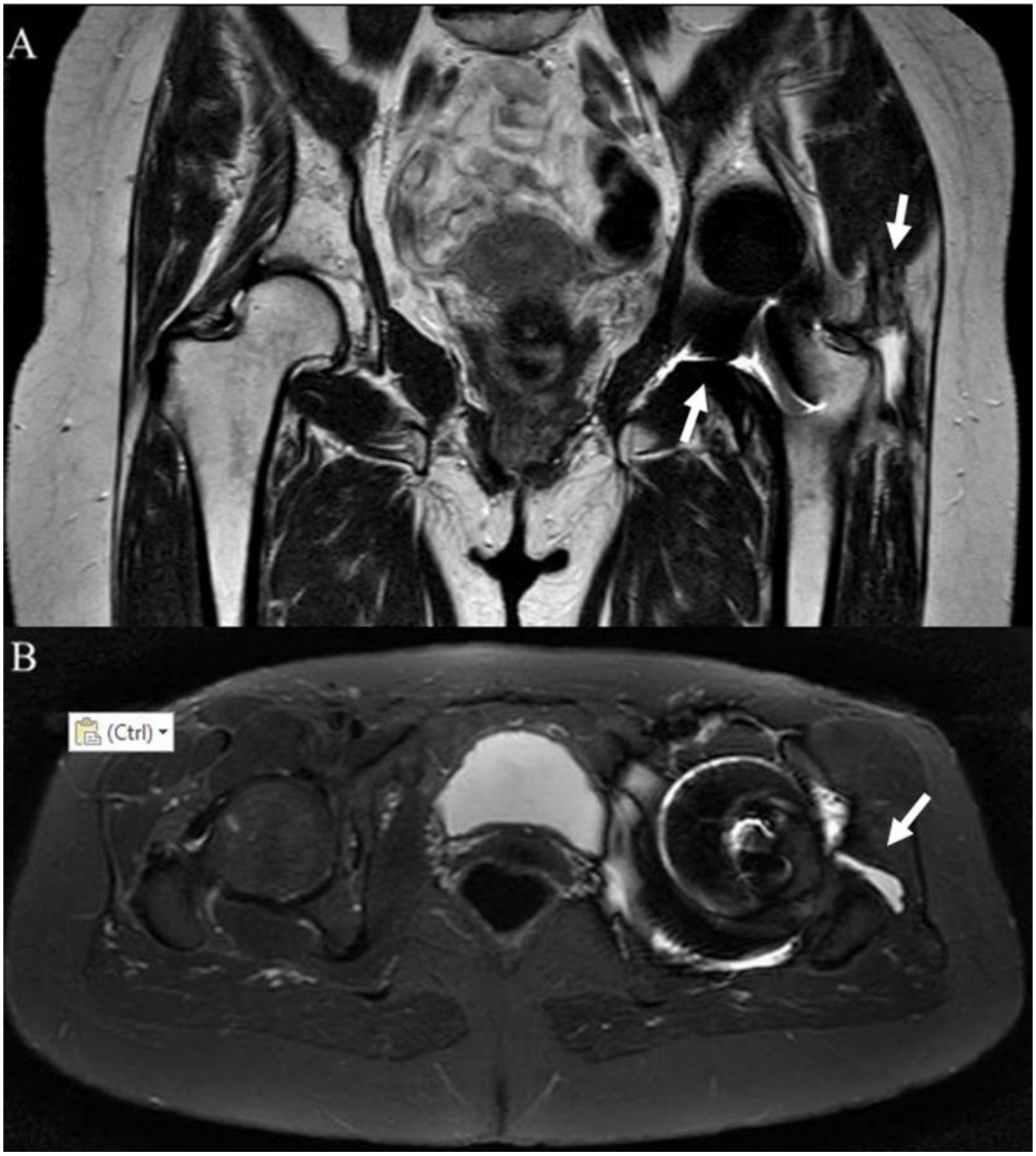

Figure 5 Picture of the 90 x 24 x 55 mm pseudotumor located at the top of trochanter major and reaching distally from there**.**

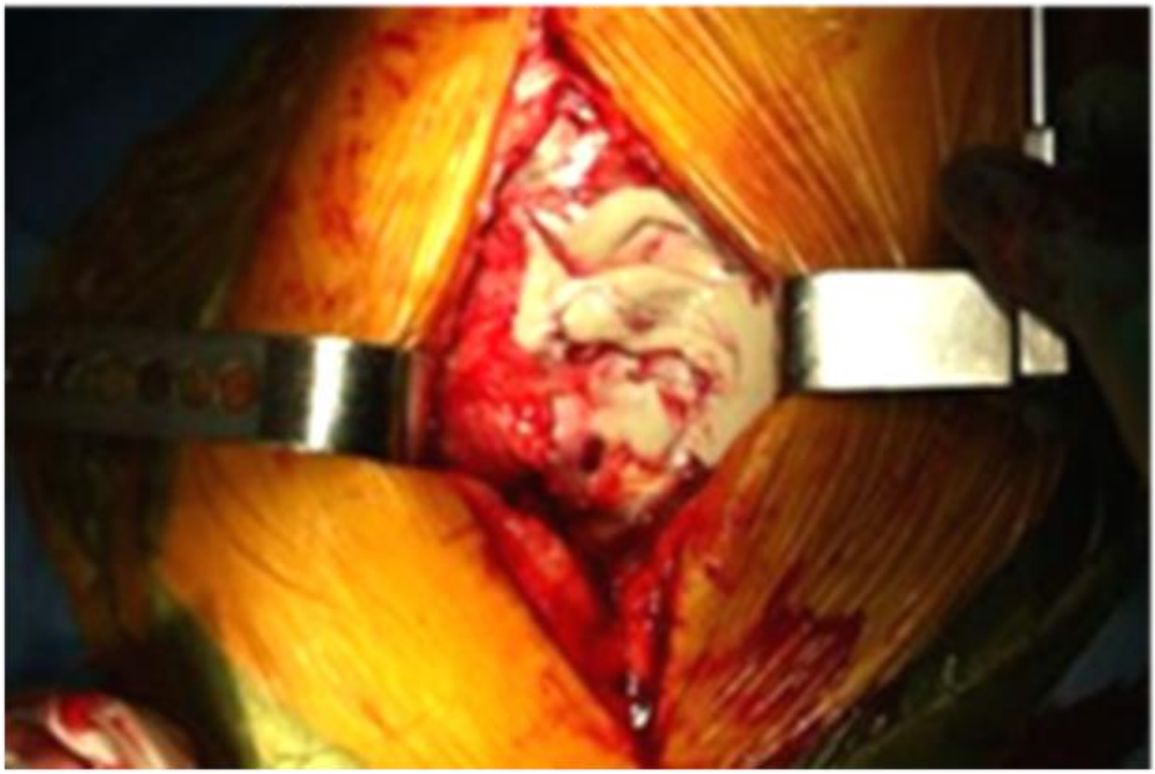

Table I Details of magnetic resonance imaging parameters used in this study

Pulse sequence name	TE (ms)	TR (ms)	TI (ms)	ST (mm) / gap (mm)	FOV	Matrix size	BW (Hz/pixel)	Coil
Coronal T1W MARS	15	450-650	-	2.5 / 1	360x450	380x356	438,6	Sense Body 16ch
Coronal STIR MARS	40	4000-8000	130	3.5 / 1	400x454	364x320	434,7	Sense Body 16ch
Coronal T2W MARS	80	3000-7000	-	2.5 / 1	360x450	380x316	438,6	Sense Body 16ch
Axial T1W MARS	16	450-650	-	2.5 / 1.5	400x454	420x348	437,7	Sense Body 16ch
Axial STIR MARS	40	4000-8000	130	3.5 / 1.5	360x447	276x272	435,5	Sense Body 16ch

W: Weighted
TSE: Turbo spin echo
STIR: Short tau inversion recovery
TE: Time of echo (ms, millisecond)
TR: Time of repetition (ms, millisecond)
TI: Time of inversion (ms, millisecond)
ST: Slice thickness (mm, millimeter)
FOV: Field of view
BW: Band width

Table III. Descriptive data of patients with pseudotumors divided into two groups based on the surgical approach used

Pt.	Age	Side	Sex	Dimensions	Position	Anderson classification	Chromium	Cobalt	OHS	HHS	Anterversion	Inclination
Patients operated by the posterior approach												
4	56	R	F	36x19x8	LD	C1	2.14	1.12	43	100	7.3	39.5
6	54	R	F	73x12x29	LD	C2	14.10	11.15	-	100	7.8	34.7
7	38	L	M	27x52x19	LD	C2	5.63	2.67	47	100	16.9	33.5
10	32	R	M	28x49x19	LD	C1	1.24	1.07	46	99.75	5.0	37.3
28	60	L	M	41x14x19	L	C1	4.69	5.58	47	99.87	17.8	43.3
32	62	L	F	24x52x10	LD	C2	6.31	2.94	46	99.95	4.9	50.1
35	40	R	F	46x5x27	L	C1	2.60	1.23	42	97.95	10.2	30.4
41	47	R	F	15x9x8	LD	C1	6.96	4.27	48	100	6.9	42.9
42	55	R	M	35x2x18	L	C1	1.32	1.04	-	99.95	12.4	45.6
43	56	R	F	70x60x42	LD	C2	4.66	3.06	44	96.02	9.3	42.4
46	46	R	M	17x7x7	L	C1	1.44	0.83	40	95.6	22.5	46.9
47	37	R	M	50x65x18	LD	C2	0.63	0.78	41	100	21.7	38.5
Patients operated by the anterolateral approach												
14	48	L	F	15x4x10	L	C1	1.23	0.84	33	94.45	15.6	38
15	55	R	M	41x5x13	L	C1	2.02	2.17	47	96.02	11.3	45.3
17	50	L	F	40x28x17	AL	C1	1.17	0.88	44	100	18.2	34.7
25	60	R	M	67x33x34	AL	C2	0.75	0.65	48	99.95	12.3	43.7
31	50	R	M	78x42x32	AL	C2	1.52	0.96	47	100	6.1	41.9
45	56	L	M	47x20x6	L	C1	1.80	3.93	48	75.75	11.9	43
49	51	R	M	15x26x10	AL	C2	1.40	0.92	47	96.02	20.4	42

Age: age of the patient at the time of primary MoM RHA
Dimensions: Maximum depth, width and height in mm
Position: Anatomical location of the pseudotumor in relation to the greater trochanter, LD = latero-dorsal, L=Lateral, AL = Anterolateral
Anderson Classification: C1 = Mild MoM disease, C2 = Moderate MoM disease
Chromium: Concentration of serum-ion chromium (µg/L)
Cobalt: Concentration of serum-ion chromium (µg/L)
Anteversion: Cup anteversion angles (º)
Inclination: Cup inclination angles (º)

Table IV Grades and anatomical location of muscle atrophy. Data available from 21 patients operated by the Post approach and 18 patients operated by the AntLat approach.

	Grade of muscle atrophy	Post approach	AntLat approach	*p*-value[a]
Gluteus maximus	0	19	15	0.79
	1	2	2	
	2	0	1[1]	
	3	0	0	
	4	0	0	
Gluteus medius	0	18[2]	5[2]	0.001
	1	0	0	
	2	1[2]	3[2]	
	3	1[2]	5[2]	
	4	1[2]	5[2]	
Gluteus minimus	0	20	9	0.004
	1	0	1[3]	
	2	0	3[3]	
	3	1	3[3]	
	4	0	2[3]	
Piriformis	0	1	10	0.001
	1	5	2	
	2	2	3	
	3	1[1]	2	
	4	2	1	
Obturatorius internus	0	1	8	0.000
	1	0	5	
	2	1	1	
	3	7	1	
	4	12	3	
Obturatorius externus	0	1	12	0.000
	1	3	2	
	2	6	2	
	3	11	2	
	4	0	0	
Iliopsoas	0	20	15	0.59
	1	1	1	
	2	0	1	
	3	0	0	
	4	0	1[4]	
Adductors	0	21	16	0.21
	1	0	0	
	2	0	1	
	3	0	1[5]	
	4	0	0	

[a] Fischer´s exact test
[1]Located to the caudal part of gluteus maximus
[2]Located to the caudal part of gluteus medius
[3]Located to the caudal part of gluteus minimus
[4]Located to the caudal part of iliopsoas
[5]Located to adductor longus

Tabel V Scores of the Harris Hip Score (HHS), the Oxford Hip Score (OHS) and measurements of chromium and cobalt metal-ions 5.3 (3.2 – 7.7) years postoperative. Values are mean (range).

	Post approach	AntLat approach	*p*-value[a]
Harris Hip Score (22/23)	97.4 (75.8 - 100)	94.2 (29 - 100)	0.57
Oxford Hip Score (18/22)	43.2 (31 - 48)	44.6 (15 - 48)	0.08
Chromium (µg/L) (23/22)	3.4 (0.59 - 14.1)	1.9 (0.65 – 4.1)	0.35
Cobalt (µg/L) (23/22)	2.51 (0.59 – 12.8)	1.68 (0.59 – 8.5)	0.47

[a] Two-sample Wilcoxon rank-sum (Mann-Whitney) test.