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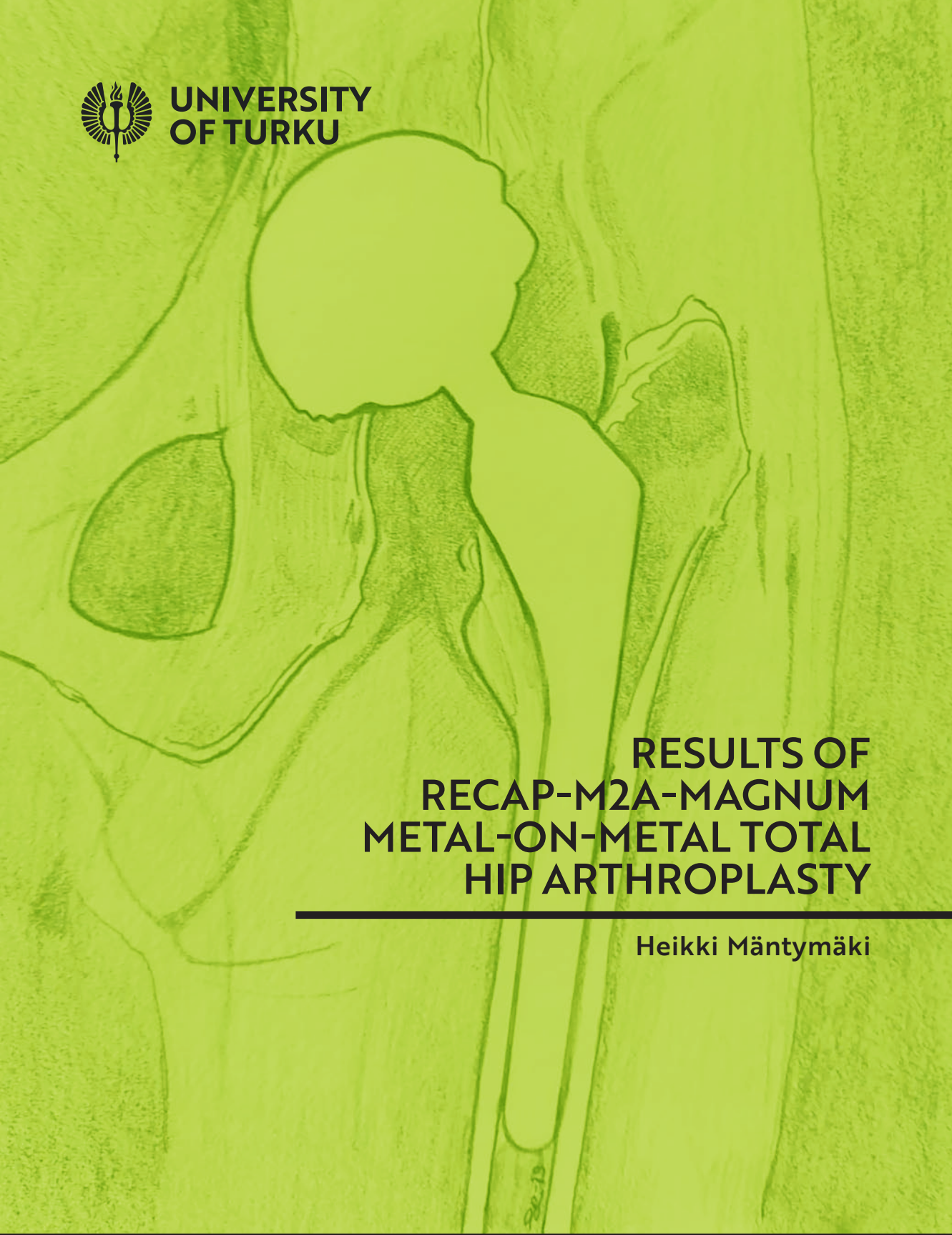

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Heikki Mäntymäki

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To My Family, Leena-Mari, Saga and Isak

” Mennäänpäs mokoman suon yli, että heilahtaa.”
-kapteeni Kaarna, Väinö Linna: Tuntematon sotilas, 1954

UNIVERSITY OF TURKU
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ABSTRACT

Metal-on-polyethylene (MoP) bearing surfaces were standardized by Sir John Charnley and are still considered the gold standard in total hip arthroplasty (THA). Nevertheless, MoP THAs caused polyethylene wear and led to osteolysis and revisions, especially among young and active patients. Metal-on-metal (MoM) bearing surfaces were developed to solve these problems.

After a brief triumph, however, poorer outcomes raised concerns over MoM THAs as well. A unique type of complication was encountered: adverse reaction to metal debris (ARMD). ARMD has been the reason for excessive failures, in MoM THA.

This thesis concentrates on ReCap-M2a-Magnum MoM THA. It has comparably low revision rate of less than 10% at ten years (Australian Orthopaedic Association National Joint Replacement Registry, 2018).

The aim of this thesis was to ascertain the frequency and risk factors of ARMD, assess the challenges in revision surgery, and clarify the role of whole blood cobalt and chromium metal ion levels in relation to the ReCap-M2a-Magnum device. Data was obtained from the Turku University Hospital and Oulu University Hospital electronic databases. This was the most common hip device used at Turku University Hospital from 2004 to 2012.

We found a high prevalence of ARMD in a systematic screening of all of the ReCap-M2a-Magnum THA patients. Out of 1329 hips, 157 (11.8%) were considered to have definitive ARMD. In revision surgery the femoral head was frequently jammed into the stem, in 29% (20/70) of operations. Head removal was complicated, increasing operation times and intraoperative bleeding. Metal ion measurements are taken frequently during follow-up of MoM THA patients, but no increase was found in unilateral ReCap-M2a-Magnum patients over a mean 2-year interval.

KEYWORDS: Metal-on-Metal, bearings, total hip arthroplasty

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TIIVISTELMÄ

Sir John Charnley kehitti sementtikiinnitteisen lonkan tekonivelen, missä komponenttien liukuparina oli metalli-polyetyleeni. Tähän liukupariin on todettu liittyvän polyetyleenihiukkasten irtoamista, minkä on todettu aiheuttavan tekonivelen viereisen luun osteolyysiä. Tästä syystä myös muita liukupareja on tutkittu.

Metalli-metalli-liukuparin arveltiin ratkaisevan tämän ongelman. Tästä syystä 2000-luvun alussa ko. liukuparia alettiin käyttää runsaasti lonkan tekonivelleikkauksissa. Varsin pian kuitenkin havaittiin, että tähänkin liukupariin liittyy ongelmia, narinaa, ääntelyä ja ns. metallihierreoireyhtymä (Adverse Reaction to Metal Debris = ARMD).

Eri metalli-metalli-liukuparitekoniveliin liittyvät ongelmat vaihtelevat. Tässä väitöskirjassa on tutkittu ReCap-M2a-Magnum -nimisen lonkan metalli-metalli liukupari-mallia. Tähän tekonivelmalliin liittyy muita vastaavia tekonivelmalleja pienempi uusintaleikkausriski. Australian tekonivelrekisterin mukaan tämä riski on alle 10% kymmenessä vuodessa.

Osatyössä 1 selvitettiin ReCap-M2a-Magnum tekonivelen nupin ja reisikomponentin kylmähitsautumisen yleisyyttä ja siitä aiheutuvia ongelmia uusintaleikkauksessa.

Osatyössä 2 tutkittiin metallihierreoireyhtymän esiintyvyyttä ja sen riskitekijöitä.

Osatyössä 3 tutkittiin potilaiden veren koboltti- ja kromipitoisuuksien muutoksia ko. tekonivelleikkauksen jälkeen.

Osatöiden potilasaineisto on kerätty Turun yliopistollisen keskussairaalan ja Oulun yliopistollisen sairaalan tekonivelrekistereistä vuosilta 2004-2012.

Tutkimusten tuloksena kylmähitsautumisilmiö ReCap-M2a-Magnum tekonivelen nupin ja reisikomponentin kartioliitoksen välissä havaittiin 29 %:ssa uusintaleikkauksia. Tämä ilmiö lisäsi leikkausaikaa ja leikkauksen aikaista veren vuotoa. Tätä tekoniveltä käyttävillä potilailla on lisääntynyt riski saada metallihierreoireyhtymä. Se todettiin 11,8 %:lla tätä tekoniveltä käyttävillä tekonivelpotilailla. Kahden vuoden seuranta-aikana koboltti- ja kromipitoisuudet eivät nouse merkittävästi ReCap-M2a-Magnum lonkan tekoniveltä käyttävillä potilailla.

AVAINSANAT: Metalli-metalli, liukupinta, lonkan kokotekonivel

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Abbreviations

ALVAL	Aseptic lymphocyte-dominant vasculitis-associated lesion
AOANJRR	Australian Orthopedic Association National Joint Replacement Registry
ARMD	Adverse reaction to metal debris
ASR	Articular Surface Replacement
BHR	Birmingham Hip Resurfacing
CI	Confidence interval
Co	Cobalt
CoC	Ceramic-on-ceramic
CoP	Ceramic-on-polyethylene
Cr	Chromium
CT	Computed tomography
FAS	Finnish Arthroplasty Society
FAR	Finnish Arthroplasty Register
FINAS	Finnish Accreditation Service
HMWP	High molecular weight polyethylene
HR	Hip resurfacing
HRA	Hip resurfacing arthroplasty
HXLPE	Highly cross-linked polyethylene
LDH	Large-diameter head
MARS-MRI	Metal artifact reduction sequence magnetic resonance imaging
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MoM	Metal-on-metal
MoMHA	Metal-on-metal hip arthroplasty (including both HR and THA)
MoP	Metal-on-polyethylene
OHS	Oxford Hip Score
OR	Odds ratio
THA	Total hip arthroplasty
THR	Total hip replacement
US	Ultrasound
WB	Whole blood

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Mäntymäki H, Mäkelä KT, Vahlberg T, Hirviniemi J, Niinimäki T. Modular to Monoblock: Difficulties of Detaching the M^{2}a-Magnum^{TM} Head Are Common in Metal-on-metal Revisions. Clin Orthop Relat Res. 2016 Sep;474(9):1999-2005.

II Mäntymäki H, Junnila M, Lankinen P, Seppänen M, Vahlberg T, Mäkelä KT. Systematic Screening of Adverse Reactions to Metal Debris after Recap-M2A-Magnum Metal-on-Metal Total Hip Arthroplasty. Scand J Surg. 2017 Dec;106(4):342-349.

III Mäntymäki H, Lankinen P, Vahlberg T, Reito A, Eskelinen A, Mäkelä KT. Repeated cobalt and chromium ion measurements in patients with large-diameter head metal-on-metal ReCap-M2A-Magnum total hip replacement. Acta Orthop. 2019 Apr 4:1-9.

1 Introduction

Total hip arthroplasty (THA) is considered to be a successful orthopedic operation. In 2007 it was named the "operation of the century" (Learmonth, Young, & Rorabeck, 2007). THA can be performed for any reason that leads to destruction of the hip joint, but in the vast majority of cases, i.e. 90%, the culprit is severe osteoarthritis (Pivec, Johnson, Mears, & Mont, 2012). The prevalence of hip osteoarthritis is roughly 4% (C. Kim et al., 2014).

Appropriately performed THA should fulfill the NICE criteria, meaning at least 90% survival rates over 10 years trending towards 95% (NICE, 2014). Due to the success of THA, the margin for improvement is narrow. Metal-on-polyethylene (MoP) bearing surfaces, standardized by Sir John Charnley, are still considered the gold standard in THA. Nevertheless, metal-on-metal (MoM) bearing surfaces were developed to resolve problems with conventional MoP, which were failing especially in young adults due to polyethylene wear and osteolysis, leading to aseptic loosening. MoM bearings also enabled the construction of a thinner cup and therefore large diameter head to prevent dislocations (Maloney et al., 1999).

MoM THA and hip resurfacing arthroplasty (HRA or HR) became very popular, with some 1,000,000 MoM hip arthroplasties performed worldwide (Kwon et al., 2014; Pivec et al., 2012). More than 20,000 MoM THAs were performed in Finland (Finnish Arthroplasty Register, n.d.). However, the triumph of MoM THAs was short lived due to rising concerns over poorer outcomes. In 2008 the Australian Orthopaedic Association's National Joint Replacement Registry (AOANJRR) reported poorer survival of the Articular Surface Replacement (ASR) THR in its annual report (Australian Orthopaedic Association National Joint Replacement Registry, 2008). A unique type of complication was encountered: adverse reaction to metal debris (ARMD). Over the years, with the same problem reported around the world, ARMD became better understood and appeared to be behind the excessive failures of MoM THAs.

The problems related to MoM bearings are now well known. Their use is no longer recommended, but a great number of people still have MoM THAs in place. Better, comprehensive understanding of the problem has led to constantly developing protocols for monitoring and managing these patients. Evaluation of

MoM patients includes blood metal ion measurements, radiographs, patient reported outcome measures like the Oxford Hip Score (OHS) and, when necessary, MRI imaging.

Outcomes differ depending on the brand of MoM THA. Implant survival of ASR THA is significantly worse than with other MoM THA devices (Seppanen et al., 2018). At Turku University Hospital, neither ASR THA nor ASR HRA has been used at all; the most common MoM THA device has been the ReCap-M2a-Magnum (Zimmer Biomet), with more than 1000 implantations.

The aims of this study were to ascertain the frequency and risk factors of ARMD, assess the challenges of revision surgery, and clarify the role of WB cobalt and chromium metal ion levels in ReCap-M2a-Magnum patients.

2 Review of the Literature

2.1 History of total hip arthroplasty

In the 19th century, the treatment for infected and ankylosed hip joints was osteotomies and hip excision arthroplasties. These were carried out by several surgeons (R. Jones, 1904; Morton, 1872; Yale, 1886) but became popularized by and hence named after Gathorne Robert Girdlestone (Girdlestone, 1924, 1926). Interpositional arthroplasty was used in the late 19th and early 20th centuries. The operation involved placing different kinds of material such as fascia and fat tissue between articulating hip surfaces (Murphy, 1913) . Usually this was done to mobilize ankylosed hips and the interposed tissue was supposed to prevent re-fusing (Wiles, 1958).

The first hip arthroplasty attempts were made by Themistocles Gluck using ivory, which he used for other interventions also. He published an article about his experiments in 1891 (Glück, 1891).

Later, Norwegian-born surgeon M. N. Smith-Petersen, who made his medical career in the United States, developed the “mold arthroplasty”, which involved placing a loose mold of glass between shaped surfaces of the femoral head and the acetabulum. This was first done in 1923. In 1938 he started using a metal alloy, Vitallium, in the same way (Charnley, 1961; Smith-Petersen, 1948).

Hemiarthroplasty was advanced through the work of Austin T. Moore and Harold Ray Bohlman, who developed a hip prosthesis to replace the femoral head, fixed with a short stem (Sinha, 2002). In 1940 they inserted the first Vitallium hemiendoprosthesis in a patient with a suspected tumor. Their case report was published in the Journal of Bone and Joint Surgery in 1943 (Moore & Bohlman, 1943). Moore developed and used hemiendoprostheses from the early 1950s, and reported encouraging results in 159 patients with a minimum of 2-years of follow-up (Moore, 1957). The Austin Moore hemiarthroplasty was a success and is still in use (Lin et al., 2012).

Figure 1. Austin-Moore hip prosthesis

Thompson wrote a comprehensive report with preliminary results from 14 patients with “Vitallium intramedullary hip prosthesis” in 1952 (Thompson, 1952). It was developed as an uncemented hemiendoprosthesis. Hence, the acetabulum was not replaced (Hernigou, Quiennec, & Guissou, 2014). The results were promising, and the success continued. The Thompson hemiarthroplasty is still used today in the treatment of hip fractures (Sims et al., 2018).

Figure 2. Thompson hip prosthesis

Attempts to invent a total hip arthroplasty, which contains an acetabular component, continued due to erosion of the acetabulum in hemiarthroplasty. John Heywood-Waddington studied patients with a Moore prosthesis and concluded that problems were encountered especially in those with osteoarthritic hip joints when the acetabulum was degenerated and required reaming (Heywood-Waddington, 1966).

The first hip resurfacing arthroplasty was described by the French Judet brothers in 1950. A few years earlier they had started to perform operations they called

"resection reconstruction", resurfacing the femoral head with an acrylic prosthesis. The prosthesis contained a short rod with steel reinforcement to fix it firmly to the femur (Judet & Judet, 1950). The good early results did not last, however, and osteolysis (possibly due to wear) and loosening prevented the popularization of this prosthesis (D'Aubigne & Postel, 1954). Danish surgeon Sven Kiær used the Judet prosthesis and fixed it with bone cement (Kiaer, 1952).

British surgeon Sir John Charnley has been considered the founder of the modern THA. His method is still considered the gold standard of THA (Charnley, 1964; Knight, Aujla, & Biswas, 2011). Charnley used bone cement to fix both the stem and acetabular component to the bone (Charnley, 1960), securing a firm fixation. He developed his "Low Friction Arthroplasty of the Hip" concept with a 22 mm femoral head to minimize frictional torque and published a detailed book on the concept in 1979 (Charnley, 1979).

Figure 3. Stem of Charnley's hip arthroplasty.

2.1.1 History of metal-on-metal total hip arthroplasty

Philip Wiles operated on six patients with Still's disease in 1938 with what counts as a MoM THA. He replaced both femoral and acetabular sides of the hip joint with pre-formed stainless-steel components. A metal cup was inserted into the pelvis and the femoral head was fixed with a stem and side plate, making it a MoM bearing hip prosthesis (Wiles, 1958). Unfortunately, he did not achieve satisfactory results (Lowy & Sweetnam, 1968).

The first to use a MoM prosthesis routinely was George McKee in England. First, he used a screw-type acetabular cup (McKee, Charnley, Hicks, & Zarek, 1957). Later this was redesigned as a McKee-Farrar prosthesis with modified Thompson stem and cement-fixed acetabular cup (McKee & Watson-Farrar, 1966).

Figure 4. McKee metal-on-metal total hip arthroplasty

Earl D. McBride started using an acetabular cup made of metal in 1953 (McBride, 1961). Moore and Thompson stems together with a McBride acetabular cup were later used as a MoM type of THA. The McBride Clinic results were reported in 1970, and it was proposed that the procedure should serve as an adjunct to simple arthroplasty, osteotomy and arthrodesis (Shorbe, 1970).

Peter Ring also worked with a MoM prosthesis but did not use bone cement. The acetabular cup was fixed with a long screw and the femoral component was a Moore-type prosthesis (Ring, 1968).

In the 1970s, MoM THA was displaced by MoP bearings due mainly to the early success of the Charnley prosthesis. At the time, there were already concerns about metal reactions like metal sensitivity and carcinogenesis (Amstutz & Grigoris, 1996).

2.2 Fixation method in hip arthroplasty

Cement fixation achieved excellent results with Charnley's low friction arthroplasty and gained popularity in the 1970s (Charnley & Cupic, 1973), displacing fixation without cement and the use of MoM bearings (Amstutz & Grigoris, 1996). The same decade, the reasons for osteolysis and prosthetic loosening were studied, and theories were formed on particle-related problems. The blame was placed squarely on cement particles (L. C. Jones & Hungerford, 1987; Mjoberg, 2018; Willert, Ludwig, & Semlitsch, 1974). Loosening of the acetabular component was frequent and a major problem, especially among younger patients (Halley & Wroblewski, 1986). Concerns about "cement disease" and component loosening led to a resurgence of cementless components. These were most commonly made of titanium alloy. Cementless acetabular components seemed to have better survival rates (Clohisy & Harris, 2001), which persuaded orthopedic surgeons to search for alternative cementless fixations of components.

The Harris-Galante cementless acetabular components were induced with an ultrahigh molecular weight polyethylene (UHMWPE) liner (Harris, Krushell, & Galante, 1988). In 1979, Greg Lord published his "experimental" results (G. A. Lord, Hardy, & Kummer, 1979). His early results were promising with cementless femoral stems (Callaghan, Dysart, & Savory, 1988; Engh & Massin, 1989; G. Lord & Bancel, 1983). The development of cementless components have led to the predominant use of cementless THA (Lehil & Bozic, 2014), although cemented THA maintains its place for example in hybrid THA, an uncemented cup together with cemented stem (Gonzalez Della Valle et al., 2016).

Figure 5. Lord's cementless femoral stem.

2.3 Bearings

2.3.1 Metal-on-polyethylene

Cementless components for THA were developed because of alleged problems with cement. However, there was still a problem with osteolysis and component loosening. Wear of the UHMWPE liner was thought to produce polyethylene debris and consequently osteolysis (Berry, Barnes, Scott, Cabanela, & Poss, 1994; Chmell, Poss, Thomas, & Sledge, 1996; Willert, Bertram, & Buchhorn, 1990).

Improvements in polyethylene were an attempt to reduce the wear originating from liners. Highly cross-linked polyethylene (HXLPE) acetabular liners are

promising (Jacobs, Christensen, Greenwald, & McKellop, 2007), but aseptic loosening is still one of the most common reasons for failure of MoP THA in the long term (Garellick, 2008).

Figure 6. Polyethylene liner inserted to Regenerex cup

2.3.2 Metal-on-metal total hip arthroplasty

Struggles with wear of polyethylene liners led to the "re-discovery" and second generation of MoM THA. Wear of the MoM interface was minimal compared to that of MoP bearing surfaces (Cuckler, 2005). MoM also enabled larger femoral head sizes to achieve a better range of motion (ROM) and prevent joint dislocations due to extended jump distance (Burroughs, Hallstrom, Golladay, Hoeffel, & Harris, 2005).

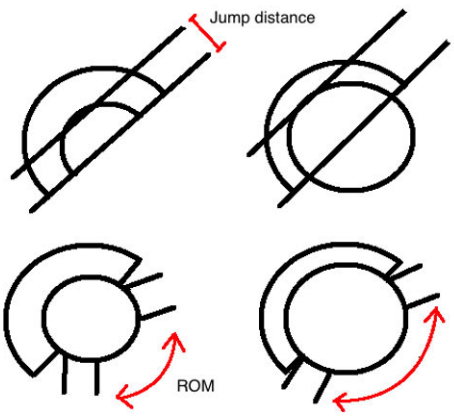

Figure 7. Illustration of jump distance and range of motion with small versus large head.

2.3.3 Hip resurfacing arthroplasty

The development of HRA continued alongside that of THA from the early days of Charnley (Charnley, 1961). Modern hip resurfacing uses a MoM bearing couple. Hip resurfacing requires bigger head sizes, which became possible with thinner rims in the cup of MoM bearings (Biomet Orthopedics, 2009; Cuckler, 2005).

Figure 8. ASR hip resurfacing

The acetabular cup used in HRA is similar to that for THA, but the femoral component is a "resurfacing" that does not include a stem, preserving the femoral neck. Modern HRA was introduced in the 1990s and good short-term results were reported with the Birmingham Hip Resurfacing (BHR) design by McMinn (McMinn, Treacy, Lin, & Pynsent, 1996). Later, however, the survival rate of HRA was found to be inferior to that of conventional THA (Johanson et al., 2010) and the procedure was curtailed or dropped altogether, including in Finland (Finnish Arthroplasty Register, n.d.; Johanson et al., 2010; Makela et al., 2019).

Figure 9. BHR hip resurfacing

2.3.4 Ceramic

Ceramic combined with ceramic or HXLPE has shown good clinical results (Y. H. Kim, Park, Kulkarni, & Kim, 2013). Osteolysis and loosening seem to be minimal when ceramic is combined with HXLPE (Malerba et al., 2016).

The difficulty with ceramic bearings has been breakage or fracture of the ceramic component. Durability has improved, however, and seems to be decent in the 4th generation ceramic (Howard, Wall, Fernandez, Parsons, & Howard, 2017). However, ceramic-on-ceramic (CoC) bearings have a specific problem of noise or squeaking of the THA. It is a fairly common problem (Goldhofer et al., 2018; Salo et al., 2017).

2.4 Adverse reaction to metal debris

Early results with second generation MoM THA were promising (Berton, Girard, Krantz, & Migaud, 2010; Dorr, Wan, Longjohn, Dubois, & Murken, 2000;

Kostensalo et al., 2012), but a specific problem was encountered with metal-on-metal hip arthroplasties (MoMHA) in both THA and HRA. The phenomenon is now known as adverse reaction to metal debris (ARMD) or adverse local tissue reaction (ALTR) (Bosker et al., 2012; Fehring, Odum, Sproul, & Weathersbee, 2014; Langton et al., 2010; Mokka, Junnila, et al., 2013; Watters et al., 2010). There are high failure rates in both MoM THA and HRA (Smith, Dieppe, Howard, & Blom, 2012; Smith, Dieppe, Vernon, Porter, & Blom, 2012), the most common reason for revision in MoM THA being ARMD (Seppanen et al., 2018).

In Australia, AOANJRR first reported increased failure rates with MoM implants in 2008. In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a medical device alert on MoM implants in April 2010 (Australian Orthopaedic Association National Joint Replacement Registry, 2008; MHRA, 2012). In May 2011, the American Food and Drug Administration (FDA) ordered post-marketing surveillance studies to be done by five US manufacturers of MoM total hip replacement devices (U.S. Food & Drug Administration (FDA), 2011). The Finnish Arthroplasty Society recommended that physicians discontinue the use of large-diameter head (LDH) MoM THA in May 2012 (Finnish Arthroplasty Society, 2015). A hazard alert for Biomet M2a (38 mm and Magnum) MoM devices was issued in Australia in February 2015 (Therapeutic Goods Administration (TGA), 2015).

ARMD is caused by metal debris released from the implant (Kwon et al., 2010). In fact, metal sensitivity and metal amounts in adjacent tissue after MoM THA had been studied back in the 1970s (Evans, Freeman, Miller, & Vernon-Roberts, 1974), before the term ARMD was coined following the histologic discovery of aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) (Willert et al., 2005).

MRI scans of patients with ARMD revealed soft tissue masses known as pseudotumors (Pandit et al., 2008). Patients often complained of the presence of a lump, pain, subluxation sensations, clicking and nerve irritation (Langton et al., 2010; Pandit et al., 2008). However, asymptomatic pseudotumors have also been seen in MoM THA patients (Matharu, Ostlere, Pandit, & Murray, 2016; Williams, Greidanus, Masri, Duncan, & Garbuz, 2011). ARMD is the main reason for failure and revision of MoM THA (Barrett, Kindsfater, & Lesko, 2012; Reito, Lainiala, Elo, & Eskelinen, 2016; Seppanen et al., 2018). Some asymptomatic pseudotumors neither change nor develop symptoms over time (Matharu, Ostlere, et al., 2016), in which case these artificial hips may not necessarily require revision surgery.

Pseudotumors are associated with MoM hip implants, but there does seem to be a high incidence of them in MoP bearings as well (Hjorth et al., 2018), as corrosion of the taper at the head-neck junction appears to play a significant role in the generation of metal ion wear debris (Scully & Teeny, 2013; Whitehouse et al., 2015).

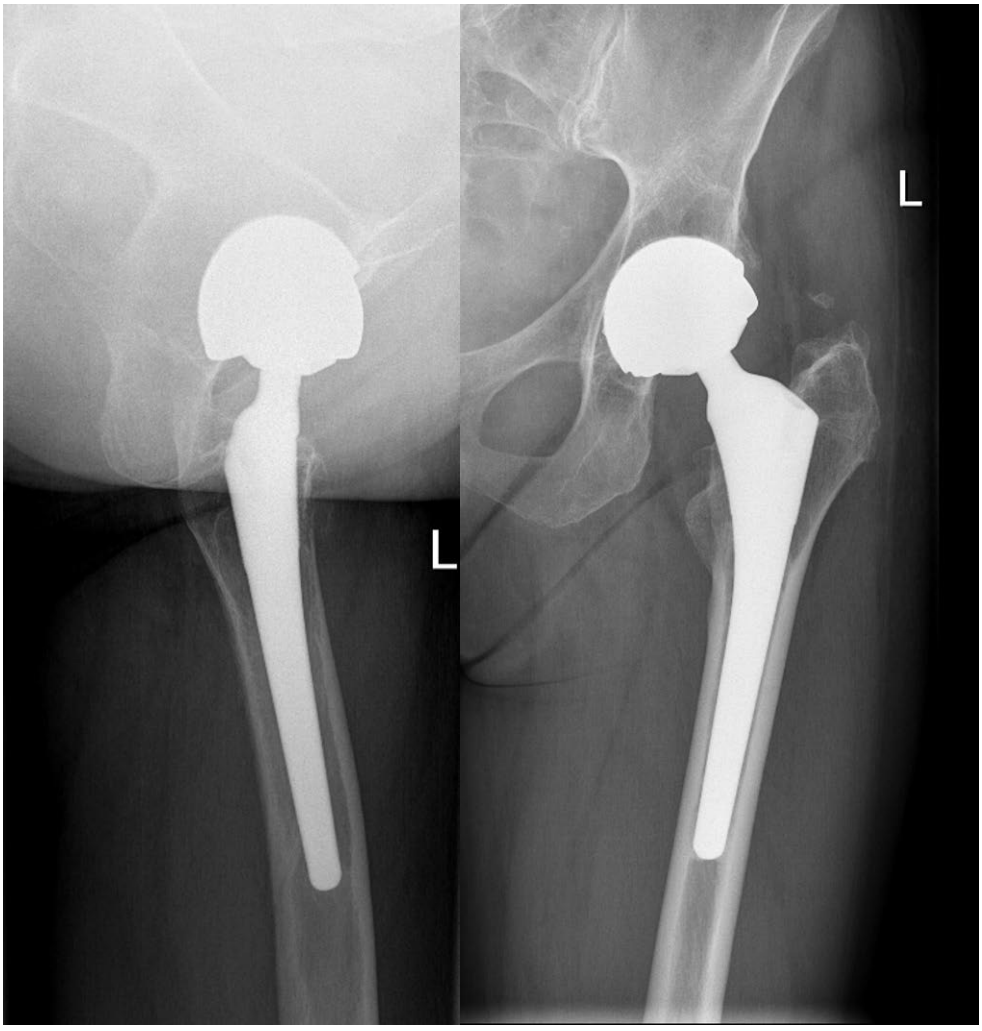

Figure 10. X-rays of well-functioning ReCap-M2a-Magnum THA in a 71-year-old woman 10 years after implantation.

2.4.1 Classification of pseudotumors

Metal artifact reduction sequence (MARS) MRI is usually recommended for cross-sectional imaging in hips with MoM THA (S. D. Chang et al., 2001). Different classifications have been introduced to grade MRI findings.

Based on their own experiences, Anderson et al. devised a grading system for MRI findings for MoM THAs. Although they found their system to be reliable, it was limited to differentiating mild disease from infection. The grading system included five states: A) normal; B) infection; C1) mild MoM disease; C2) moderate MoM disease; and C3) severe MoM disease (Anderson et al., 2011).

Hart et al. introduced a classification of pseudotumors into three groups, the second of which is subdivided, as follows: 1) thin-walled, fluid-like; 2a) thick-walled or irregular, fluid-like; 2b) thick-walled or irregular, atypical fluid; and 3) solid throughout (Hart et al., 2012; Matthies, Skinner, Osmani, Henckel, & Hart, 2012).

Hauptfleisch et al. described a third classification of pseudotumors, this one in terms of prognosis. Pseudotumor masses were classified in three stages: I thin-walled cystic mass; II thick-walled cystic mass; and III predominantly solid mass. They concluded that solid anterior pseudotumors were associated with severe symptoms and need for revision surgery (Hauptfleisch et al., 2012).

All three grading systems seem to have moderate agreement in terms of interobserver evaluation reliability (Smeekes et al., 2018).

2.4.2 Metal wear

The role of wear debris in prosthetic failure, especially loosening, has been of interest for decades (Mjoberg, 1994). In THA with a polyethylene liner, the most damaging particles are from wear of the polyethylene (Orishimo, Claus, Sychterz, & Engh, 2003; Santavirta et al., 1990). Testing in a hip simulator showed over hundredfold levels of volumetric wear in MoP compared to MoM bearings (St John, Zardiackas, & Poggie, 2004). MoM implants generate a lubricating film between the bearing couples, which reduces wear rates (Dowson & Jin, 2006).

Even if MoM THAs have lower wear rates than MoP THAs, they nonetheless release metal particles, mainly cobalt and chromium. Several studies have demonstrated that pseudotumors are associated with high levels of wear (Kwon et al., 2010; Langton et al., 2011).

2.5 Problems related to trunnion

Corrosion of the head-neck junction or trunnion is termed trunnionosis and was described in 1991 by Collier et al. (Collier, Surprenant, Jensen, & Mayor, 1991).

In MoM THAs, the sources of metal debris are the bearing surfaces and modular junctions (Kop, Keogh, & Swarts, 2012; Lavigne et al., 2011). The interface between the head and neck, the stem and sleeve, or the neck and stem allows variable reconstruction to adjust the femoral version, offset and leg length (Srinivasan, Jung, & Levine, 2012). Friction between bearing surfaces and the corrosion of modular junctions generate wear debris.

In MoM THAs, the taper junction may also play a minor role in ARMD. In HRA there are no modular junctions, only bearing surfaces as a source of metal debris. However, HRA is only slightly superior in terms of survival when comparing

analogous THA designs (Junnila et al., 2014). In addition, a titanium sleeve does not reduce the frequency of pseudotumors in MoM THA (Hjorth et al., 2016).

Metal reactions are also seen in THAs without MoM bearings, for example MoP (Cooper et al., 2012). A case report of a pseudotumor in a MoP patient was described as early as 1988 by Svensson et al. (Svensson, Mathiesen, Reinholt, & Blomgren, 1988). In the case of a MoP implant, corrosion of the head and neck taper junction or trunnion seems to be the source of metal debris (Scully & Teeny, 2013; Whitehouse et al., 2015).

Corrosion in modular junctions can also lead to cold welding (Whittaker et al., 2017). In revision surgery, removal of the well-fixed stem is often unnecessary. If the head-neck junction is cold-welded and inseparable, also the stem must be removed, or the head must be sectioned to remove it (Mokka, Junnila, et al., 2013).

2.6 Screening protocol of metal-on-metal total hip arthroplasty

There is insufficient evidence to determine when revision surgery should be performed, and for whom, in response to ARMD. As a result, regulatory authorities worldwide have a variety of recommendations (Matharu, Eskelinen, Judge, Pandit, & Murray, 2018). Screening or follow-up of patients with MoM implants includes clinical examination, testing for blood metal ions, and/or imaging (plain radiographs, ultrasound or MARS MRI) (Hannemann et al., 2013; MHRA, 2017; U.S. Food and Drug Administration (FDA), 2013).

Essentially, clinical examination and often blood metal level tests are routinely recommended for all patients with MoM THA or HRA. Imaging is usually recommended depending on symptoms and blood metal ion levels (Hannemann et al., 2013; MHRA, 2017; U.S. Food and Drug Administration (FDA), 2013).

2.6.1 Symptoms

There is a wide range of symptoms associated with ARMD, like discomfort, pain, squeaking, clicking, spontaneous dislocation and nerve palsy (Kwon et al., 2011; Langton et al., 2010; Pandit et al., 2008; Reito, Puolakka, Elo, Pajamaki, & Eskelinen, 2013; Wynn-Jones et al., 2011). Pseudotumor can even cause leg swelling or a palpable lump at the hip region (Bosker et al., 2012; Grote, Cowan, Anderson, & Templeton, 2018). On the other hand, clinical symptoms do not correlate with the presence of pseudotumor (E. Y. Chang et al., 2012). Many patients with ARMD and soft tissue pathology are asymptomatic (Kwon et al., 2011; Wynn-Jones et al., 2011).

The Oxford Hip Score (OHS) is a patient-reported outcome measure tool to assess function and pain in patients undergoing hip replacement (Dawson, Fitzpatrick, Murray, & Carr, 1996). Patients with ARMD have low OHS (Grammatopoulos et al., 2009; Mokka, Junnila, et al., 2013).

2.6.2 Metal ion concentrations

Concerns over reactions to metals in body tissues were raised as early as 1957 by George McKee, who was the first to use MoM bearings in THA (McKee 1957). Metallic debris surrounding failed cobalt-chromium McKee-Farrar prostheses was reported early (Charosky, Bullough, & Wilson, 1973).

MoM hip implants are mainly produced of cobalt and chromium (Biomet Orthopedics, 2009). When metal debris is released from MoM THAs, metal particles can dissolve in body fluids to form metal ions (Ferguson, Laing, & Hodge, 1960). Cobalt and chromium concentrations have been reported in literature using two different units, ppb (parts per billion) and µg/l (micrograms per litre). The density of blood almost equals the density of water, and 1 liter of blood weights approximately 1 kilogram (Trudnowski & Rico, 1974). In other words, these units, ppb and µg/l, are interchangeable. Cobalt and chromium ion concentrations can be measured in blood and play a role in the diagnosis of failed MoM hip implants; concentrations reflect the amount of wear of the bearing surfaces (K. De Smet et al., 2008). Plasma and serum Co and Cr levels appears to be higher than WB levels (Malek et al., 2015; Newton, Ranganath, Armstrong, Peter, & Roberts, 2012; Smolders et al., 2011).

Figure 11. ReCap-M2a-Magnum metal-on-metal total hip arthroplasty.

The background concentration of blood chromium (Cr) and cobalt (Co) concentrations in the population is 1.5 µg/l (0.6 to 8.6) and 0.5 µg/l (0.3 to 6.7), respectively (Sidaginamale et al., 2013). According to Hart et al., a cut-off level of 7 ppb shows good specificity, but relatively low sensitivity to discriminate between a well-functioning and failed MoM hip device (Hart et al., 2011). The risk of developing a pseudotumor is fourfold with serum metal ion levels of >5 µg/L (Bosker et al., 2012). In a study by Lardanchet et al. (Lardanchet, Taviaux, Arnalsteen, Gabrion, & Mertl, 2012), persistent pain was found to be more common in patients with higher metal ion levels with a Co cut-off level of 8 ppb. Van der Straeten et al. defined a safe upper limit (SUL) for HR patients (Van Der Straeten et

al., 2013). The SUL for unilateral MoM THR patients was Cr 4.6 ppb and Co 4.0 ppb, and for bilateral THR patients Cr 7.4 ppb and Co 5.0 ppb.

There is no universal consensus on metal ion values, but there are various guidelines in different countries. Cut-off values should provide some guidance as to how to treat and follow up patients, but decisions as to revision surgery should be based on the overall situation of each patient. Differences in protocols regarding cut-off values for managing patients are notable.

The MHRA in Britain and Health Canada in Canada have recommend the same cut-off level for serum Co and Cr of 7 µg/L (Health Canada, 2012; MHRA, 2012). In addition, the MHRA recommends repeated measurements within 3 months if an abnormal result is detected. The European Federation of National Associations of Orthopaedics and Traumatology (EFORT) has prepared European guidelines which suggest that metal ion concentrations between 2 ppb and 7 ppb should be concerning (European Federation of National Associations of Orthopaedics and Traumatology (EFORT), 2012). Despite the evidence available, neither the FDA in the US nor the Therapeutic Goods Administration in Australia state any cut-off ion concentration thresholds (Therapeutic Goods Administration (TGA), 2012; U.S. Food and Drug Administration (FDA), 2013).

Although there are several guidelines for understanding metal ion levels of concern, the need for follow-up is less well known. Reito et al. concluded that it is useful to perform regular WB metal ion measurements in certain patients (Reito, Moilanen, Puolakka, Pajamaki, & Eskelinen, 2014). It might be relevant to determine individual metal ion thresholds for every implant (Matharu, Mellon, Murray, & Pandit, 2015).

2.6.3 Imaging of metal-on-metal hip arthroplasty

Guidelines generally recommend x-rays during follow-up and cross-sectional imaging with MARS-MRI, computed tomography (CT) scans, or ultrasound to detect pseudotumors (Hannemann et al., 2013; MHRA, 2017).

MRI is superb for assessing soft tissues but is impaired by artifacts from MoM hip prostheses (Laakman et al., 1985). MARS-MRI provides imaging with fewer metal artifacts (S. D. Chang et al., 2001; Eustace et al., 1998). MRI can also be useful when planning revision arthroplasty for ARMD and pseudotumors (Hart et al., 2012), but during follow-up repeated MRIs seem to have little value (Reito, Elo, et al., 2014).

Ultrasound has good sensitivity and specificity for detecting pseudotumors (Lainiala, Elo, et al., 2015). MRI might be more sensitive to small deep lesions than ultrasound, but the latter can be a cost-effective tool when screening for pseudotumors (Garbuz et al., 2014; Kwon et al., 2011).

CT is inferior to MRI for detecting pseudotumors but better at detecting osteolysis adjacent to MoM implants (Robinson et al., 2014).

2.7 Cobalt and chromium toxicity

Systemic effects of metal ion release from metal implants was studied as early as 1980 (Dobbs & Minski, 1980). Co and Cr wear particles can be cytotoxic in vitro (Madathil, Lin, Hew, & Mohanty, 2010). However, it seems that blood Cr concentrations associated with MoM THA do not pose a health risk for patients (Finley et al., 2017).

There are reports of Co toxicity and at least a theoretical risk of poisoning (Steens, von Foerster, & Katzer, 2006; Zywiel et al., 2013). Higher metal ion levels are more likely to develop systemic symptoms. According to a review analysis, median serum Co levels were as high as 35 ppb (14–288) before generating systemic effects (Zywiel et al., 2016).

Systemic metal ion toxicity due to a failed hip replacement is rare; however, there have been several case reports of systemic Co toxicity, including symptoms like fatigue, weakness, hypothyroidism, cardiomyopathy, polycythemia, visual and hearing impairment, cognitive dysfunction, and neuropathy (Gilbert et al., 2013; Ikeda et al., 2010; Khan, Verma, Bajpai, & Mackey-Bojack, 2015; Leikin et al., 2013; Rizzetti et al., 2009; Steens et al., 2006; Zywiel et al., 2013).

The greatest risk of systemic Co toxicity seems not to result from primary MoMHA, but rather from Co-containing revision after a failed ceramic prosthesis (Bradberry, Wilkinson, & Ferner, 2014). After revision surgery the residual debris from the fractured ceramic liner is entrapped between the new articulating metal-on-metal surfaces and the friction leads to metallosis (Gilbert et al., 2013).

In addition, MoMHA has not been associated with an increased overall risk of cancer (Makela et al., 2012).

2.8 Revision surgery for ARMD

Five- and 10-year revision rates for large-head MoM THA implants are higher than for standard THA (Pijls et al., 2019). The main reason for revisions of MoMHAs is ARMD (Matharu, Judge, Murray, & Pandit, 2016). Initial reports on ARMD revisions showed poor outcomes (de Steiger et al., 2010; Grammatopoulos et al., 2009). Complication rates were up to 50% and re-revision rates 38% (K. A. De Smet et al., 2011; Grammatopoulos et al., 2009). This led to recommendations of early revisions to prevent the destructive lesions with muscle necrosis and large pseudotumors. Early revisions were thought to prevent poor outcomes (K. A. De Smet et al., 2011; Haddad et al., 2011).

There is not enough evidence to set exact thresholds for performing revision due to ARMD in MoM THA patients (Matharu et al., 2015). Therefore, it can be difficult for surgeons to determine whether revision surgery is indicated. Guidelines give advice to help with decision making but lack global consensus and vary widely (Finnish Arthroplasty Society, 2015; Hannemann et al., 2013; MHRA, 2017; U.S. Food and Drug Administration (FDA), 2013). However, the prevalence of ARMD revision surgery is high (Australian Orthopaedic Association National Joint Replacement Registry, 2018; Matharu, Judge, et al., 2016). The decision to revise a MoMHA should not be based on a single investigation but made rather on a case-by-case basis. It should take into account several points including patient symptoms, activity level and comorbidities, implant type, metal ion levels and imaging findings (Berber, Skinner, & Hart, 2016). Fortunately, the results of revisions have improved, and complication rates have dropped (Lainiala, Reito, et al., 2015; Matharu, Judge, Pandit, & Murray, 2017; Munro, Masri, Duncan, & Garbuz, 2014).

In MoMHA revision for ARMD, the MoM bearing should be replaced with non-MoM bearing surface (Lainiala, Reito, et al., 2015). Alternatives for bearing surfaces are MoP, CoP or CoC. In other words, a metal or ceramic head should be coupled with polyethylene liner, or ceramic head coupled with ceramic liner (Matharu et al., 2018). CoP might have the lowest risk for re-revision after ARMD revision (Matharu, Judge, et al., 2017). Revision of MoMHA for ARMD can be made by retaining the femoral stem and possibly acetabular cup when these are well fixed and positioned without significant damage at the trunnion (Lainiala, Reito, et al., 2015; Matharu et al., 2018; Munro et al., 2014). If the stem is retained, a titanium taper sleeve over an existing trunnion is recommended, especially together with ceramic head (Leibiger & McGrory, 2015; Waterson et al., 2018). Corrosion or even cold welding at the trunnion can lead to complicated revision with replacement of the stem (Whittaker et al., 2017).

Figure 12. M2a-Magnum head after difficult removal

3 Aims

The main aim of the study was to investigate the frequency of ARMD and cold welding, and the role of metal ion measurements, in follow-up of ReCap-M2a-Magnum MoM THA.

The specific aims were to investigate the following:

Study I: Difficulties removing the femoral head from the trunnion, and related complications in patients undergoing revision surgery of ReCap-M2a-Magnum metal-on-metal total hip arthroplasty at Turku University Hospital and Oulu University Hospital.

Study II: Prevalence of adverse reaction to metal debris in patients operated on with ReCap-M2a-Magnum metal-on-metal total hip arthroplasty at Turku University Hospital.

Study III: Change of cobalt and chromium ion levels over time in patients operated on with ReCap-M2a-Magnum metal-on-metal total hip arthroplasty at Turku University Hospital.

4 Patients and Methods

4.1 Patients

At the time that ARMD was becoming better understood and the implantation of MoM THAs had ceased, revisions were already being made due to ARMD. Difficulties in ReCap-M2a-Magnum revisions were encountered at two tertiary-level hospitals, Oulu University Hospital and Turku University Hospital. The revision surgery included exchange of the entire MoM bearing couple. Theoretically, it could have been performed by femoral head exchange and cup revision, but the femoral head was commonly cold-welded to the femoral stem, requiring stem removal and extended surgery.

For the purposes of Study I, we identified all patients who had undergone THA revision surgery at Turku University Hospital and Oulu University Hospital between April 2004 and January 2012. During this period 2,326 THA revisions were performed. Of those, 296 (13%) were performed for THAs with MoM implants. Of this group, we looked specifically at primary THAs with MoM implants performed with a stem provided from one manufacturer with a similar type of taper (Biomet, Type 1), and either a M2a-Magnum or M2a-38 modular head based on surgeon's preferal. After excluding three patients who had insufficient operation data and patients for whom an exchange of the femoral stem or of both components was planned, 124 remained (54 patients with M2a-38 and 70 with M2a-Magnum femoral head). None of the patients had died or were lost to follow-up less than 1 year after the revision surgery (Table 1).

Table 1. Demographic data of patients in Study I who underwent revision of M2a-38 or M2a-Magnum implant

Variables	Femoral head		p value*
	M²a-38™	M²a-Magnum™	
Hips, number	54	70	
Age, years, mean (range)	64 (44–81)	64 (35–92)	0.95
Females, number (%)	32 (59)	48 (69)	0.28
BMI, mean (range)	28 (20–45)	29 (18–38)	0.27
Follow-up, years, median (range)	1.5 (1.0–6.3)	2.0 (1.0–8.7)	
Stem model			
Bimetric	49	63	
Taperloc	1	2	
Reach	0	5	
Mallory-Head	3	0	
Integral	1	0	

*Chi-square or t-test

For the purposes of Study II, a systematic screening of ReCap-M2a-Magnum THA was launched. Between August 2005 and April 2012, in total 1,188 patients (1,329 hips) underwent ReCap-M2a-Magnum LDH MoM THA. It was the most used MoM THA device at our institution.

Metal ion measurements were routinely taken during follow-up of MoM THA patients. For the purposes of Study III, we identified all patients with unilateral ReCap-M2a-Magnum implants (1,047 patients) among the 1,188 patients (1,329 hips) from Study II. Of these 1,047 patients, 336 (336 hips) had undergone two follow-up visits, but eight patients had still only one Co ion measurement. Nine patients had bilateral MoM hip devices and were excluded (Figure 13). All unilateral ReCap-M2a-Magnum patients operated on at our institution formed the control group, and patients with two WB ion measurements were referred to as the study group.

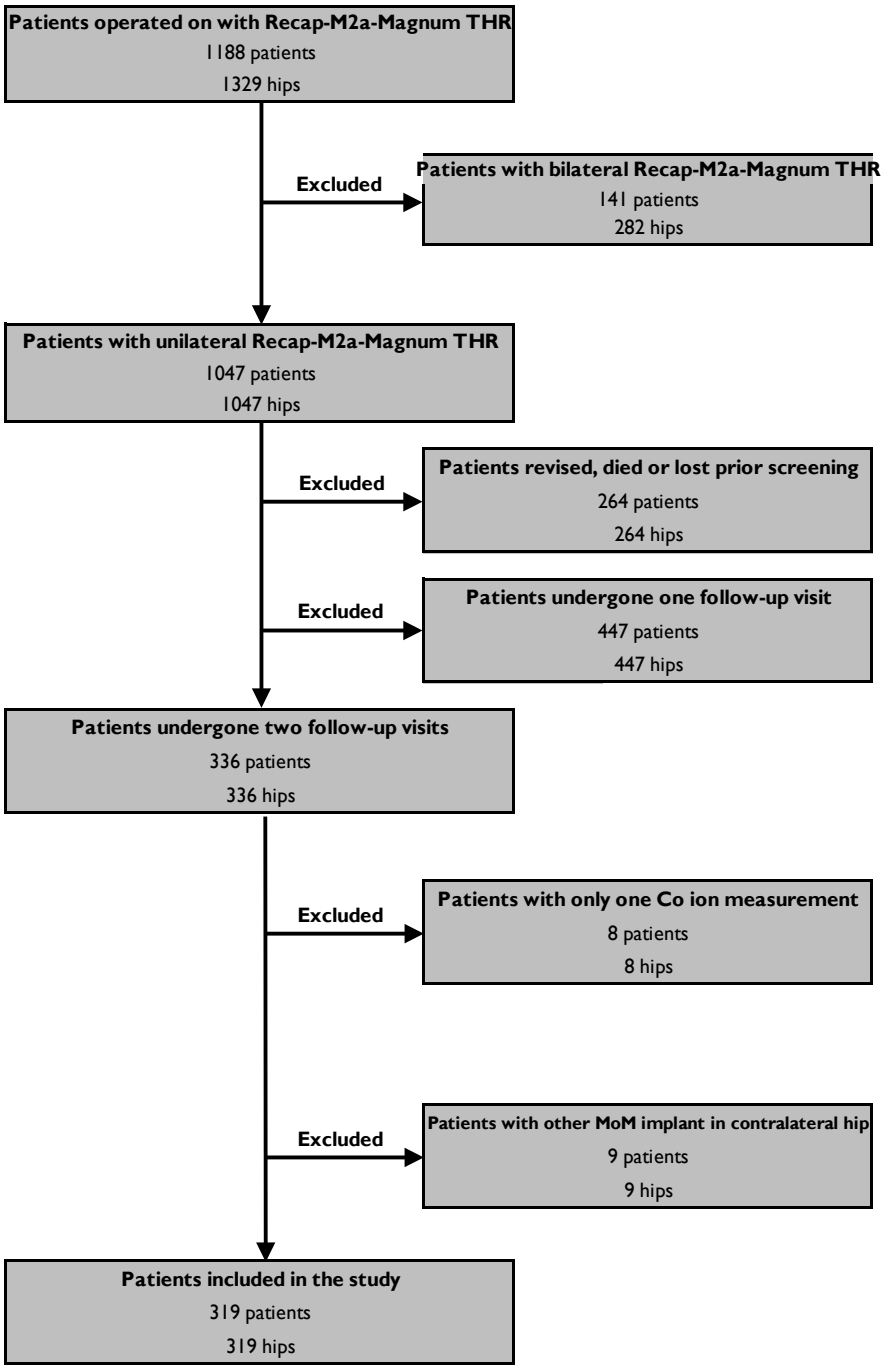

Figure 13. Flow chart of Study III

4.2 Methods

4.2.1 Study I

In Study I, information on the preoperative plan for the revision, performed revision, implants, operation date, perioperative bleeding, and complications was recorded retrospectively from the patient records. Preoperative serum Cr and Co ion levels were measured as described below. The method of modular head removal, any difficulties removing the femoral head from the trunnion, operation time, and complications were recorded based on a chart review.

The primary outcome measure was our ability to remove the femoral head. The method of modular head or adapter removal was categorized into four groups:

(1) Punch and mallet

(2) Special femoral head extractor tool

(3) Diamond saw cut

(4) Not removable

With a diamond saw, the head and adapter sleeve were cut almost through (without damaging the trunnion), after which the head could be removed by levering out with an osteotome and punching the adapter sleeve with a mallet.

The secondary outcome measures were operation time, blood loss, and complications during the first year after revision. Our secondary outcome variable on complications evaluated the proportion of patients who experienced periprosthetic infection or fracture. We considered infection potentially relevant, as the risk of infection may increase the longer the surgical procedure, and periprosthetic fracture was considered because these revisions may have entailed imparting more force to the proximal femur while attempting to remove the femoral head, or extended trochanteric osteotomy had to be performed owing to an unremovable femoral head or severely damaged trunnion. The infection diagnosis was based on clinical suspicion of infection, and patients underwent debridement during which several bacterial specimens were taken from around the implant (deep specimens). The periprosthetic infection diagnosis was confirmed if the same bacteria were cultured in two or more specimens. We believe that none of the measured outcome complications were missed, because our institutions treat all periprosthetic fractures, infections or suspicion of infection in the region.

We compared the M2a-38 group with 54 patients versus the M2a-Magnum group with 70 patients. We also compared THAs that had the M2a-Magnum implant with easy-to-remove heads (50 patients) versus hard-to-remove heads (20 patients). If the

head was easy to remove, it was defined as ‘‘head removal, punch’’ and if special instruments were used or the head could not be removed, it was defined as ‘‘head removal, other’’.

4.2.2 Metal ion measurements (Study I, II and III)

All patients in Studies I, II and III had their blood samples taken from the antecubital vein using a 21-gauge BD Vacutainer Eclipse blood collection needle (Becton, Dickinson and Co, Franklin Lakes, NJ, USA). The first 10 mL tube of blood was used for analysis of standard laboratory tests such as C-reactive protein and erythrocyte sedimentation rate measurement. The second blood sample was taken in a Vacuette NH trace elements tube (Greiner Bio-One GmbH, Kremsmünster, Austria) containing sodium heparin. Co and Cr analyses from WB were performed using an accredited method with Inductively Coupled Plasma Mass Spectrometry (ICP-MS, VITA Laboratory, Helsinki, Finland in collaboration with the Medical Laboratory of Bremen, Germany). The detection limit for Cr was 0.2 ppb and for Co 0.2 ppb. The intra-assay variation for WB Cr and Co was 2.2% and 2.7% and inter-assay variation 6.7% and 7.9%, respectively (ICP-MS specifications declared by VITA Laboratories).

4.2.3 Follow-up protocol (Studies II and III)

All patients in Studies II and III were part of systematic screening according to the follow-up protocol recommended by the Finnish Arthroplasty Society (Finnish Arthroplasty Society, 2015). The screening and follow-up included an OHS questionnaire, anteroposterior and lateral radiographs of the hip, and WB Cr and Co ion concentration measurements for all patients with ReCap-M2a-Magnum THA. All patients who did not undergo revision surgery were scheduled for annual or biennial repeat visits. Borderline cases were evaluated more frequently.

4.2.4 Study II

4.2.4.1 Oxford Hip Score (Study II)

An OHS of 42–48 points was considered excellent, 34–41 good, 27–33 fair and 0–26 poor according to Kalairajah et al. (Kalairajah, Azurza, Hulme, Molloy, & Drabu, 2005). The OHS questionnaire was not filled out preoperatively, and the total points were available for 742 patients. Generally, patients with bilateral ReCap-M2a-Magnum THA had only one OHS questionnaire available, and we could not pinpoint

which hip was of concern. Therefore, patients with bilateral ReCap-M2a-Magnum procedures were omitted from the regression analyses.

4.2.4.2 Anteroposterior and lateral radiographs (Study II)

The cup inclination and anteversion angle were measured using pelvic and hip x-rays.

The inclination angle was measured between the line joining the ischial tuberosities and the line through the margins of the acetabular component on anteroposterior pelvic x-ray. The anteversion was defined as the angle between the line joining the acetabular cup margins and the horizontal line in the lateral view. X-rays were assessed using Carestream PACS® imaging software (Carestream Health, Inc., 2011. Version 11.3 turpacs. Rochester, NY: Onex Corp.).

Because the measurement of the anteversion angle is relatively inaccurate in lateral hip x-rays, we categorized the cups into two subgroups for regression analysis: retroverted and not retroverted. The manufacturer recommends positioning the acetabular component at 45 degrees of inclination and 20 degrees of anteversion.

4.2.4.3 Clinical examination

Patients with symptomatic hips or elevated Co and Cr levels (≥ 5 μg/L) were clinically examined by a senior orthopedic surgeon at our outpatient clinic. Attention was paid to symptoms like clicking, subluxation sensation and swelling of the hip.

4.2.4.4 Metal Artifact Reduction Sequence MRI

Patients with symptomatic hips, moderate or poor OHS score, and/or patients with WB Cr or Co concentration ≥ 5 ppb were referred for MARS-MRI. This was used to identify ARMD changes such as fluid collection and soft tissue masses around the prostheses. In study II patient was considered to have a definitive ARMD if there was a solid mass or fluid collection ≥ 50 mm on MRI.

4.2.4.5 Revision surgery

In Study II, revision surgery for ARMD was considered by an experienced orthopedic surgeon if the patient had severe hip symptoms such as pain, clicking and swelling, and if there was a clear pseudotumor on MRI. Revision surgery was also considered if an asymptomatic patient had very high WB metal ion levels (> 10 ppb) to avoid symptoms of Co poisoning.

4.2.4.6 Definig the ARMD

Method for defining ARMD in Study II

Definitive ARMD was established in three ways:
1. Diagnosed during revision surgery.
2. Solid mass or fluid collection ≥ 50 mm on MRI.
3. Serum Cr or Co ≥ 10 μg/L.

Probable ARMD was established with either of the following:
1. A collection of fluid < 50 mm on MRI.
2. Serum Cr or Co ≥ 5 but < 10 μg/L.

ARMD was confirmed intraoperatively if there was milky fluid, a solid pseudotumor mass or muscle necrosis. The revision surgery involved several operations: head exchange with or without acetabular revision and stem revision with or without acetabular revision. Patients with clearly elevated metal ion levels or pseudotumor findings did not undergo surgery if the patient refused on the basis of an asymptomatic hip or poor overall health.

4.2.4.7 Risk factors

The following risk factors for ARMD were assessed: age, sex, laterality, inclination angle of the cup (categorical variables <30°, 30°–50° and >50°), anteversion angle of the cup (categorical variables >0° and ≤ 0°) and head size (categorical variables ≤ 44, 46–50 and ≥ 52 mm). The associations between OHS score (poor, fair or good vs excellent), pain (none, mild, moderate or severe), symptoms (clicking, subluxation sensation and/or swelling) and ARMD were also examined. We further assessed the same risk factors and symptoms for the occurrence of an ARMD revision.

4.2.5 Components (Studies I, II and III)

The ReCap-M2a-Magnum consists of a monoblock, press-fit acetabular component articulating with a femoral head, both made of a high carbon-cobalt-chrome-molybdenum alloy. The cup is hemispheric and has a shell thickness of 3 mm. The femoral head is 6 mm smaller than the respective acetabular component and is connected to a neck with a modular taper adapter, which provides the option to adjust the neck length. The stem, taper and taper adapter are made of a titanium, aluminum and vanadium alloy (Ti-6Al-4V).

The M2a-38 (Biomet) has a solid, fixed 38-mm Co-Cr head and does not contain a separate titanium taper adapter, as opposed M2a-Magnum. The M2a-38 may be attached to the same stems and tapers as the M2a-Magnum. In other words, as opposed to the M2a-Magnum, the M2a-38 does not include a titanium-titanium interface between the taper adapter and stem.

4.3 Statistical analysis

A chi-square test was used to compare the sex distribution between groups in Studies I and III.

The differences in age and BMI between groups in Study I, and difference in age, inclination angle, and femoral head diameter between the control and study groups in Study III were analyzed with a two-sample t-test.

In Study I, logistic regression was used to compare complications between groups. In Study II the potential risk factors for ARMD were analyzed via univariable multinomial logistic regression. The dependent variable consisted of three groups (definitive ARMD, probable ARMD and no ARMD), with no ARMD being used as the reference group. In both studies the results were expressed using odds ratios (ORs) with a 95% confidence interval (CI). The goodness-of-fit for the logistic regression models was evaluated with a deviance test, while the multivariable logistic model was obtained using backward elimination (inclusion criteria, $p < 0.10$) to examine the potential confounding effect of the other risk variables.

To test the differences in operation time, blood loss, and Cr and Co ion levels between groups in Study I, the Mann-Whitney U test was used and median differences with 95% CI were calculated using Hodges-Lehmann estimates.

In Study II, the generalized estimating equation (GEE) was used for the hipwise data to account for the correlation between hips from the same patient. Kaplan-Meier estimates for revision operations (for any reason) and for ARMD were calculated. The Cox regression analysis was used to analyze the association between risk factors and symptoms and ARMD revision. The hipwise survival data were analyzed with a lognormal frailty model to account for the correlation between hips from the same patient, and the results of the Cox regression were expressed using hazard ratios (HRs) with a 95% CI. The proportional hazard assumptions were evaluated with a log-cumulative hazard plot, and the assumptions were met.

In Study III, the individual change in two consecutive metal ion measurements from the same patients was modelled using a random coefficient model. Log-transformed ion values were used in conditional models due to positively skewed distribution of ion levels.

The results are expressed as geometric means for better interpretability. SUL values for WB Co were 4.0 ppb and for WB Cr 4.6 ppb as reported earlier (van der Straeten et al., 2013). The change over a 2-year measurement interval was calculated and plotted as frequency distributions for both metal ions separately.

In all our studies, a p-value < 0.05 was considered statistically significant. The statistical analyses were performed using SAS System for Windows, Version 9.4 (SAS Institute Inc, Cary, NC, USA).

4.4 Ethics

Ethics committee approval was not sought for Studies I, II or III. These were retrospective studies and the patients were not contacted directly. Study II was based on the national recommendations for the systematic screening protocol of all LDH MoM THA patients provided by the Finnish Arthroplasty Society.

5 Results

5.1 Frequency of cold-welding and related complications in M2a-Magnum revisions

In 29% (20/70) of revisions of the M2a-Magnum, the modular head and taper adapter could not be detached by knocking it with a punch and mallet. It can be considered to be cold-welded. No difficulty was noted with head extraction in the M2a-38 group (Table 2).

Difficulties with head removal and corrosion of the taper led to unplanned stem revision in 17% (12/70) of hips. For patients with the M2a-Magnum (n = 20) implant in which head removal was difficult, the median operative time was longer and bleeding more profuse (Table 3).

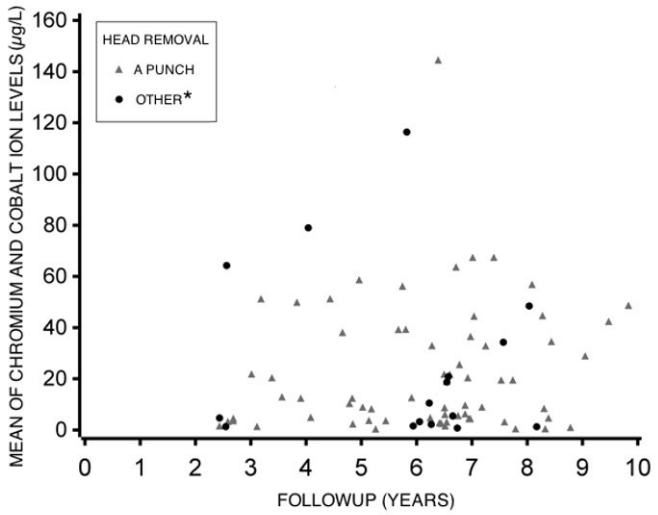

Figure 14. Association between preoperative Cr and Co ion levels, follow-up time, and method of head removal in Study I. Preoperative Cr and Co ion levels were not associated with the method of head removal (difficult versus easy; median difference, 1.6, [95% CI, −7.9 to 9.9], p = 0.53). *Other = head removal with a special extraction tool or a diamond saw cut, or the head was not removable

Table 2. Comparison of M2a-38 and M2a-Magnum groups in Study I.

Variables	M2a-38 (n = 54)	M2a Magnum (n = 70)
Head removal, n		
- Punch	54	50
- Special extraction tool	0	7
- Diamond saw	0	2
- Not removable	0	11
Preoperatively planned operation, n		
- Head exchange	0	11
- Head exchange + acetabular revision	54	59
Performed operation, n		
- Head exchange	0	13
- Head exchange + acetabular revision	54	43
- Stem revision	0	2
- Stem revision + acetabular revision	0	2
- Acetabular revision + stem revision requiring extended trochanteric osteotomy	0	10

Table 3. Comparison of easy and hard head removals in the M2a-Magnum group in Study I

Variables	M2a-Magnum		Median difference (95% CI)	p-value**
	Easy removal* (n = 50)	Hard removal* (n = 20)		
Head removal, n				
- Punch	50	0		
- Special extraction tool	0	7		
- Diamond saw	0	2		
- Not removable	0	11		
Preoperatively planned operation, n				
- Head exchange	8	3		
- Head exchange + acetabular revision	42	17		
Performed operation, n				
- Head exchange	12	1		
- Head exchange + acetabular revision	36	7		
- Stem revision	0	2		
- Stem revision + acetabular revision	2***	1		
- Acetabular revision + stem revision requiring ETO	0	9		
Operation time, minutes, median (range)	77 (33–197)	144 (75–274)	59 (95% CI 37–83)	<0.001
Intraoperative blood loss, ml, median (range)	475 (50–1500)	725 (300–2200)	251 (95%CI 100-300)	0.004

*Easy removal was recorded as a punch and mallet, and hard removal consisted of removal of the head with a special extraction tool, a diamond saw cut, or the head was not removable; **Mann-Whithey U-test; ***Two of the stems were revised because of perioperative findings of chronic infection unrelated to head removal; ETO = extended trochanteric osteotomy; CI = confidence interval

5.2 Incidence and risk factors of ARMD in ReCap-M2a-Magnum patients

Out of 1,329 hips, probable ARMD was determined in 114 (8.6%) and definite ARMD in 190 (14.3%). Out of 1,329 hips, 1,025 (77.1%) did not have ARMD. Throughout the follow-up period of mean 5.2 years (range 0.003–9.1 years), 33 patients (33 hips, 2.5% of all hips) required revision operations due to ARMD (Tables 4 and 5).

Pain, subluxation sensation, clicking, small head size (≤ 44 vs ≥ 52 mm) and fair/poor OHS scores were associated with definitive ARMD. In the multi-variable model, female gender, clicking, large head size (≥ 52 vs 46–50 mm) and pain (moderate/severe vs no pain) were associated with ARMD (results and statistics are summarized in tables 6, 7 and 8).

Table 4. Demographic data of the 1,329 study hips presented hipwise in Study II.

	Total hips (n=1,329)	**ARMD (n=190)**	**Probable ARMD (n=114)**	**No ARMD (n=1,025)**
Mean age (years)	64.2	64.3	64.5	64.1
Mean follow-up years (range)	5.2 (0.003-9.1)	5.8 (0.3-8.8)	5.5 (0.2-8.8)	5.0 (0.003-9.1)
Mean head size in mm	49.2	48.8	48.8	49.4
Head size ≤ 44mm, number (%)	170 (13%)	31 (16%)	19 (17%)	120 (12%)
Head size 46-50mm, number (%)	744 (56%)	109 (57%)	62 (54%)	573 (56%)
Head size ≥ 52mm, number (%)	415 (31%)	50 (26%)	33 (29%)	332 (32%)
Mean inclination angle of the cup, degrees¤	42.8	44.5	44.0	42.4
Inclination angle of the cup <30 degrees, number (%)¤	29 (2%)	2 (1%)	2 (2%)	25 (3%)
Inclination angle of the cup 30-50 degrees, number (%)¤	1013 (84%)	146 (82%)	86 (80%)	781 (85%)
Inclination angle of the cup >50 degrees, number (%)¤	157 (13%)	29 (16%)	19 (18%)	109 (12%)
Anteversion angle of the cup ≤0 degrees, number (%)	30 (2%)	6 (3%)	1 (1%)	23 (2%)
Anteversion angle of the cup >0 degrees, number (%)	1299 (98%)	184 (97%)	113 (99%)	1002(98%)
Mean serum Co, µg/l (range)*	4.4 (0.3-196.2)	16.4 (0.6-196.2)	4.3 (0.5-9.5)	1.7 (0.3-4.9)
Mean serum Cr, µg/l (range)*	3.0 (0.5-44.7)	7.8 (0.5-44.7)	3.6 (0.8-7.4)	1.8 (0.6-4.8)

¤ Data of cup inclination angle based on pelvic radiographs were available for 1,199 hips. *Metal ion data was available for 1,094 hips: 802 hips in no ARMD group, 107 in probable ARMD group, and 185 in definite ARMD group.

Table 5. Patient characteristics of Study II for those with unilateral arthroplasty.

	Patients with a unilateral study device (n=1047)	ARMD (n=143)	Probable ARMD (n=70)	No ARMD (n=834)
Males, number (%)	469 (45%)	45 (31%)	29 (41%)	395 (47%)
Mean OHS*	40.4	36.0	41.3	41.1
OHS excellent, number (%)*	464 (63%)	44 (42%)	31 (63%)	389 (66%)
OHS good, number (%)*	135 (18%)	22 (21%)	11 (22%)	102 (17%)
OHS fair, number (%)*	60 (8%)	17 (16%)	5 (10%)	38 (6%)
OHS poor, number (%)*	83 (11%)	23 (22%)	2 (4%)	58 (10%)
No pain, number (%)#	377 (51%)	38 (36%)	22 (45%)	317 (54%)
Mild pain, number (%)#	280 (38%)	42 (40%)	20 (41%)	218 (37%)
Moderate or severe pain, number (%)#	82 (11%)	26 (25%)	7 (14%)	49 (8%)
Swelling yes, number (%)**	39 (5%)	11 (11%)	3 (6%)	25 (4%)
Swelling no, number (%)**	681 (95%)	89 (89%)	46 (94%)	546 (96%)
Clicking yes, number (%)***	62 (9%)	21 (21%)	6 (12%)	35 (6%)
Clicking no, number (%)***	655 (91%)	79 (79%)	43 (88%)	533 (94%)
Subluxation sensation yes, number (%)¤	106 (15%)	23 (22%)	6 (12%)	77 (13%)
Subluxation sensation no, number (%)¤	620 (85%)	80 (78%)	43 (88%)	497 (87%)
Mean serum Co, µg/l (range)****	3.6 (0.3-71.5)	12.9 (0.6-71.5)	4.2 (0.5-9.5)	1.5 (0.3-4.8)
Mean serum Cr, µg/l (range)****	2.6 (0.5-34.2)	6.5 (0.5-34.2)	3.2 (0.8-7.4)	1.7 (0.6-4.8)

OHS=Oxford hip score, 42–48=excellent, 34–41=good, 27–33=fair, 0–26=poor.

* OHS data available for 742 patients with a unilateral study device.
# Data available for 739 patients with a unilateral study device.
** Data available for 720 patients with a unilateral study device.
*** Data available for 717 patients with a unilateral study device.
¤ Data available for 726 patients with a unilateral study device.
**** Data available for 844 patients with a unilateral study device.

Table 6. Crude odds ratios (ORs) and 95% confidence intervals (CIs) of associations between risk factors and symptoms with ARMD in Study II.

	ARMD versus no ARMD		Probable ARMD versus no ARMD	
	Crude OR (95% CI)	**p-value**	**Crude OR (95% CI)**	**p-value**
Age*	1.00 (0.99-1.01)	0.9	1.00 (0.99-1.02)	0.7
Gender, female vs. male**	1.96 (1.34-2.86)	0.0005	1.27 (0.78-2.09)	0.3
Side, left vs. right*	0.91 (0.68-1.21)	0.5	1.12 (0.80-1.57)	0.5
Pain, mild vs. no pain**	1.61 (1.00-2.58)	0.05	1.32 (0.70-2.48)	0.4
Pain, moderate or severe vs. no pain**	4.43 (2.47-7.93)	<0.001	2.06 (0.84-5.07)	0.1
Subluxation sensation**	1.86 (1.10-3.13)	0.02	0.90 (0.37-2.19)	0.8
Clicking**	4.05 (2.24-7.31)	<0.001	2.13 (0.85-5.33)	0.1
Swelling**	2.70 (1.28-5.68)	0.009	1.42 (0.41-4.90)	0.6
Head size ≤ 44mm vs. ≥ 52mm*	1.72 (1.02-2.87)	0.04	1.59 (0.84-3.03)	0.2
Head size 46-50mm vs. ≥ 52mm*	1.26 (0.86-1.86)	0.2	1.09 (0.68-1.74)	0.7
Inclination angle of the cup, <30 vs. 30-50 deg***	0.43 (0.10-1.82)	0.3	0.73 (0.17-3.08)	0.7
Inclination angle of the cup, >50 vs. 30-50 degrees***	1.42 (0.90-2.24)	0.1	1.58 (0.91-2.76)	0.1
Anteversion angle of the cup, >0 vs ≤0 degrees*	0.70 (0.28-1.76)	0.5	2.59 (0.35-19.43)	0.4
OHS poor vs. excellent**	3.51 (1.97-6.23)	0.04	0.43 (0.10-1.86)	0.1
OHS fair vs. excellent**	3.96 (2.06-7.59)	0.02	1.65 (0.61-4.50)	0.2
OHS good vs. excellent**	1.91 (1.09-3.33)	0.4	1.35 (0.66-2.79)	0.3

* Multinomial logistic regression using GEE-estimation based on data of all hips and *** all pelvic radiographs (1199).

** Multinomial logistic regression based on data of patients with a unilateral study device.

Table 7. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of associations between risk factors and symptoms with ARMD using multiple multinomial logistic regression based on data of 714 patients with a unilateral study device in Study II.

	ARMD versus no ARMD		Probable ARMD versus no ARMD	
	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Gender, female vs. male	2.22 (1.19-4.15)	0.01	0.88 (0.41-1.85)	0.7
Pain, mild vs. no pain	1.06 (0.58-1.94)	0.9	1.40 (0.68-2.89)	0.4
Pain, moderate or severe vs. no pain	2.67 (0.97-7.34)	0.06	8.57 (2.08-35.34)	0.003
Clicking	2.85 (1.49-5.45)	0.002	2.31 (0.87-6.16)	0.09
Head size ≤ 44mm vs. ≥ 52mm	1.12 (0.49-2.55)	0.8	2.32 (0.78-6.96)	0.1
Head size 46-50mm vs. ≥ 52mm	0.49 (0.26-0.94)	0.03	0.98 (0.44-2.20)	1.0
OHS poor vs. excellent	1.35 (0.50-3.67)	0.6	0.07 (0.01-0.51)	0.008
OHS fair vs. excellent	2.14 (0.92-4.95)	0.08	0.59 (0.16-2.24)	0.4
OHS good vs. excellent	1.38 (0.69-2.74)	0.4	0.96 (0.41-2.24)	0.9

Table 8. Crude hazard ratios (HRs) and 95% confidence intervals (CIs) of associations between risk factors and ARMD revisions in Study II.

	Risk factors of ARMD revisions	
	Crude HR (95% CI)	p-value
Age*	1.00 (0.97-1.04)	1.0
Gender, female vs. male**	1.87 (0.79-4.40)	0.2
Side, left vs. right*	1.66 (0.84-3.32)	0.1
Pain, mild vs. no pain**	0.46 (0.09-2.27)	0.3
Pain, moderate or severe vs. no pain**	2.37 (0.59-9.46)	0.2
Subluxation sensation**	0.57 (0.07-4.43)	0.6
Clicking**	3.97 (1.05-14.99)	0.04
Swelling**	1.94 (0.25-15.21)	0.5
Head size ≤ 44mm vs. ≥ 52mm*	3.35 (1.08-10.38)	0.04
Head size 46-50mm vs. ≥ 52mm*	2.06 (0.77-5.51)	0.2
Inclination angle of the cup, <30 vs. 30-50 degrees*	0.01 (0.000-34081149)	0.7
Inclination angle of the cup, >50 vs. 30-50 degrees*	1.28 (0.55-2.99)	0.6
Anteversion angle of the cup, ≤0 vs. >0 degrees*	7.63 (2.19-26.6)	0.001
OHS poor vs. excellent**	3.26 (0.78-13.64)	0.1
OHS fair vs. excellent**	1.24 (0.14-10.59)	0.8
OHS good vs. excellent**	1.67 (0.32-8.62)	0.5

* Cox regression with random intercept for patient (frailty model) based on data of all hips.

** Cox regression based on data of patients with a unilateral study device.

5.3 Metal ion concentrations in repeated measurements

A total of 319 patients met the criteria for Study III. The mean time elapsing from the first metal ion assessment to the second was 2.0 years (SD 0.5, range 0.6–3.0) and the mean follow-up time (time between the index operation and the first metal ion measurement) was 5.5 years (range 1.8–9.3 years) (Tables 9 and 10).

Table 9. Comparison of demographic variables between the control group (=overall unilateral ReCap-M2a-Magnum THR group, n=1047) and the study group (n=319).

	Study group	Control group	p-value
Proportion of female patients	59 %	55 %	p=0.2
Age, years (SD)	64 (9)	65 (10)	p=0.2
Median femoral head diameter, mm, mean (SD)	49 (4)	49 (4)	p=0.4
Mean acetabular inclination, degrees (SD)	43 (7)	43 (8)	p=1

Table 10. Differences in WB Co and Cr levels (ppb). There was a statistically significant decrease in repeated WB Co and Cr values.

	Initial	Control	p-value
WB Co, n=319 median (range)	1.4 (0.4-63)	1.1 (0.2-68)	
geometric mean	1.5	1.2	p<0.001
WB Cr, n=317 median (range)	1.6 (0.6-13)	1.1 (0.3-19)	
geometric mean	1.7	1.2	p<0.001

At the first measurement, 6.6% of the Co ion measurements exceeded the SUL. The proportion rose slightly to 7% at the control measurement. The proportion of SUL-exceeding Cr ion levels decreased during the measurement interval from 5% to 4%. The Co value increased from safe to above safe in eight patients and the Cr value from safe to above safe in six. The Co and Cr levels dropped over time and stayed mostly below the SUL if the initial value was low. Exceptions were patients with high values from the start (Figures 15, 16 and 17).

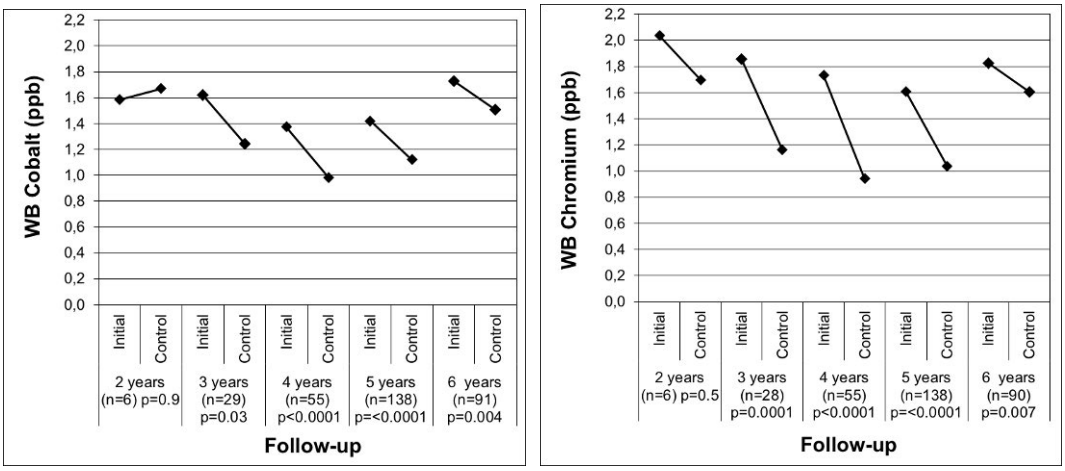

Figure 15. Geometric mean WB Co and Cr values divided across the follow-up time before initial measurement.

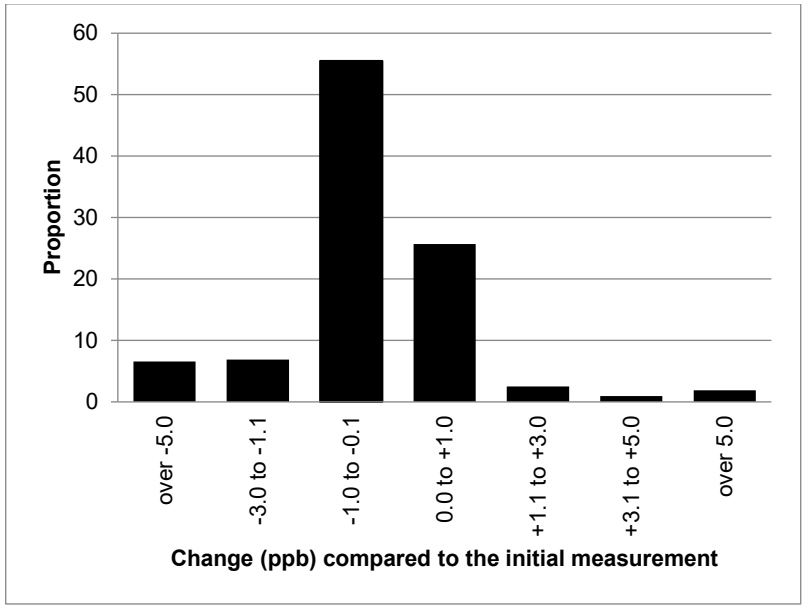

Figure 16. Frequency distribution of change in WB Co levels compared to the initial measurement.

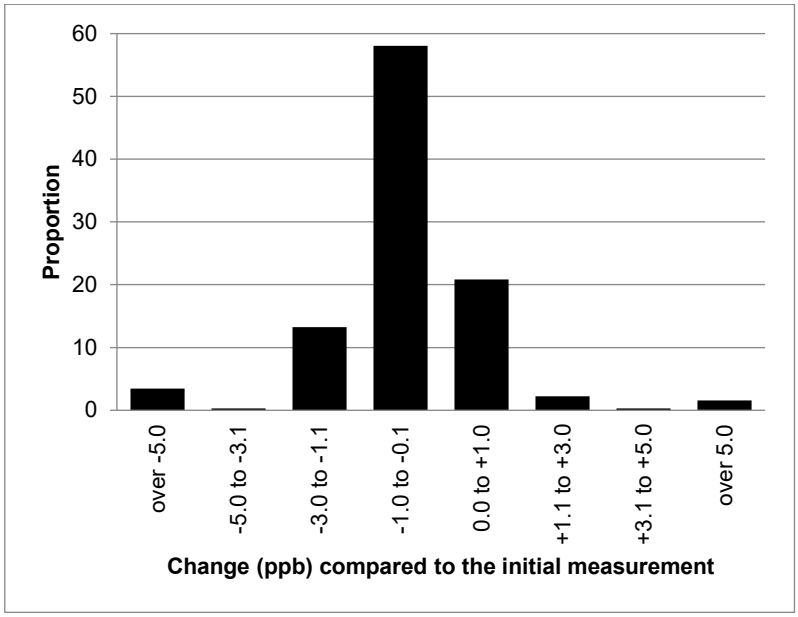

Figure 17. Frequency distribution of change in WB Cr levels compared to the initial measurement.

6 Discussion

6.1 Failure rates of ReCap-M2a-Magnum

In Study II, throughout the follow-up period of mean 5.2 years 104 patients (106 hips, 8.0% of all hips) required a revision operation for any reason. We determined that ARMD was a frequent complication after ReCap-M2a-Magnum THA. Of 1,329 hips, 157 (11.8%) were considered to have definitive ARMD, in which revision operations were not performed, and 33 (2.5%) had undergone revision operations due to ARMD. Hence, the prevalence of ARMD in our cohort was 14.3% (190/1329).

The revision rate of ReCap-M2a-Magnum THA is higher than in conventional THA, but lower than with most other MoM THA designs (Seppanen et al., 2018). According to the Australian registry data, the cumulative revision percentage of ReCap-M2a-Magnum THA at 10-years is 8.7% (95% CI, 7.0–10.9). The revision rate is fair compared to other models; for example the cumulative revision percentage of ASR at 10-years is 45.1% (95% CI, 43.5–46.7) and BHR 14.4% (95% CI, 12.9–16.1) (Australian Orthopaedic Association National Joint Replacement Registry, 2018).

According to the Finnish Arthroplasty Register, the cumulative revision percentage of ReCap-M2a-Magnum is 10.8% (95% CI, 9.9–11.7), of ASR 54.9% (95% CI, 50.5–58.9) and BHR 18.6% (95% CI, 15.1–21.9) at 10-years (Finnish Arthroplasty Register, n.d.).

Mokka et al. reported short-term survivals of 8,059 cementless LD MoM THAs (Mokka, Makela, et al., 2013). The data was collected from the Finnish arthroplasty register. They compared the survival of cementless LD MoM THA with conventional cemented THA and compared the cementless LD MoM models with each other. One of the implants analyzed was ReCap/BiMetric, that is to say ReCap-M2A-Magnum, with 4,202 implants. The mean follow-up of ReCap/Bi-Metric was 1.8 years (range 0.0-5.0 years). At 3 years the survival of 1,190 hips was 97% (95% Cl, 97–98) and at 5-years that of 59 hips was 97% (95% CI, 96–98). The short-term survival of the ReCap-M2a-Magnum THA was shown to be comparable to that of the conventional cemented THA. Considering the shorter follow-up time, the results do not differ from ours in Study II.

Mokka et al. reported a high prevalence of ARMD in ReCap-M2a-Magnum THA patients. All 80 hips were studied with MRI, metal ion measurements, OHS and clinical examination. They found that 14% (11/80) of the hips had ARMD at a mean follow-up time of 6.0 years (range 5.5–6.7 years). Three of the hips had needed revision surgery (Mokka, Junnila, et al., 2013). These results were similar to ours in Study II. A limitation of the study by Mokka et al., and of our Study II, is that we divided the "definite" and "probable" ARMD groups by the amount of fluid collection on MRI. The dichotomy between MRI ≥ 50 and <50 mm is artificial; thus, we hypothesized that a fluid collection ≥ 50 mm in any dimension was a clinically significant amount of fluid with regard to the diagnosis of ARMD.

Based on the Finnish Arthroplasty Register, in 2018 Seppänen reported the ReCap-M2a-Magnum to have a 10-year survival of 88% (95% CI, 86–90). The lowest survival was 46% (95% CI, 41–51) for the ASR. The Finnish Arthroplasty Register began registering ARMD as a reason for revision in May 2014. The most common reason for revision in the MoM THA group was ARMD (69.2%) (Seppanen et al., 2018).

Bosker et al. reported in 2012 a pseudotumor incidence of 39% and revision rate of 12% 3.6 years after the ReCap-M2a-Magnum THA procedure (Bosker et al., 2012). Later, in 2015, Bosker et al. screened 706 ReCap-M2a-Magnum hips using CT and found 228 pseudotumors (32%) (Bosker et al., 2015). In all, 76 hips (11%) were revised after a median of 5.3 years (range 1.0–8.3 years). CT-detected pseudotumor formation in their study was markedly more common than the MRI/ion measurement-based ARMD prevalence in our Study II, which was based only on selective imaging and thus accounts for the difference. There may have been asymptomatic patients in our study with low ion levels, fluid collection or soft tissue masses in their hips, but we consider the clinical importance of imaging findings in asymptomatic patients with normal ion levels to be somewhat minimal. The overall revision rate in our Study II was slightly lower than in the study by Bosker et al. (Bosker et al., 2015). Most of our revisions were performed for reasons other than ARMD, such as periprosthetic fracture, lack of osteointegration of uncemented implants, or infection. The reasons for revision were not assessed in the study by Bosker et al. (Bosker et al., 2015), but we agree that early detection of pseudotumors is important, as revision surgery performed before the onset of substantial soft tissue damage will likely have better outcomes.

In a study of 280 hips (240 patients) with the ReCap Hip Resurfacing system, different results were reported (van der Weegen, Hoekstra, Sijbesma, Austen, & Poolman, 2012). There were no revisions due to ARMD, and no indications of ARMD were observed during a mean follow-up period of 3.3 years (range 1.0–6.3 years). However, two cases of ALTR were found in histopathological investigations. Later, as the concept of ARMD became clearer, the terms ARMD and ALTR came

to refer to the same phenomenon. The differences to our study can also be explained by shorter follow-up time of 3.3 vs. 5.2 years and the imaging method used (ultrasound vs. MRI). However, ultrasound has been found to be effective for detection of pseudotumors (Lainiala, Elo, et al., 2015).

6.2 Symptoms and risk factors in ARMD

ARMD may occur in asymptomatic LDH MoM hips (Kwon et al., 2011; Pandit et al., 2008). However, pain, subluxation sensation, clicking, and fair/poor OHS were significantly associated with ARMD in our Study II. Pain was also associated with ARMD in the study by Bosker et al. (Bosker et al., 2015). In the study of Pandit et al., patients with pseudotumors experienced symptoms like pain, spontaneous dislocation, nerve palsy and a palpable lump (Pandit et al., 2008).

In addition, female gender and small diameter head sizes (≤ 44 mm) have been reported as risk factors for ARMD in previous studies (Reito et al., 2013); but in one multivariable model, larger head sizes were associated with ARMD when compared to medium sizes. Glyn-Jones et al. also reported that female gender, age under 40 years, small component size and dysplasia increased the failure rate in HR patients. Theoretically, it is possible that the lubrication between the bearing surfaces works best with medium sized heads. In our study, retroverted cups were scarce, but they were significantly associated with the ARMD revisions. The probability of edge loading is increased with malpositioned cups.

6.3 Metal ion thresholds

There are currently no robust guidelines on how to interpret metal ion levels. It is known that elevated Co and Cr levels are associated with failure and ARMD of the MoMHA (K. De Smet et al., 2008; Grammatopoulos, Munemoto, Pollalis, & Athanasou, 2017; Hart et al., 2014). To clarify low and high rates, it is known that people in general, as background levels, have WB Co and Cr concentrations of 1.5 µg/L (0.6 to 8.6) and 0.5 µg/L (0.3 to 6.7) respectively (Sidaginamale et al., 2013). Then, Langton et al. recommended revision surgery if Co ion concentration alone is above 20 µg/L due to ARMD and osteolysis (Langton et al., 2013).

In Study II we state that patients with high ion levels (≥ 10 µg/L) had definitive ARMD. We increased the cut-off level from 8 µg/L, as suggested by Lardanchet et al. (Lardanchet et al., 2012), to 10 µg/L due to inclusion of bilateral THA. We used a metal ion level of ≥ 5 µg/L as a criterion for possible ARMD.

Different authorities have different thresholds for what they consider alarming Co and Cr ion concentrations. Both the MHRA in Britain and Health Canada have set the level of acceptable serum Co and Cr at 7 µg/L (Health Canada, 2012; MHRA,

2012). European guidelines suggest that ion concentrations between 2 ppb and 7 ppb are of concern (European Federation of National Associations of Orthopaedics and Traumatology (EFORT), 2012). However, it seems that fixed thresholds for all MoMHA designs are defective compared to implant-specific lower (2–5.5 ppb) thresholds (Matharu, Berryman, et al., 2017).

Van der Straeten et al. defined the SUL for unilateral HR patients at Cr 4.6 ppb and Co 4.0 ppb, and for bilateral HR patients at Cr 7.4 ppb and Co 5.0 ppb. (Van Der Straeten et al., 2013). Patients below these limits had well-functioning artificial hips without clinical or radiological findings. Ion levels above these values predicted poor function. Sidaginamale et al. stated that WB Co levels ≥ 4.5 μg/L indicate a poorly functioning joint (Sidaginamale et al., 2013). A study of 1,748 patients with MoM THA and HR implants observed that MoM THAs had significantly higher blood metal ion concentrations compared with HR patients (Lainiala et al., 2016). In Study III we decided to use the cut-off levels suggested by van der Straeten et al. (Van Der Straeten et al., 2013).

A limitation of Study II was that we included patients with bilateral MoM implants, which may have biased the metal ion analyses.

In Study I we had preoperative ion levels measured in only 68% of patients. Therefore, we cannot reach a firm conclusion regarding the role of ion levels, but the median ion levels were higher among patients without head removal problems, which suggests that the head-detaching problem is not associated with high ion levels.

6.4 Revision surgery and cold welding

In Study I we found that head removal from a M2a-Magnum implant was frequently problematic in revision surgery. No problems in head removals were encountered with M2a-38 implants. In 29% (20/70) of hips with M2a-Magnum implants, removal of the head was difficult, which led to increased operation time and bleeding. In 17% (12/70) of cases, difficulties led to unplanned and unwanted stem revision.

There are only a few reports of cold welding of the head-neck junction in revisions. Revisions of MoM implants have a high risk for complications in general, and improvement of symptoms and function can be modest (Lainiala, Reito, et al., 2015; Stryker, Odum, Fehring, & Springer, 2015; Wyles, Van Demark, Sierra, & Trousdale, 2014). One study with a 7-year follow-up showed similar survival after ARMD revision compared to revision of conventional THA. However, 39% of the patients experienced a poor outcome following ARMD revision (Matharu et al., 2019).

The head-neck junction has been shown to be exposed to corrosive processes that can lead to premature implant failure (Matthies et al., 2013; Urish, Giori,

Lemons, Mihalko, & Hallab, 2019). Corrosion at the taper junction can lead to cold welding or fatigue fractures of the modular neck adapters (Fraitzl, Moya, Castellani, Wright, & Buly, 2011; Grupp, Weik, Bloemer, & Knaebel, 2010; Kop et al., 2012).

Explant analysis of five ReCap-M2a-Magnum THA revealed the wear of the articulating surfaces to be more extensive than that of the taper junction. The mean volumetric wear rate of the bearing surfaces was 6.1 mm^3/year (range 4.1–7.6 mm3/year). Additionally, the femoral head wear volume was larger than the wear volume from the acetabular cup. The volumetric wear for tapers was 0.054 mm3/year, ranging from 0.16 to 0.96 mm3. (Scholes et al., 2017).

Whittaker et al. reported cold welding in four different kinds of THA designs: M2a-Magnum/type 1 taper, ASR XL/Corail, Cormet/Zweymuller and Mitch/Exeter. M2a-Magnum had the highest prevalence of cold welding. The same type of implant and taper was used in our Study I. Whittaker et al. had 27 implants clinically cold-welded, but 11 of them could be separated with a special extraction tool. This strengthens our conclusion in Study I that it is crucial to be prepared for revision surgery with the correct equipment.

In Study I we compared revisions of M2a-Magnum implants in which the head could be removed with or without problems. The risk of periprosthetic fracture or joint infection was similar in both groups, but the trend for complications was greater in patients with difficult head removal (25%; 5/20) compared with patients with no difficulties (8%; 4/50). The titanium-titanium taper junction can be difficult to separate during revision THA, and if not anticipated this problem can result in larger and more complicated revision procedures in patients with the M2a-Magnum implant. These unexpected difficulties may arise even if the primary operation was performed recently (within 2 years) and even if serum metal ions are low. The problems with head removal increase the operation time and amount of bleeding, and the surgeon should inform the patient of the possibility of a more extensive operation than preoperatively planned, including extended trochanteric osteotomy for stem revision. These technical problems may also arise suddenly in emergency THA revisions for septic infections and periprosthetic fractures. In revision procedures with the M2a-Magnum implant, it is crucial to be prepared with special tools, including a femoral head extraction tool provided by the stem manufacturer and a diamond saw. We also note that the use of a titanium sleeve over an existing titanium trunnion is increasing (Jack, Molloy, Walter, Zicat, & Walter, 2013). Based on the results of our Study I, we raised the concern that a titanium sleeve may be cold-welded over a titanium stem, and removal of the sleeve may be difficult in the case of re-revision.

A limitation of Study I was that for the first head removals, we did not have a specific extraction tool, and our knowledge of the risk of cold welding among M2a-Magnum heads was limited. Therefore, it is possible that some of the stem revisions

could have been avoided in the M2a-Magnum group by using an extraction tool or diamond saw.

6.5 Follow-up protocol

The Finnish Arthroplasty Society has recommended following MoMHA patients biannually using patient questionnaires, metal ion level measurements, and imaging techniques like MRI, CT or ultrasound when needed (Finnish Arthroplasty Society, 2015). There was clearly a need for systematic screening of patients who had undergone THA with a MoM bearing couple in order to identify those with ARMD. Our patients in Studies I-III were part of the screening protocol.

The strengths of Study II included the fact that all of the ReCap-M2a-Magnum implantations were performed at our institution. The Bi-Metric stem and Hardinge approach were used in every operation, so the stem or approach did not cause bias. A limitation of Study II was that the assessment of some ARMD cases was made based on the surgical findings in the medical reports, and some revisions were performed before the surgeons were familiar with the concept of ARMD.

Increase of pseudotumors has been reported in patients with ReCap-M2a-Magnum THA in prolonged follow-up. This was seen especially in patients with pain, Co levels ≥ 4 μg/l and local swelling at the hip. Therefore, annual follow-up of ReCap-M2a-Magnum patients was suggested for the lifetime of the implant (Bosker et al., 2015). On the other hand, in a study of 152 patients with HR, none of the asymptomatic patients with normal ultrasound and low blood metal ions (< 2 μg/L) developed new pseudotumors within 5 years (Low, Matharu, Ostlere, Murray, & Pandit, 2016). Based on these findings, patients with symptoms, elevated metal ion levels or pseudotumor should be monitored frequently. Our findings in Study III also imply that patients with unilateral ReCap-M2a-Magnum THA with low metal ion levels do not benefit from routine metal ion level screening, at least in a mean 2-year interval. However, we do not know how the WB metal ion levels develop in the long term in unilateral ReCap-M2a-Magnum patients. Wear and corrosion of the bearing surface and the trunnion may well increase in long-term follow-up.

Matharu et al. have suggested further research to clarify specific blood metal ion thresholds for different implants (Matharu et al., 2015). Our results in Study III strengthen this impression. Implant-specific thresholds seem to be more effective to detect ARMD.

In 2013, Langton et al. studied repeated metal ion measurements of 205 patients with ASR or BHR HR. The mean time interval between the initial and control measurements was 27.3 months (range 6–52). They concluded that blood metal ion tests could be used in asymptomatic patients as an indicator of the risk of early implant failure (Langton et al., 2013).

Reito et al. assessed 254 unilateral patients, of whom 156 had received an ASR XL THR and 98 patients an ASR HR (n = 254) (Reito, Moilanen, et al., 2014). The second blood sample was taken 8 to 16 months after the first. In the THR group there was a significant increase in WB Co levels over the measurement interval, and 32% of the patients exceeded the SUL during the measurement interval (Van Der Straeten et al., 2013). They recommended regular WB metal ion measurements in ASR XL THR patients, but not in ASR HR patients (Reito et al. 2014). Although the measurement interval of our study was even longer (mean 2 years) than in the study of Reito et al. (2014), the decreasing tendency of WB ion levels was clear. The ASR device has a poor overall performance and it may explain the difference in WB ion level development compared with the ReCap-M2a-Magnum THR (Australian Orthopaedic Association National Joint Replacement Registry, 2018; Seppanen et al., 2018).

Group-level results may not be relevant from a single patient perspective. For the patient, it is more relevant to know whether or not the metal level in their blood is high, what the expected change is in a repeated measurement, and which levels will raise concern. Therefore, we assessed our data additionally by modelling the individual change. However, also on an individual level, the increase in ion levels on repeated measurements was rare.

A limitation of our Study III was that the inclusion criterion used was arbitrary. We aimed to study changes in WB metal ion levels by repeated measurements, and the practical measurement interval was 2 years. The time frame from the first measurement to the second was not constant, however, in our patients. Therefore, we were compelled to select a time range, and 7 to 36 months (mean 2 years) was deemed most suitable. It is possible that a longer time range between the measurements such as 5 or 10 years might give different results.

7 Conclusions

I We found that the titanium–titanium taper junction can be very difficult to separate during revision THAs, and if not anticipated, this problem can result in larger and more complicated revision procedures in patients who have the ReCap-M2a-Magnum implant. It is crucial to be prepared with special tools, including a femoral head extraction tool and diamond saw. The patient has to be informed of the possibility of a more extensive operation than preoperatively planned.

II We found a high prevalence of adverse reaction to metal debris in ReCap-M2a-Magnum THA patients; however, most of them did not require revision surgery.

III Our findings suggest that repeated metal ion measurements in unilateral ReCap-M2a-Magnum patients over a mean 2-year time interval did not show any increase. Long-term ion levels are, however, not yet known.

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