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UNIVERSITY OF TURKU

OUTCOME OF METAL-ON-METAL HIP ARTHROPLASTY

with Special Interest in Repeated Whole Blood Chromium and Cobalt Measurements

Sakari Pietiläinen

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In dedication to my family

"*However difficult life may seem,*
there is always something you can do and succeed at.
It matters that you don't just give up."

-Stephen Hawking

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ABSTRACT

It is now more than a decade since the full scale of problems with modern large diameter (LD) metal-on-metal (MoM) hip arthroplasties was recognized, leading to the withdrawal of most MoM implants around 2012. About 1.5 million MoM hip devices have been implanted worldwide, of which more than 20 000 were performed in Finland. According to estimates, a million of these implants are still in situ. In general, the revision risk of MoM hip implants has been higher than in conventional total hip arthroplasty (THA) due to adverse reactions to metal debris (ARMD). High, even toxic, levels of whole blood (WB) cobalt (Co) and chromium (Cr) are encountered in these patients, especially those with poorly functioning implants. Several different MoM implant brands were used at Turku University Hospital. These patients would benefit from updated follow-up guidelines from the authorities.

The aims of this thesis were as follows: In studies I and IV, we investigated the role of repeated WB metal ion measurements in medium- and long-term follow-up of ReCap-M2A-Magnum THA patients. In study II, we studied changes in the WB Co and Cr in Birmingham Hip Resurfacing (BHR) hip resurfacing arthroplasty (HRA) or BHR THA patients. In Study III we assessed the change in repeated WB metal ion measurements in Durom THA and MMC THA patients. Operations were performed at Turku University Hospital and in the Hospital District of Southwest Finland between 2004 and 2012. In studies II, III, and IV also the clinical outcomes, risk factors for revision surgery and radiological outcomes were assessed. Survival analysis was performed for metal-related adverse events (pseudotumor, metal ions above the safe upper limit (SUL), or revision due to ARMD) and for any reason for revision.

Mean WB metal ion levels did not increase during follow-up in any patient group. The proportion of patients with metal ion levels above the SUL did not increase. ARMD was the most common reason for revision in all studies. The amount of metal-related adverse events was high in all studies, but most of them did not require revision. Patient satisfaction was relatively good. Based on our data, we suggest that the appropriate measurement interval for the studied implants should be longer, e.g. 5 years, for WB Co and Cr in asymptomatic patients.

KEYWORDS: ARMD, BHR, Durom, MMC, M2A-ReCap-Magnum, MoM

TURUN YLIOPISTO
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TIIVISTELMÄ

On kulunut jo yli vuosikymmen siitä, kun modernien metalli-metalli (MoM, metal-on-metal) liukuparisten lonkan kokotekonivelien ongelmat havaittiin. Tämä johti lopulta siihen, että suurin osa näistä tekonivelistä poistettiin käytöstä vuoden 2012 paikkeilla. Maailmanlaajuisesti metalli-metalli liukuparisia lonkan tekoniveliä on implantoitu noin 1.5 miljoonaa, joista yli 20 000 Suomessa. On arvioitu että jopa miljoona näistä on kuitenkin vielä paikallaan. Näihin tekoniveliin liittyy kohonnut uusintaleikkausriski haitallisten metallihierrereaktioiden vuoksi (ARMD, adverse reactions to metal debris). Huonosti toimiva metalli-metalliliukuparinen lonkan tekonivel voi nostaa veren kromi ja koboltti-ionipitoisuuksia jopa myrkylliselle tasolle. Kokoveren kromi ja koboltti -ionimittaukset ovatkin tärkeä osa seurantaa. Viime aikoina on kliinisin perustein alkanut vaikuttaa siltä, että MoM tekonivelten seurantasuositukselle olisi päivittämisen tarvetta.

Tämän väitöskirjatutkimuksen tavoitteet olivat seuraavanlaiset: I ja IV osatyössä analysoitiin veren metalli-ionitasojen käyttäytymistä toistomittauksissa M2A-ReCap-Magnum-potilailla keskipitkän ja pitkän aikavälin seurannassa. Osatyössä II tutkittiin veren metalli-ionitasojen käyttäytymistä toistomittauksissa BHR pinnoite-tekonivel ja BHR kokotekonivelpotilailla. Osatyössä III tutkittiin veren metalli-ionitasojen käyttäytymistä Durom- ja MMC kokotekonivelpotilaiden toisto-mittauksissa. Kaikki leikkaukset tehtiin Varsinais-Suomen sairaanhoitopiirissä vuosien 2004 ja 2012 välillä. Osatöissä II, III ja IV raportoitiin myös kliiniset tulokset, uusintaleikkauksien riskitekijät ja radiologiset tulokset. Metallihierteeseen liittyvät haittatapahtumat (pseudotuumori, turvarajojen yli kohonneet metalliarvot tai uusintaleikkaus metallireaktioista johtuen) analysoitiin erikseen.

Kokoverestä mitatut keskimääräiset metalli-ioniarvot laskivat toistomittauk-sissa, ja metalli-ionien turvarajojen yläpuolella olevien potilaiden osuus ei kasvanut. Metallihierteeseen liittyviä haittatapahtumia oli suhteellisen paljon, mutta ne johtivat harvoin uusintaleikkaukseen. Tavallisin uusintaleikkauksen syy oli metallihierteestä johtuva pehmytkudosreaktio. Potilastyytyväisyys oli keskimäärin varsin hyvää. Tutkimustulokseemme perustuen oireettomien potilaiden metalli-ionimittausten aikaväliä olisi turvallista pidentää viiteen vuoteen tutkittujen implanttien osalta.

AVAINSANAT: ARMD, BHR, Durom, MMC, M2A-ReCap-Magnum, MoM

Table of Contents

Abbreviations

ALTR	Adverse local tissue reaction
AOANJRR	Australian Orthopaedic Association National Joint Replacement Registry
ARMD	Adverse reaction to metal debris
BHR	Birmingham Hip Resurfacing
CAAA	Cup articular arch angle
Co	Cobalt
CoC	Ceramic on ceramic
CoCrMo	Cobalt chrome molybdenum
CoP	Ceramic on polyethylene
Cr	Chromium
CT	Computed tomography
FAR	Finnish Arthroplasty Register
FDA	Food and Drug Administration
HRA	Hip resurfacing arthroplasty
HXLPE	Highly crosslinked polyethylene
LD	Large diameter
MARS-MRI	Metal artefact reduction sequence magnetic resonance imaging
MHRA	Medicines and Healthcare products Regulatory Agency
MoM	Metal on metal
MoP	Metal on polyethylene
NJR	National Joint Registry for England, Wales, Northern Ireland and the Isle of Man
PMMA	Polymethylmethacrylate
ppb	Parts per billion
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SUL	Safe upper limit
TGA	Therapeutic Goods Administration
THA	Total hip arthroplasty
UHMWPE	Ultrahigh molecular weight polyethylene
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 Pietiläinen S, Mäntymäki H, Vahlberg T, Reito A, Eskelinen A, Lankinen P, Mäkelä K. Repeated cobalt and chromium ion measurements in patients with bilateral large-diameter head metal-on-metal ReCap-M2A-Magnum total hip replacement. *Acta Orthopaedica.* 2020; *378–382, 3674(4)*

II Pietiläinen S, Lindström M, Laaksonen I, Venäläinen MS, Lankinen P, Mäkelä KT. Long-term blood metal ion levels and clinical outcome after Birmingham hip arthroplasty. *Scandinavian Journal of Surgery*. 2022;111(1):145749692110661.

III Pietiläinen S, Smedberg E, Laaksonen I, Venäläinen MS, Lankinen P, Mäkelä KT. Repeated metal ion measurements and long-term outcome of Durom/MMC total hip arthroplasty. *Acta Orthopaedica*. 2022;93:241–8.

IV Pietiläinen S, Linnovaara A, Venäläinen MS, Mäntymäki H, Laaksonen I, Lankinen P, Mäkelä KT. Median 10-year whole blood metal ion levels and clinical outcome of ReCap-M2a-Magnum metal-on-metal total hip arthroplasty. *Acta Orthopaedica.* 2022;93:444–50

1 Introduction

Total hip arthroplasty (THA) is a safe and cost-efficient treatment method for osteoarthritis of the hip. It has been considered the operation of the twentieth century. A THA device consists of a femoral component, and an acetabular component. These parts can be modular, meaning that they are assembled from separate parts, or a monoblock, where the component is manufactured as a single piece. The fixation method for femoral stems and acetabular components can be cemented, uncemented or hybrid, depending on the patient characteristics, implants used, and preference of the surgeon. In hip resurfacing arthroplasty (HRA), the acetabular cup articulates with a large-diameter (LD) femoral component attached to the trimmed native bone of the femoral head. Cemented arthroplasties typically use polymethylmethacrylate (PMMA) between cancellous bone and the component. Uncemented THA relies on bony ingrowth into the surface coating of the implant (Learmonth et al., 2007; Morshed et al., 2007).

Throughout the history of THA, many different bearing-surface options have been experimented with. All combinations have their advantages and disadvantages. Highly crosslinked polyethylene liners paired with either a ceramic or metal femoral head are currently the most used bearing couple.

The first metal-on-metal (MoM) bearing couples were introduced back in the 1930s. The development of metal on polyethylene (MoP) bearing surfaces in the 1960s replaced MoM bearings and became the new standard in hip arthroplasty (Rieker, 2016). However, due to polyethylene wear and osteolysis problems, hip resurfacing arthroplasty (HRA) and LD MoM THA were re-introduced in the 2000s. At their peak, MoM implants accounted for one-third of the U.S. market (Bozic et al., 2009). LD MoM devices performed well in mechanical studies, with very low wear rates, but in vivo they caused unpredictable problems due to wear debris, with clinical presentation of local soft tissue reactions (Pandit et al., 2008a). Many of the MoM THA and HRA implants had higher revision rates due to adverse reaction to metal debris (ARMD) than conventional bearing surfaces already at mid-term follow-up, which eventually led to the withdrawal of most MoM implants in 2012 (Smith et al., 2012).

ARMD is an umbrella term to describe MoM implant failures associated with pain, pseudotumors, macroscopic soft tissue necrosis, or metallosis. Gross

discoloration of the surrounding tissues due to metal debris is common. The term pseudotumor indicates fluid collections and/or solid soft tissue masses often associated with failing MoM implants (Langton et al., 2010).

Regulatory authorities worldwide have recommended follow-up schemes for MoM hip arthroplasty patients to detect bearing related complications (U.S. Food and Drug Administration [FDA], 2019; Finnish Arthroplasty Society 2014; Scientific Committee on Emerging and Newly Identified Health Risks [SCENIHR], 2014). However, systematic follow-up of MoM hip arthroplasties is both expensive and resource heavy. Because many hips with mild ARMD are asymptomatic, scrutiny tools like patient reported outcome measurement (PROM) questionnaires maybe be inadequate to detect failing implants when used alone (Konan et al., 2017; Kwon et al., 2011). Radiographs may also appear normal in the presence of soft tissue pseudotumors. Metal artefact reduction sequence magnetic resonance imaging (MARS-MRI) is currently the gold standard imaging modality for detecting soft tissue abnormalities. However, the utility of MARS-MRI in screening may be limited by availability, cost, and patient compliance (Robinson et al., 2014; SCENIHR, 2014; Van der Weegen et al., 2013b).

Small concentrations (below one parts per billion [ppb]) of chromium (Cr) and cobalt (Co) ions exist in the normal human body without any implants. Co is an important part of vitamin B12, and Cr is a stimulator in fatty acid and cholesterol synthesis. As the bearing surfaces of MoM devices consist mainly of these metals, elevated whole blood (WB) Co and Cr ion levels are often encountered in MoM hip arthroplasty patients. Systemic health effects are rarely seen when blood concentrations are below 300ppb (Langton et al. 2013, Kovochich et al. 2018). Higher Co levels are toxic and can cause systemic pathological effects such as cardiomyopathy, thyroid-, hepatic- and hematology disorders and neurological symptoms (Cheung et al., 2016). High Cr levels can be both carcinogenic and genotoxic (Wang et al., 2017). Co and Cr ion measurements are used in the follow-up of MoM hip arthroplasty patients to detect toxic levels, but also because elevated levels may indicate that the patient's MoM hip device may be failing (de Smet et al., 2008; Lehtovirta et al., 2017).

Our primary aim was to evaluate how WB metal ion concentrations change over repeated measurements during mid- to long-term follow-up of patients with several MoM hip brands. Our secondary aim was to report the clinical and imaging outcome of these implants and risk factors for revision surgery to optimize follow-up. Our cohort consisted of patients with five commonly used MoM hip devices: ReCap-M2A-Magnum THA, BHR HRA, BHR THA, Durom THA, and MMC THA. Operations were performed at Turku University Hospital and in the Hospital District of Southwest Finland from 2004 to 2012.

2 Review of the Literature

2.1 History of MoM hip arthroplasty

2.1.1 First generation of MoM hip arthroplasty

In 1938, Philip Wiles was the first to implant a prosthetic THA using a steel bearing couple. The implant had similarities to later HRA devices because the patient's own femoral neck was spared and distal support from the femur was achieved using an extramedullary plate (Reynolds & Tansey, 2006).

The first-generation MoM bearings are attributed to George McKee, who produced an all-metal prototype in 1940. He started using it on a regular basis, even though his work was not published until 1951. McKee was one of Wiles' registrars. The first THA implants used in the 1930s and 1940s were made of steel, but after 1950 the steel was changed to a cobalt chrome molybdenum (CoCrMo) alloy to achieve better durability and reduce wear (Triclot, 2011).

In 1953, McKee started using a modified Thompson stem paired with a CoCrMo (also known as vitallium) one-piece acetabular cup by Venable. Later, in 1966, he refined his prosthesis to become the McKee-Farrar device (Figure 1). Peter Ring was also one of the pioneers of MoM THA. The Mark III Ring THA had a single pelvic component and three sizes of femoral stem. Both Ring and McKee used CoCr implants (Pritchett, 2012).

In 1962, Sir John Charnley revolutionized the treatment of hip osteoarthritis using his "low friction" arthroplasty (Figure 1). He introduced and popularized the use of PMMA bone cement and the idea of low friction torque arthroplasty. Charnley's implant had an ultra-high molecular weight polyethylene (UHMWPE) acetabular component paired with a stainless steel femoral monoblock component. UHMWPE is often referred to as conventional polyethylene in the literature. A small femoral head reduced volumetric wear due to the smaller bearing surface area. The principles of Charnley's "low friction" arthroplasty are still used today in modern THA (Reynolds & Tansey 2006, Learmonth et al. 2007).

Figure 1. McKee-Farrar MoM THA (left) and Charnley's low-friction arthroplasty stem (right) (image courtesy of Heikki Mäntymäki).

The first generation of MoM implants had relatively high failure rates, mainly due to mechanically provoked aseptic loosening of the cup caused by the neck of the femoral stem coming repeatedly into contact with the acetabular component. High frictional torque also sometimes resulted in seizing and corrosion of the bearing surfaces. Some patients suffered from immunological reactions to metal wear debris, which at the time were thought of as "hypersensitivity". (Kovochich et al., 2018; Long, 2005; Migaud et al., 2012).

Due to unsatisfactory results and the popularity of Charnley's "low friction" THA, MoM THA fell out of favor in the 1970s (Knight et al., 2011; Triclot, 2011). In retrospect, the survival of McKee's early MoM THA was reasonably good (Brown et al., 2002). More "conservative" surgical options in the 1970s included femoral-neck-sparing HRA implantations with an LD head and polyethylene cup. However, the high frictional torque and thin acetabular polyethylene caused high implant wear and disastrous outcomes, even in the short term, with these early HRA implants (Head, 1981; Jolley et al., 1982).

2.1.2 Second and third generation of MoM hip arthroplasty

The polyethylene wear, osteolysis and loosening problems associated with the MoP bearing coupling were referred to in the 1980s as “polyethylene disease” (Oparaugo et al., 2001). At the same time, certain MoM implants had demonstrated good survival and low wear rates (Müller, 1970), leading to the re-introduction of metal couplings in 1988 by Weber.

As component impingement was considered an important reason for aseptic loosening with earlier MoM THA, second-generation MoM THAs had higher femoral offset and narrower neck structure to decrease the risk of impingement. Head sizes were smaller, typically 28mm shrinking the frictional torque (Amstutz & Grigoris, 1996).

Harder metal alloys, and advances in machinery provided consistent, and more accurate component interface dimensions. Forged CoCr alloys with high-carbon content were harder and would wear more slowly than cast alloys (Long, 2005; Walker et al., 1974; Zywiel et al., 2011). The high carbon content proved to be an important factor providing better results than low-carbon implants (Milosev et al., 2006; Rieker & Köttig, 2002).

The third generation of MoM THA was the uncemented version of the second-generation implants generally used in the 1990s. A diagnosis of hypersensitivity was considered a possible explanation for many of the failed second and third generation of MoM THA implants. It was suggested that metal debris from bearing surfaces caused tissue sensitization, leading in turn to bone destruction and tissue necrosis. The tissue response to metal wear debris differed histologically from the response to polyethylene wear debris (Long, 2005). The histological changes in “hypersensitivity” reactions were further characterized by Willert and colleagues (Willert et al., 1996).

The failures associated with second- and third-generation MoM THAs were both biological and mechanical. The incidence of aseptic loosening was lower with both these generations than with the first, but it was still present (Griffin et al., 2012; Triclot, 2011).

2.2 History of other articulating surfaces

2.2.1 Ceramic on ceramic

The first ceramic-on-ceramic (CoC) bearing couple was implanted in France in 1970. It consisted of an aluminum oxide (Al_2O_3) cup/liner paired with an alumina ceramic femoral head. The first generation of CoC bearings included either cemented or uncemented, threaded monoblock cups. Bulky and skirted ceramic heads were

attached to a metallic femoral stem. At that time the ceramic components required a long sintering time, which resulted in a large grain size and brittleness of the components. They were used in the 1970s and 1980s, but aseptic loosening and ceramic fractures were frequently seen related to implant wear and inferior materials and design (Jenabzadeh et al., 2012; Willmann, 2000; Zagra & Gallazzi, 2018).

In 1992, contemporary ceramic materials with improved formula, finer grain size and lower impurities were introduced. The cups were modular, containing a Ti shell and a ceramic liner. The first and second generation of CoC implants were sintered in air. The introduction of third generation ceramics (Biolox forte, CeramTec, Plochingen, Germany) in 1995 presented a new, enhanced manufacturing process. After sintering, hot isostatic pressing (HIP) was used to achieve finer grain size. Manufacturing was performed in a clean room and all implants were proof tested (Jenabzadeh et al., 2012; Zywiel et al., 2011).

The introduction of a fourth generation CoC coupling, Biolox Delta (CeramTec, Plochingen, Germany), in the 2000s reduced the component fracture rate dramatically and led to the widespread use of CoC coupling (Rieker, 2016). These modern ceramic implants are manufactured from an alumina matrix composite, consisting of approximately 82% alumina, 17% zirconium, and less than 1% chromium and strontium oxides (Jenabzadeh et al., 2012).

The possibility of implant fracture has been a considerable weakness in CoC bearings. The implant fracture rate of first generation models has been reported to range from 1.3% to as high as 13%. (Zywiel et al., 2011). Based on a study by Aldrian et al., the risk of ceramic fracture in second generation CoC implants was 2.8% (Aldrian et al., 2009). In a recent meta-analysis, the ceramic fracture risk of third generation implants (Biolox forte) was 0.5%, and the ceramic fracture risk of fourth generation CoC coupling (Biolox Delta) was 0.2% at 19 years follow-up (Yoon et al., 2020).

According to the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR), the general revision rate of CoC coupling is 4.9% at 10 years and 9.3% at 20 years. Due to their relatively low wear rate, they can be considered for younger, more active patients (AOANJRR, 2021; Zagra & Gallazzi, 2018). However, the squeaking sound that is sometimes associated with these implants can be problematic for the patient. It can even lead to revision operation of an otherwise well-functioning hip arthroplasty. The incidence of squeaking varies from 0.5% to 21% (Hoskins et al., 2021; Lee & Kim, 2017; Salo et al., 2017). CoC bearings can also be considered for patients who would benefit from a larger femoral head size, since the revision rate is similar with 32mm, 36–38mm, and ≥40mm femoral head sizes up to at least 10-year follow-up (AOANJRR, 2021). Maxera (ZimmerBiomet, Warsaw, IN, US) is an example of an LD CoC bearing with reasonably good mid-term results. Blakeney et al. reported a low revision rate of

1.4% for Maxera hip implants during a 7-year follow-up. The proportion of patients with a disturbing noise in their LD CoC hip was rather high, however, with up to 30% reporting squeaking or clicking in their hip implants (Blakeney et al., 2018; Castagnini et al., 2021).

2.2.2 Ceramic on metal

Ceramic-on-metal (CoM) bearing surfaces were in clinical use in the 2000s for a relatively short time. They had low in-vitro wear, but in vivo these implants caused significant elevation of WB metal ions. The usage of CoM bearings was stopped because they did not show any advantages over MoM bearings, and the small fracture risk of the ceramic femoral head was always present (Higgins et al., 2020; Rieker, 2016).

2.2.3 Hard on soft bearing couples

Historically, MoP was the mainstream bearing couple for four decades after their introduction by Charnley in 1962. The 25-year survival of Charnley's low friction arthroplasty was 80–85% (Caton & Prudhon, 2011; Hernández-Vaquero et al., 2008). Modular or monoblock acetabular components with UHMWPE bearing were paired with a metal (CoCr) femoral head size ranging from 22mm to 32mm (Learmonth et al., 2007; Rieker, 2016). The rates of loosening and osteolysis in metal-UHMWPE coupling varied from 9% to almost 50% (Clohisy et al., 2004; Hallan et al., 2006; Hernández-Vaquero et al., 2008)

The common sterilization method for UHMWPE was high-energy radiation and the implants were stored in the presence of oxygen. This was later discovered to cause delamination wear due to slowly occurring oxidation (Bistolfi et al., 2021). Ceramic femoral heads were suggested to have better wear properties with UHMWPE liners than metal heads (Meftah et al. 2013). However, there does not seem to be differences in the survival of these bearing combinations in 15 years follow-up (AOANJRR, 2021).

To address the issue of excess wear in UHMWPE implants, crosslinking of polyethylene was experimented with, since crosslinking was already used in industrial applications. Highly crosslinked polyethylene (HXLPE) for acetabular components was introduced in the 1990s. The crosslinking is performed by irradiation of the UHMWPE with electron beams or gamma rays, which cause free radicals to modify the polymeric chains of the UHMWPE, creating a structure that has substantially higher resistance against adhesive wear (McKellop et al. 1999). After gamma or electron beam radiation, the HXLPE was annealed or remelted with

thermal treatments to eliminate residual free radicals and decrease the risk of long-term oxidation (Kurtz et al., 2011).

During the past decade, synthetic vitamin E (alpha-tocopherol), which is a highly effective free radical neutralizer, has been added to HXLPE to prevent oxidative degradation and delamination wear. Vitamin E can be added either by blending, where it is mixed with UHMWPE before radiation and crosslinking, or by diffusion, where the HXLPE is doped with vitamin E after radiation (Bistolfi et al., 2021; Rieker, 2016).

The use of HXLPE has reduced the risk of osteolysis and revision regardless of the fixation method. In a recent systematic review, the incidence of osteolysis with UHMWPE in younger patients was 25%, dropping to 4.0% with HXLPE. In patients older than 60 years the risk of osteolysis with UHMWPE was 30% and with HXLPE 6.6%. The review included 2539 patients over a 5–15-year follow-up. The mean revision percentage was 9.3% with UHMWPE and 1.4% with HXLPE in a 10-year follow-up (Prock-Gibbs et al., 2021).

Both metal-HXLPE and ceramic-HXLPE bearings have demonstrated excellent long-term outcomes also in younger population (Cafri et al., 2017; Kim & Park, 2020; Rames et al., 2019; Zagra & Gallazzi, 2018). According to the Australian registry AOANJRR, the 15-year revision rate for ceramic-UHMWPE was 12% and for ceramic-HXLPE 5.8%. Comparably, the 15-year revision rate for metal-UHMWPE was 11% and for metal-HXLPE 6.2%. A similar trend continues up to 20 years. The revision rate for metal-UHMWPE was 15.2% while the revision rate of metal-HXLPE was 8.3% at 20 years from implantation (AOANJRR, 2021).

2.3 Bearing surfaces and wear

Tribology is the branch of science that deals with the study of friction, wear, and lubrication. Every implant type is subject to wear since current materials cannot provide a sufficient lubricating film in the human body. The amount of wear depends on the THA or HRA brand, bearing surfaces, and individual patient characteristics (Rieker & Köttig, 2002). Obesity does not seem to be associated with increased wear in MoM hip arthroplasty patients, although it might be associated with inferior clinical outcome (Ray et al., 2020; Sawalha et al., 2012; Yeung et al., 2011). There does not seem to be a clear association between increased activity level and excess wear in MoM implants either, but female sex appears to be associated with increased wear and inferior outcome in MoM hip arthroplasty patients (Haughom et al., 2015; Heisel et al., 2005; Pattyn et al., 2011; Smith et al., 2012). Smaller femoral head size is associated with a higher rate of wear in MoM HRA, while larger femoral head sizes may be associated with a higher risk of failure in MoM THA implants (Cross et al., 2012; Jack et al., 2013; Ollivere et al., 2009; Smith et al., 2012).

Implant wear can be measured in vitro using simulators, directly in vivo through explant analysis, or indirectly in vivo with radiographs. The amount of wear can be elaborated as linear or volumetric (Merola & Affatato, 2019). The wear of modern hard-on-hard bearings is often below the detection limit of conventional radiographs (Cuckler, 2005). Table 1. gives a rough comparison of linear wear rates of different bearing surfaces.

Table 1. Approximate linear wear rates of different bearing surfaces.

BEARING SURFACE	PAIRED MATERIALS	LINEAR WEAR RATE (MM/YEAR)	REFERENCE
MoP	CoCr-UHMWPE	0.14± 0.05	(Meftah et al., 2013)
	CoCr-HXLPE	0.038± 0.01	(Kurtz et al., 2011)
	Steel-HXLPE	0.068± 0.01	(Ise et al., 2009)
CoP	Ceramic-UHMWPE	0.086± 0.05	(Meftah et al., 2013)
	Ceramic-HXLPE	0.031± 0.01	(Guy et al., 2021)
CoC	Early ceramic-on-ceramic	0.013	(Hernigou et al. 2009)
	Later ceramic-on-ceramic	0.0041 ± 0.002	(Higuchi et al., 2018)
	Fourth generation ceramic-on-ceramic	0 *	(Lee et al., 2017; van Loon et al., 2021)
MoM	Small head CoCr-CoCr	0.0054 ± 0.002	(Higuchi et al., 2018)
	Metasul	0.0025 **	(Sieber et al., 1999)
	CoCrMo	0.0035 **	(Rieker & Köttig, 2002)

* only radiological studies where no wear was detected
** wear decreased to 0.0005 after the first year

Further metal tribology studies suggested that larger diameter MoM articulations with optimal clearance could promote complete fluid film lubrication of the articulation, which would then decrease the wear of the coupling (Rieker et al., 2005).

Radial clearance refers to the difference between the internal radius of the cup and the femoral component radius (Figure 2). The fluid entrapped in this inter-bearing space provides lubrication to the artificial joint (Van der Straeten, 2017). Hip simulator tests have demonstrated that lower clearance leads to better wear properties in vitro. Radial clearance varies in different LD MoM implants (Heisel et al., 2009).

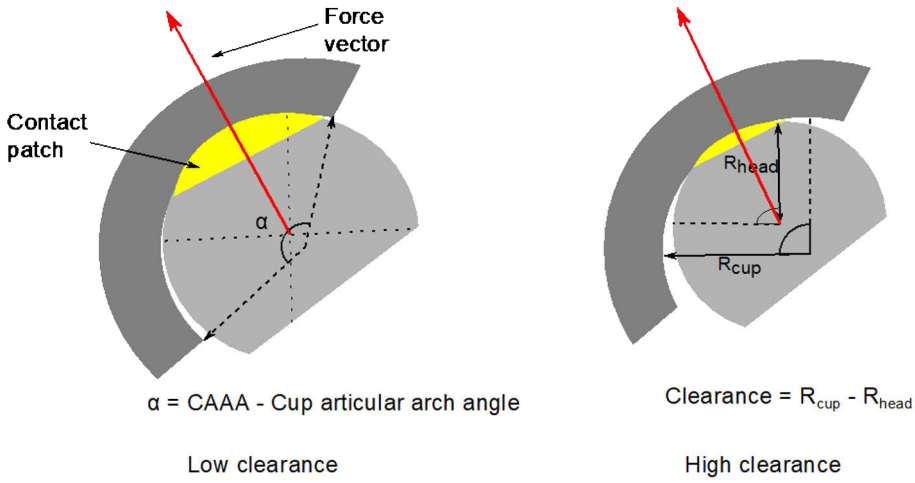

Figure 2. Lower clearance and larger contact patch may predispose the implant to edge loading.

However, lower clearance increases the contact patch and may predispose the implant to edge loading, especially if the contact patch reaches close to the edge of the cup. Edge loading may lead to increased wear and failure of the implant (Underwood et al., 2011). On the other hand, higher clearance will result in a smaller contact patch, which can increase volumetric wear during the "run-in phase" (Langton et al., 2011c; Rieker et al., 2005). The clearance of most commonly-used MoM hip devices varies from 150µm to 50µm. A clearance of more than 100µm can be considered high, of 75–100µm medium, and of 50–75µm low (Heisel et al., 2009). However, the correlation between radial clearance and implant wear is not as straightforward as it may seem (Bergiers et al., 2020).

The cup articular arch angle (CAAA, Figure 2), refers to the coverage of the acetabular component. A smaller CAAA may increase the ROM before impingement (Figure 4), but implants with low CAAA have lower tolerance to cup malposition. In conventional THA implants, the CAAA is normally 180°. According to a study by Griffin et al., a cup with a CAAA of 151° and implantation inclination of 55° will perform like an acetabular component with CAAA of 180° implanted at an abduction angle of almost 70° (Griffin et al., 2010).

Furthermore, the excess inclination may predispose the hip device to edge loading and clinical failure (de Haan et al., 2008; Shimmin et al., 2010; Underwood et al., 2011).

Many different metal alloys have been used in the manufacture of MoM hip implants. High-carbon alloys have approximately 0.2% carbon and low-carbon alloys have below 0.05%. The wear tolerance of high-carbon alloys is superior to that of low-carbon alloys due to the strengthening effect of carbides. Most recently, MoM bearing couples have been made of high-carbon content CoCrMo alloys and

bearing surfaces have consisted mostly of Cr (59–70%), Co (27–30%) and Mo (5–7%). Additionally, small amounts of carbon, nickel, iron, manganese, and silicon are used in the manufacture of these implants (Liao et al., 2013).

2.4 Modern MoM hip implants

2.4.1 Introduction of modern MoM hip implants

The era of modern MoM hip arthroplasty implants started in the 1990s when Derek McMinn re-introduced HRA with MoM bearing surfaces. When tribological studies had suggested that larger head size would provide advancements with lubrication, the modern HRA implants had significantly larger head sizes than earlier MoM generations. LD MoM THA implants were introduced soon after HRA (Triclot, 2011).

In addition to this, LD heads provided increased jump distance and reduced the risk of dislocation. Jump distance is defined as the amount of lateral translation of the rotational center of the femoral head before hip dislocation occurs (Figure 3) (Sariali et al., 2009). Also, an increased femoral head-to-neck ratio would decrease the risk of impingement and increase the range of motion (ROM, Figure 4) (Forsthoefel et al., 2017).

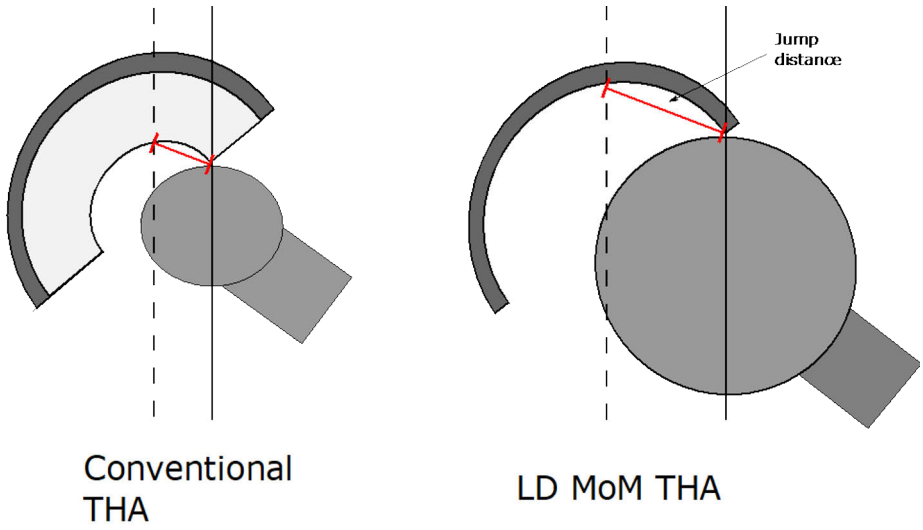

Figure 3. The “jump distance” is higher in LD MoM implants.

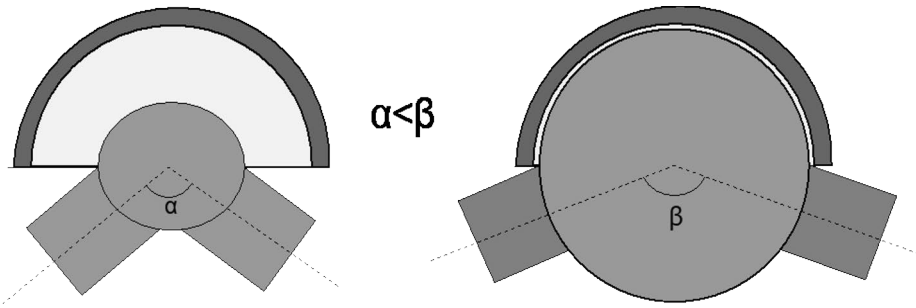

Figure 4. Larger head size enables a more favorable head-to-neck ratio and larger ROM before component impingement occurs.

First LD MoM HRA was Birmingham Hip Resurfacing (BHR), which had a cemented femoral component femur and cementless cup, with promising mid-term results (McMinn et al., 1996). BHR is an example of one of the few MoM HRA implants still used today (Figures 5–7).

Figure 5. Birmingham Hip Resurfacing implants. HRA implants (left) and THA option with the acetabular dysplasia cup and Synergy femoral stem (right).

At the same time, there were some concerns regarding the safety of MoM THA implants. Brodner et al. noticed that MoM articulations generate systemic release of Co, and Doorn et al. reported cases of soft tissue deterioration and peri-implant muscle necrosis in older MoM THA patients (Brodner et al., 1997; Doorn et al., 1996). Visuri and colleagues suggested that MoM THA might increase the risk of cancer when

compared to conventional THA (Visuri et al., 1996). However, more recent literature has disproved this association with cancer and MoM hip implants (Ekman et al., 2018; Mäkelä et al., 2012). The relatively good outcomes of BHR eased the way to the worldwide use of LD MoM hip arthroplasty (McMinn, 2003). At this time, HRA implants were considered class IIb medical devices, which meant that testing with patients was not required before entering the EU market (Cohen, 2012).

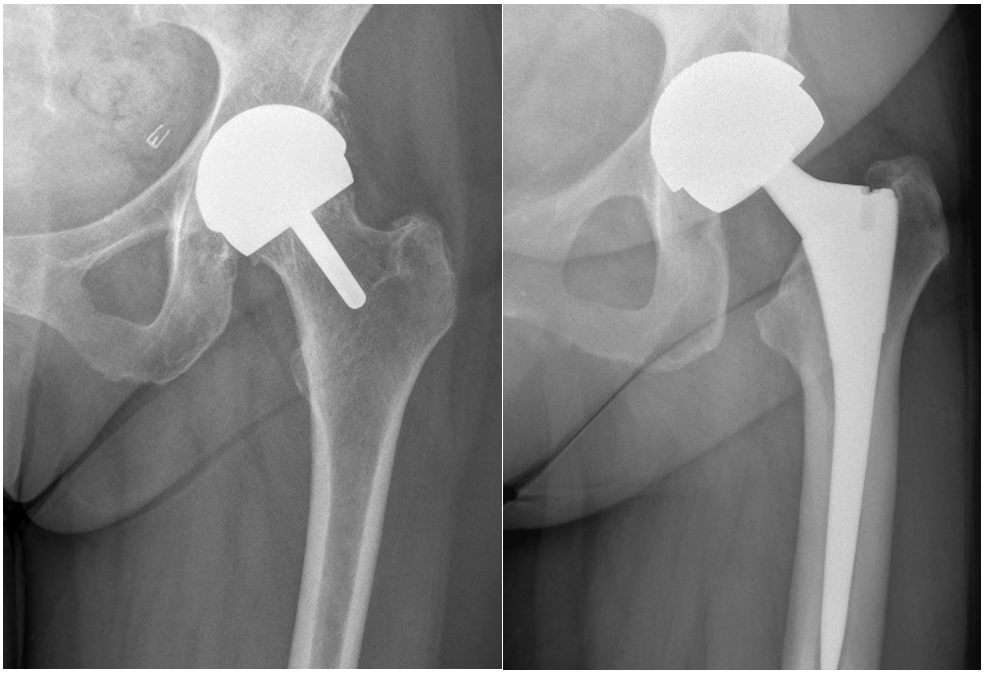

Figure 6. Plain AP radiographs from BHR HRA (left) and BHR THA (right).

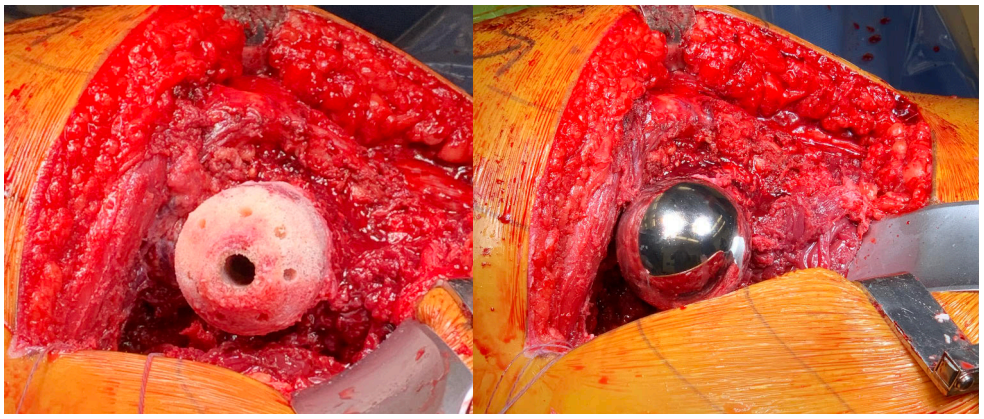

Figure 7. In MoM HRA, the cartilage of the femur is removed and the head trimmed (left). The femoral head is then capped with a cemented resurfacing head (right).

2.4.2 Implant specifics

In BHR hip devices, both the cup and the femoral component are a CoCrMo alloy (Smith&Nephew, 2018). The CAAA of BHR implants varies from 158° to 164°, depending on the internal diameter of the BHR cup. Larger sizes have a higher CAAA. The radial clearance of BHR implants was approximately 100µm, which can be considered high (Langton et al., 2009; Matthies et al., 2011a).

The small-head Metasul system (Centerpulse, Winterthur, Switzerland) was manufactured from a high-carbon-content CoCrMo alloy. The hemispherical cup included a 28mm or 32mm modular metal insert inside a plastic liner. The outside of the cup was manufactured from Ti alloy for better osseointegration. (Liu et al., 2005; Rieker, 2016; Triclot, 2011). The clearance of small-head Metasul MoM THA is rather low, at approximately 60µm (Liu et al., 2003).

Durom implants (Zimmer, Warsaw, IN) are also manufactured from high carbon content CoCrMo alloy. The CAAA of Durom cups is 165° in all cup sizes. The rim of the outer surface of the cup is 2mm wider than the dome to provide press-fit cup stability. The outer surface of the cup was also relatively smooth. The Durom cup was recalled in 2008 by the manufacturer due to a high revision rate from lack of osteointegration and loosening. The clearance of Durom implants is about 70µm (Long et al., 2010; Zimmer, 2009b).

Zimmer MMC cup (Zimmer, Warsaw, IN) is fully hemispherical with a CAAA of 180° in all cup sizes, and the outer surface of MMC cups had titanium plasma spray coating for enhanced osseointegration. The MMC bearing surfaces are manufactured from high carbon content, forged CoCrMo alloy, and the clearance of MMC implants is similar to Durom implants. (Zimmer, 2009a, 2009b)

The ReCap-M2a-Magnum (ZimmerBiomet, Warsaw, IN, US) hip device consists of a cup with varying CAAA of 155° for the 38mm cup to 164° for the 60mm implant (Scholes et al., 2017). The cup has four rim indentations and a press-fit design. Smaller head sizes (38mm and 40mm) are monoblock and do not have a modular taper insert. Head sizes 42mm and larger are paired with a modular tapered titanium (Ti) insert and a suitable femoral stem. The clearance of ReCap-M2a-Magnum implants is high, at approximately 120µm and the bearing surfaces consists of high carbon content, as-cast CoCrMo alloy (Biomet, 2009; Heisel et al., 2009; Scholes et al., 2017)

Articular Surface Replacement (ASR, Depuy, Warsaw, IN) hip implants have a low clearance of 50µm. ASR implants also consist of a CoCrMo alloy (Langton et al. 2009). The CAAA in ASR implants is size dependent and varies from 144° in the 44mm component to 155° in the 70mm acetabular component. ASR implants are manufactured using high carbon content CoCrMo alloy, the head is factory-made by casting and the cup is finalized by HIP. It has been suggested that high failure rates of ASR implants may be partly due to low clearance combined with low CAAA (Heisel et al., 2009; Shimmin et al., 2010).

ADEPT (MatOrtho Ltd., UK) and Conserve Plus (MicroPort Orthopaedics, Arlington USA) both have medium clearance (ADEPT 90µm and Conserve Plus 80µm). The CAAA of ADEPT is 160° and that of Conserve Plus 170° in all component sizes. Both implants are manufactured using high carbon content CoCrMo alloy. Both implants are produced with as-cast technique, while Conserve Plus bearing surfaces are finalized with HIP (Heisel et al., 2009).

2.4.3 Trunnionosis

The MoM bearing surface is not the only potential source of systemic metal ion exposure in patients with modern LD head MoM THA. These implants usually have a modular head, which allows easy exchange or head removal in revision operations. Modularity provides flexibility for the surgeon to optimize the offset and size and thus better regain the individual anatomic hip mechanics of the patient. The metal components develop an oxidization film in vivo which passively resists corrosion, but excessive loading during gait and hip movement causes micromotion, which may lead to breakage of the film and expose the metal to corrosion. The downside of modularity is that it creates an additional metal-metal interface where wear and corrosion may occur (Osman et al., 2016; Wight & Schemitsch, 2022).

Large head size in MoM implants increases the risk of trunnionosis when compared to smaller heads. Trunnionosis refers to the corrosion occurring at metallic head-neck or stem-neck junctions in poorly functioning modular implants. The corrosion in is often referred to as “mechanically assisted crevice corrosion”, since it is often triggered by mechanical stress or mechanical motion. When physical shearing forces remove the protective passive oxidization film, the metal is predisposed to corrosion. Further, if this corrosion occurs in a crevice at the head taper junction in an isolated space, oxygen may be depleted locally which will further accelerate corrosion (Urish et al., 2019).

It has been suggested that trunnionosis may even cause more metal-related problems than the bearing surface wear. Vendittoli and colleagues reported a significantly higher incidence of ARMD in patients with a modular stem compared to monoblock stems (Vendittoli et al., 2019).

As trunnionosis cannot occur in HRA implants, the incidence of ARMD has been suggested to be smaller in HRA than in MoM THA (Palazzuolo et al., 2021; Ridon et al., 2019). However, after 7 years from implantation, metal-related pathology is the most common reason for revision in HRA patients as well. The three most common reasons for revision for MoM HRA are metal-related pathologies (28%), loosening (25%), and fractures (18%) (AOANJRR, 2021).

ARMD type reactions have been described also in conventional THA implants due to trunnionosis, but they are quite rare. In a register study based on the

AOANJRR, the cumulative risk of revision due to ARMD was less than 0.3% in conventional THA implants. CoCr heads and head sizes of ≥36mm were associated with a higher risk of ARMD in conventional THA patients (De Steiger et al., 2020).

In MoM revision operations the femoral head can usually be removed with a punch and mallet. ReCap-M2a-Magnum THA implants, however, include a modular Ti taper adapter, which provides the option of neck length adjustment. Corrosion and fretting of this Ti-Ti taper junction may cause cold-welding of the implants, which can create problems during revision operations. This is a specific problem with ReCap-M2a-Magnum THA revisions and should be considered before deciding on revision of these implants (Figure 8) (Mäntymäki et al., 2016).

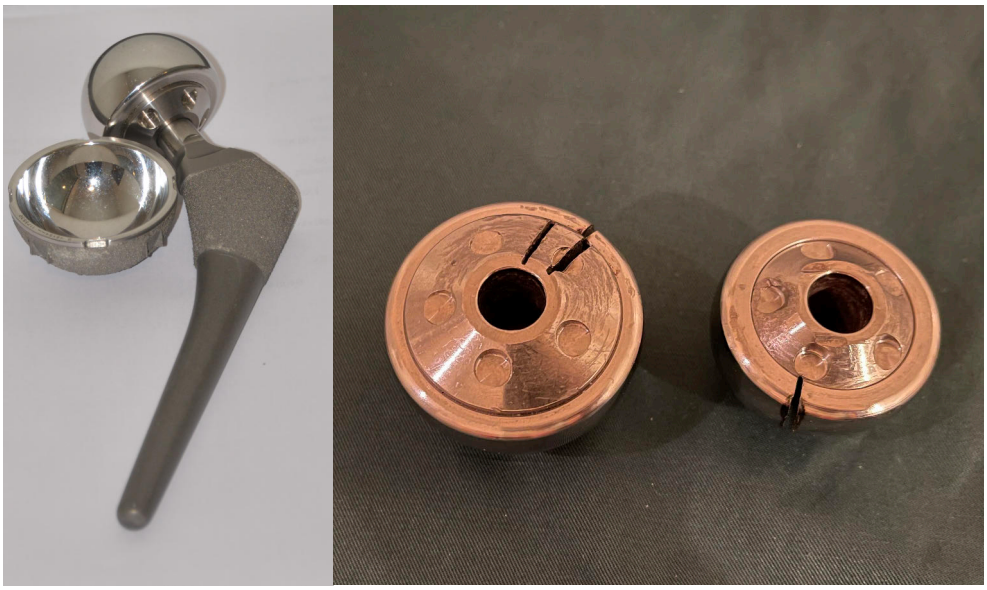

Figure 8. ReCap-M2A-Magnum MoM THA (left). Modular ReCap-M2a-Magnum heads after problematic revision operation (right).

2.4.4 Withdrawal of MoM implants

Revision surgeries due to periarticular metallosis were gradually increasing worldwide around 2010. The AOANJRR annual report of 2007 showed higher than anticipated revision rates for Articular Surface Replacement (ASR, Depuy, Warsaw, IN) HRA. It was also discovered that the revision rates were almost equally high for both ASR HRA and ASR XL THA implants, (AOANJRR, 2007; De Steiger et al., 2011). The Durom Metasul LD MoM acetabular device also had a higher than anticipated revision rate. Initially the problems were thought to be associated only with certain LDH MoM implants (AOANJRR, 2007). The Durom cup was found to

have a high incidence of failure due to lack of osseointegration, and it was recalled in 2008 (Long et al., 2010; Therapeutic Goods Administration (TGA)., 2012). The Zimmer MMC acetabular component was released in 2009 to address the fixation problem with the Durom cup (Figure 9) (Zimmer, 2009b)

Figure 9. Fully hemispherical MMC acetabular components and femoral heads.

In 2009, ASR MoM implants were withdrawn from the Australian market due to high revision rates, and later in 2010 the ASR was withdrawn worldwide (TGA, 2012).

It became evident that it was metal—mostly Co and Cr—wear debris from ASR implants that was leading to the destruction of soft tissues around the joint in a failing ASR hip. In individuals without any implants, Co or Cr levels do not exceed 1ppb (Langton et al. 2013, Kovochich et al. 2018). High, even toxic levels of Co and Cr ions were seen in the blood and cerebral spinal fluid of ASR patients (Cohen 2011). According to a study by Langton et al., more than one-fourth of ASR patients had a Co or Cr value above 7ppb and up to 13% had levels above 20ppb at mid-term follow-up (Langton et al., 2011a). It was understood that some MoM hip implants were associated with a higher risk of revision and systemic or local adverse effects, while other implants seemed less problematic (Haddad et al., 2011).

Still, it took 4 years from recognition of the problems associated with ASR before the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (U.K.) published a safety alert regarding all MoM THA and HRA devices (MHRA, 2012). This led to a full-scale acknowledgment of the problems associated with MoM hip implants. As with MoM THA, the implant survival of most MoM HRA brands was poor compared to conventional bearing surfaces (Pijls et al., 2019).

However, the BHR device, Cormet Resurfacing System, and a few other MoM HRA brands are still in infrequent use, especially in England, Australia, and the United States (FDA., 2019; Oak et al., 2017; Harrison-Brown et al. 2019), because of satisfactory outcomes compared to other HRA brands (AOANJRR, 2021; NJR, 2021). The 10-year overall survival rate for all HRA has been 86%, while that for BHR HRA in Finland has been 91% (Seppänen et al., 2016). The 10-year revision rate of BHR HRA is 6.6% in Australia and 7.5% in the U.K.

In 2007, the market share of the MoM bearing couple was 20% in the U.K. (Cohen, 2012). At its height, MoM THA and HRA accounted for 35% of all hip arthroplasties in the U.S. (Smith et al., 2012). To date, approximately 1.5 million MoM hip devices have been implanted worldwide, more than 20 000 of them in Finland (Lainiala et al., 2021; Matharu et al., 2018c; Pijls et al., 2019). While HRA implants with MoM bearings are still used, primary HRA has a lower risk of revision than conventional THA only during the first month after implantation. HRAs are very stable due to the large head size, and dislocation revisions are extremely rare. Later on, the risk of revision is higher with HRA compared to conventional devices. ARMD is the most common reason for revision in MoM HRA implants after 7 years of follow-up (AOANJRR, 2021).

2.5 Local adverse effects

2.5.1 Metallosis

Sterile joint effusion in MoM THA was described already in the 1970s with the McKee-Farrar device (Jones et al., 1975). During the first and second generation of MoM THAs, soft tissue reactions were described grossly as metallosis. Metallosis is defined as aseptic fibrosis and local necrosis in the joint cavity and surrounding tissues. The term also includes the greyish discoloration of the tissue, which is thought to be caused by Co and Cr ions from the bearing surfaces (Figure 10) (Haddad et al., 2011; Xu et al., 2020).

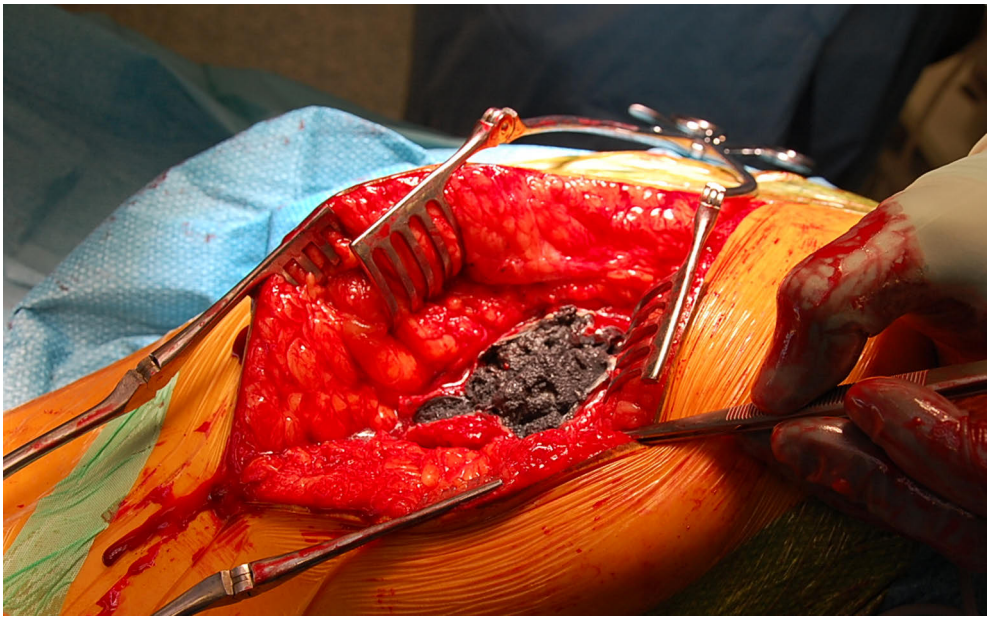

Figure 10. Metallosis, shown by the gross greyish discoloration of tissues encountered during revision surgery (image courtesy of Jari Mokka).

2.5.2 ALVAL

Aseptic lymphocyte-dominated vasculitis associated lesion (ALVAL) was first described by Willert, who analyzed periprosthetic tissue from retained second generation MoM THA implants (Willert et al., 2005). ALVAL is a histological diagnosis describing cellular changes in response to metal particles when no infection is present. Davies et al. detailed this perivascular inflammatory phenomenon further (Davies et al., 2005; Willert et al., 2005).

Pseudotumors tend to occur in association with severely worn MoM implants, but they also appear around well-positioned implants with low wear and no obvious explanation for failure (Ebramzadeh et al., 2011; Grammatopoulos et al., 2013). Histological findings in ALVAL include an abundance of lymphocytes in the pericapsular tissue and dense perivascular inflammatory infiltrate. This perivascular infiltrate is a unique histological feature of ALVAL (Watters et al., 2010).

While macrophage infiltrate and necrosis are seen consistently in histological samples of pseudotumors, ALVAL-type reaction is not encountered in all pseudotumors (Kwon et al., 2011). This suggests that the extensive necrosis and soft tissue destruction around failed MoM implants is due not only to the cytotoxic effects of metal debris but also to a delayed hypersensitivity-type reaction in some patients (Grammatopoulos et al., 2013).

ALVAL is defined as a chronic, type IV delayed immunological hypersensitivity reaction to foreign-body particles from MoM implants. The incidence of ALVAL does not seem to correlate with the amount of wear, suggesting that ALVAL is not dose dependent but rather an "all or nothing" type of immunological reaction (Berstock et al., 2014). On the other hand, some histological features of ALVAL such as presence of lymphocytes and plasma cells have been criticized as wildly unspecific, as they can also appear in other types of implant failures (Watters et al., 2010).

Campbell and colleagues suggested the use of an ALVAL scoring system for more standardized reporting and grading of the histological characteristics of soft tissues around MoM hips. The ALVAL score varied from 1 to 10. A result of 0–4 was considered low, 5–8 moderate, and 9–10 high. A higher score was associated with lower wear in their study, suggesting a hypersensitivity reaction as the cause of pseudotumor in these cases (Table 2) (Campbell et al., 2010). Grammatopoulos et al. suggested that the discriminatory criteria associated with Campbell's ALVAL score did not provide enough distinction between highly worn and lightly worn implants. Instead, they proposed a slightly altered version, the Oxford ALVAL score, which took into account tissue necrosis, amount of inflammatory cells, and strength of the ALVAL-type reaction (Grammatopoulos et al., 2013). Both scoring systems have since been criticized as lacking reproducibility (Smeekes et al., 2017). Ricciani et al. commented that the histological patterns of ARMD are too diverse to describe with an ALVAL score (Ricciardi et al., 2016), and Berstock et al. suggested that a simple descriptive histological analysis may be more useful than a complicated scoring system (Berstock et al. 2014).

Table 2. Campbell's ALVAL score criteria.

SYNOVIAL LINING	
Intact synovial lining	0
Focal loss of synovial surface; fibrin attachment may occur	1
Moderate to marked loss of synovial surface, fibrin attachment	2
Complete loss of synovium, abundant attached fibrin and/or necrosis of lining tissue	3
INFLAMMATORY INFILTRATE	
Minimal inflammatory cell infiltrates	0
Predominantly macrophages; occasional lymphocytes may occur	1
Mix of macrophages and lymphocytes, either diffuse and/or small (<50%) perivascular aggregates	2
Mix of macrophages and lymphocytes, either diffuse and/or large (>50%) perivascular aggregates	3
Predominantly lymphocytes, mostly in multiple, large (>50%) perivascular aggregates; follicles may be present	4
TISSUE ORGANIZATION	
Normal tissue arrangement	0
Mostly normal tissue arrangement; small areas of synovial hyperplasia, focal necrosis may occur	1
Marked loss of normal arrangement, appearance of distinct cellular and acellular zones; thick fibrous layers may occur	2
Perivascular lymphocytic aggregates mostly located distally; thick acellular areas may occur	3

2.5.3 Pseudotumors

Pandit et al. defined the term "pseudotumor" as a cystic or solid soft tissue mass associated with MoM implants. The term pseudotumor describes this condition fairly well, since these masses are neither infective nor malignant (Figure 11) (Pandit et al., 2008a). Pseudotumor tissues are histologically characterized by extensive connective tissue necrosis and type IV hypersensitivity reactions with abundant lymphocytes, which are recognized in ALVAL (Pandit et al., 2008a; Phillips et al., 2014).

In the presence of a highly wearing MoM device, a macrophage-dominant histological reaction may be seen in pseudotumors which can be categorized as a "non-ALVAL" response. Berstock et al. described a third distinct histological entity which had mixed elements of both processes (Berstock et al., 2014). Histologically there is irregularity in the quantity and distribution of metal ions and degree of necrosis in pseudotumors, while macrophages and lymphocytes are seen in all cases. Soft tissue samples with extensive amounts of macrophages tend to have fewer lymphocytes and vice versa. A higher level of synovial ulceration and tissue destruction is often associated with patients with an ALVAL-type metal

hypersensitivity reaction and lower wear (Davis & Morrison, 2016; Van der Merwe, 2021).

Pseudotumors are mainly associated with MoM hip implants, but they can rarely occur around conventional MoP and CoP THA implants as well mostly due to trunnionosis (Bisseling et al., 2015; Hjorth et al., 2018).

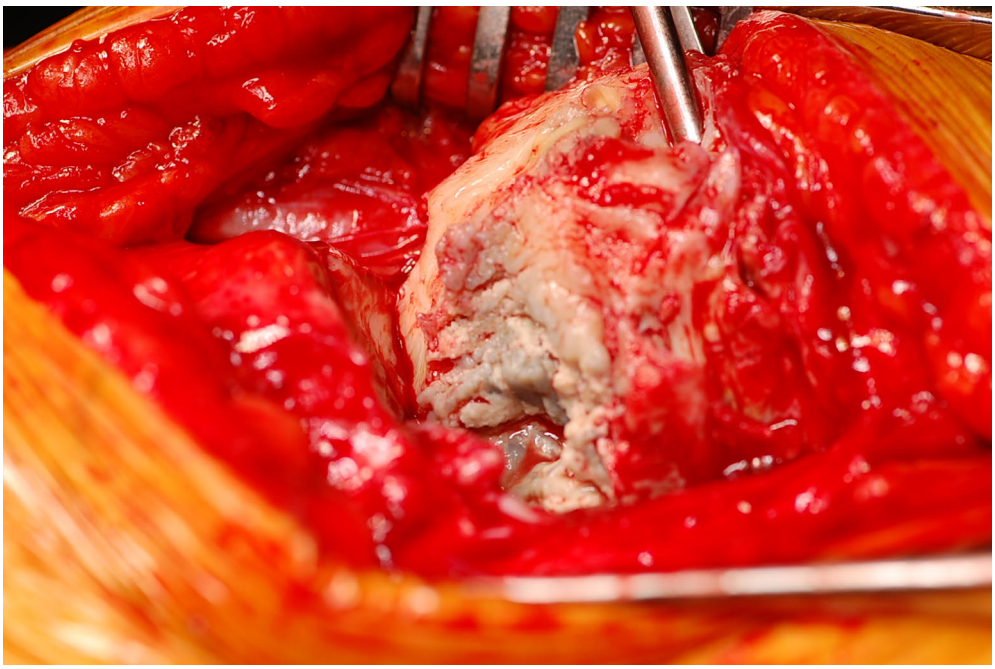

Figure 11. Solid pseudotumor in a revision operation (image courtesy of Jari Mokka).

2.5.3.1 Classifications

Different pseudotumor classification systems based on MARS-MRI have been described. Andersson and colleagues used a three-grade classification system where A was normal, B was infection, and C was "MoM disease". Grade C had three subgroups with C1 considered mild, C2 moderate, and C3 severe MoM disease. The authors acknowledged that their grading system had limited ability to differentiate mild MoM disease from infection (Anderson et al., 2011).

Similarly, Hauptfleisch et al. suggested a three-grade pseudotumor classification, Grade 1 being a thin-walled cystic mass with wall dimension <3mm. Grade 2 pseudotumors had thicker walls (>3mm but less than the diameter of the cystic component). If the pseudotumor was predominantly solid, it was considered a Grade 3 pseudotumor (Hauptfleisch et al., 2012).

Hart et al. described a classification separating simple, thin-walled fluidlike (Hart 1) lesions from complex fluid lesions (Hart 2) and mainly solid pseudotumors (Hart 3) on MARS-MRI. Further, Hart 2A pseudotumors had thicker or more irregular walls than Hart 1 but still fluidlike contents, while Hart 2B pseudotumors had atypical or partly solid contents. The Hart pseudotumor classification did not take into account the size of the pseudotumor (Hart et al. 2012).

Van der Weegen et al. (2014) suggested that the pseudotumor classification by Andersson had the best intraobserver reliability compared to other classifications (Van der Weegen et al., 2014). Smeekes et al., on the other hand, suggested that the Hart grading system would have the better intraobserver reliability. They reported only a moderate agreement in reproducibility for all three classifications (Smeekes et al., 2018). These pseudotumor classification systems are described in Table 3.

Table 3. Different pseudotumor classification systems.

	ANDERSSON	HART	HAUPTFLEISCH
NORMAL	**A** - Normal postoperative changes		
	B - Infection		
MILD	**C1** - Periprosthetic soft tissue mass without hyperintense T2W fluid signal, or peri-prosthetic cavity <5cm in diameter	**1** Thin-walled (<2 mm), flat, with fluidlike contents	**1** Thin-walled cystic mass (cyst wall <3 mm)
MODERATE	**C2** - Periprosthetic soft tissue mass without hyperintense T2W fluid signal, or peri-prosthetic cavity >5cm in diameter	**2A** Thick-walled or irregular with fluidlike contents	**2** Thick-walled cystic mass (cyst wall >3 mm)
		2B Thick-walled or irregular with fluidlike and solid contents	
SEVERE	**C3** - Fluid-filled cavity extending through deep fascia, (2) a tendon avulsion, (3) intermediateT1W soft tissue cortical or marrow signal, (4) fracture	**3** Solid pseudotumors	**3** Solid pseudotumors

2.5.4 ARMD

ARMD was developed as an umbrella term by Langton et al. to describe metal-related MoM hip arthroplasty failure associated with metallosis, soft tissue necrosis, pseudotumors, sterile effusions, and pain. Natu and colleagues did further studies on the histology of ARMD and defined ARMD as a spectrum of changes ranging from pure metallosis-type reaction to ALVAL (Langton et al., 2011b; Natu et al., 2012).

Adverse local tissue reaction (ALTR) includes all types of local adverse reactions to wear debris, not only metal. However, in the literature on MoM hip arthroplasties, ARMD and ALTR are used to describe the same phenomenon (Lohmann, 2014). The clinical variety of ARMD is wide, ranging from small asymptomatic cysts to large cystic or solid soft tissue pseudotumors. Further, ARMD can cause large osteolysis and bone defects as well as destruction to the pelvis or femur (SCENIHR, 2014).

Soft tissue responses and ARMD-like changes can occur in all THA bearing surfaces. Matharu and colleagues reported that between 2008 and 2015 in the U.K., 92.5% of all hip revisions due to ARMD were performed to MoM hip arthroplasties and 7.5% to conventional THA. The risk of ARMD was slightly higher in CoC bearings than hard-on-soft bearings, and 36mm MoP bearings had a higher risk of ARMD than smaller MoP THAs (Matharu et al., 2016c)

The revision burden of MoM THA is declining, as a significant portion of these patients have had revision surgery and usage of MoM THA implants is no longer recommended. ARMD remains the most common reason for revision surgery on uncemented and hybrid MoM THA patients (NJR, 2021), and ARMD revisions for MoM hip arthroplasty are associated with worse outcomes than revisions for any other reason (Grammatopoulos et al., 2009; Lainiala et al., 2019; NJR, 2021). ARMD was still the most common reason for hip revision arthroplasty in Finland in 2015 (16% of all hip revisions). In 2021, infection was the most common cause (26%), dislocation the second (23%), periprosthetic femoral fracture the third (13%), and ARMD the fourth most common reason (11%) for revision hip arthroplasty in Finland (Finnish Arthroplasty Register [FAR]., n.d.).

2.6 Follow-up of MoM hip arthroplasty

2.6.1 Follow-up protocols

After concerns emerged over the high revision rates of ASR MoM HRA and THA, MHRA issued a Medical Device Alert and market withdrawal for ASR hip replacement implants in April 2010 (MHRA, 2010). Shortly after this, in August 2010, DePuy Orthopaedics issued a voluntary recall for ASR hip implants (DePuy, 2010). After the withdrawal, it became clear that the problems associated with ASR implants were present in other MoM devices as well. Data from both joint registries and independent reports led to the withdrawal of several MoM THAs and HRAs (AOANJRR, 2011; FAR, n.d.; Naal et al., 2011; Smith et al., 2012). Authorities worldwide recommended the follow-up and monitoring of all MoM hip arthroplasties to detect ARMD early (European Federation of National Association of Orthopaedics and Traumatology [EFORT]., 2012; FDA, 2019; Government of Canada, 2016; MHRA, 2012; TGA, 2012).

MHRA recommended that all patients with a withdrawn implant model or symptomatic MoM hip arthroplasty should remain in annual follow-up for the life of the implant. Follow-up recommendations differed. Screening included clinical evaluation, plain X-rays, WB Cr and Co measurements, and cross-sectional imaging such as ultrasound (US), computed tomography (CT) or MARS-MRI.

MHRA, TGA and Health Canada recommended a safe upper limit (SUL) or cut-off level for WB Cr and Co as high as 7ppb. EFORT recommended that already lower values (2–7ppb) should raise concern. The Finnish arthroplasty association recommended in 2012 not to continue implantations of MoM THA or HRA and recommended a SUL of 5ppb for both Cr and Co ions (EFORT, 2012; Finnish Arthroplasty Society, 2014; MHRA, 2012; TGA, 2012). These guidelines have been criticized for not being uniform, evidence based or cost effective, and they have since been updated (Hannemann et al., 2013; Matharu et al., 2015b).

While the survival of different MoM hip implants varies (AOANJRR, 2021; FAR, n.d.), it might also be sensible to have differing follow-up protocols for each MoM hip brand from a cost-effectiveness point of view. Various SUL values for metal ions have been suggested to detect failing MoM HRA or MoM THA implants and more recent SUL values are implant specific (Donahue et al., 2019; Matharu et al., 2016a; Van der Straeten et al., 2013a).

2.6.2 Metal ions

WB Co and Cr levels have been shown to correlate reasonably well with the wear of MoM hip arthroplasty (De Smet et al., 2008; Keegan et al., 2007b; Lehtovirta et al., 2017). While normal metal ion levels cannot exclude ARMD, they are invaluable in the screening of MoM THA or HRA patients (Grammatopoulos et al., 2017; SCENIHR, 2014).

The wear pattern of HRA and THA implants is biphasic, especially with MoM articulations. Wear rate is higher initially after implantation during the “run-in” phase. During this period, blood concentrations of Co/Cr peak, decreasing thereafter when implant wear slows down (Mont & Schmalzried, 2008). The “run in” period seems to last for the first year after implantation with HRA, but it may be longer with THA implants (Bernstein et al., 2012; Heisel et al., 2008; Lee et al., 2008; Maurer-Ertl et al., 2012).

This phenomenon where articulating surfaces reach conformity with each other is called the “bedding-in” process, after which the wear rate decreases, reaching a “steady state” (Bowsher et al., 2009; Daniel et al., 2009; Naito et al., 2021).

In an ex vivo analysis of 297 retained Metasul MoM implants, the rate of wear was 35 µm/year during the first year but only 5 µm/year during the second. Authors

also observed a size-mismatched head-cup implant with a yearly wear rate of 950µm, demonstrating how mismatching causes excessive wear (Rieker & Köttig, 2002).

Small measurable levels of Co and Cr ions can be found in normal human blood, but high concentrations are toxic. In a population without CoCr implants, Co concentrations are below 1ppb in 93% and Cr below 2ppb in 97% of patients (Sidaginamale et al., 2013). High metal ion concentrations may cause renal, immunological, and reproductive issues and developmental toxicity, carcinogenesis, and neurological problems (Keegan et al., 2007a).

Metal ion concentrations do not normally rise to toxic levels in well-functioning MoM implants, but poorly functioning implants have the potential to cause heavy metal toxicity. Systemic health effects are reported to be rare in cases where Co and Cr ion levels are below 300ppb (Kovochich et al., 2018). Co ions exert pathological effects through direct cellular toxicity, which is why high levels are so toxic. Co ions can cause apoptosis and necrosis through multiple mechanisms at cellular level, and Co is considered a possibly carcinogenic substance following in-vitro studies that show Co-induced DNA fragmentation and reactive oxygen species production (Cheung et al., 2016). Elevated WB Co and Cr levels seem to be associated with increased risk of pseudotumors (Kwon et al. 2011, Bosker et al. 2012), but this correlation is not clear (Matthies et al., 2012).

The current guidelines by MHRA, TGA, the SCENIHR, and the Finnish Arthroplasty Society recommend using WB Cr and Co in the follow-up of all MoM hip replacements (Finnish Arthroplasty Society 2014; MHRA, 2017; SCENIHR, 2014; TGA, 2012). The FDA, on the other, does not recommend routine usage of WB metal ion measurements in the screening of MoM patients (FDA, 2019).

Implants are either modular, meaning that they are assembled from separate parts, or monoblock, where the component is manufactured as a single piece. Femoral stems and the metal shell of modular cups are usually manufactured from Ti alloys, while monoblock cups are most often made of CoCr alloy (Hjorth et al., 2016; SCENIHR, 2014). Ti alloys are sometimes used in the coating of implants. Stems and acetabular cups can be coated with hydroxyapatite or plasma-sprayed Ti to enhance the circumstances for bone ingrowth (Figure 12). Modular necks can be manufactured using Ti or CoCr alloys (Hjorth et al., 2016; SCENIHR, 2014). Based on the literature, Ti can be considered a relatively safe metal that rarely causes systemic toxicity or hypersensitivity problems in humans (Keegan et al., 2007a; Kim et al., 2019).

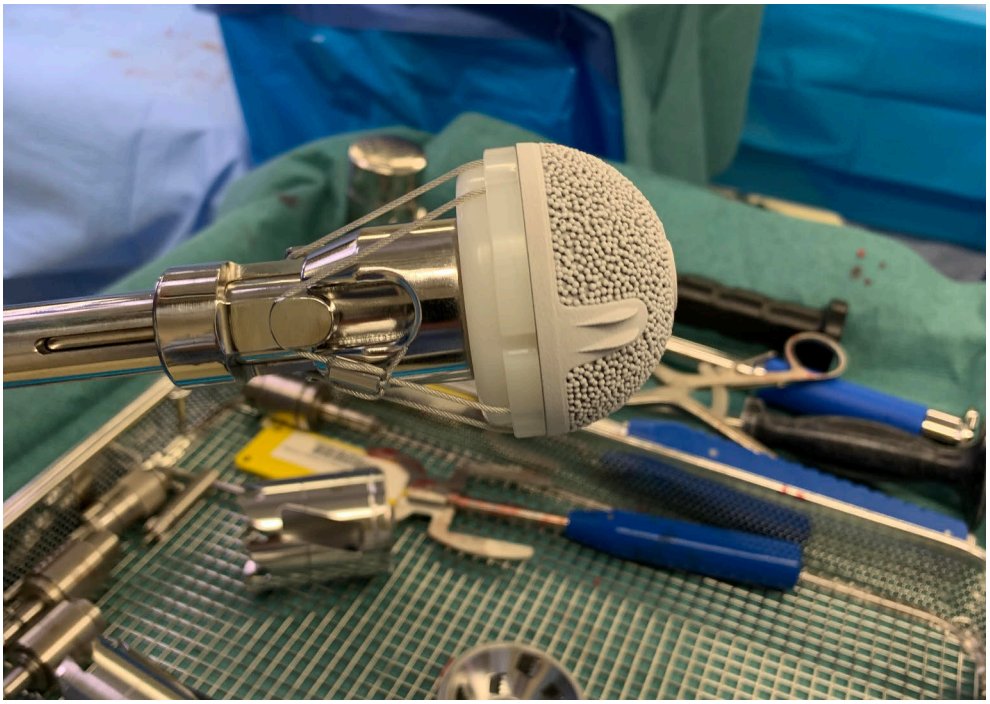

Figure 12. Cementless BHR acetabular component coated with hydroxyapatite to stimulate bone ingrowth and osseointegration.

2.6.3 Imaging

Plain radiographs can distinguish periprosthetic fractures and loose implants in some instances and should be done on all patients with a symptomatic MoM hip arthroplasty. On the other hand, their ability to diagnose soft tissue masses such as pseudotumors is poor, and normal X-rays can be falsely reassuring (Figure 13) (Van der Weegen et al., 2013b). Abnormalities on plain radiographs are more common in MoM hip arthroplasties with a pseudotumor than in those without. Still, further soft tissue imaging or radiological intervention is often necessary for patients with unexplained pain in their operated hip, if plain radiographs appear normal (Johnston et al., 2007; Matharu et al., 2017).

US is a practical, safe, and low-cost imaging tool that can be used to detect soft tissue abnormalities. Garbuz et al. have reported an impressive sensitivity of 100% for US in pseudotumor detection in a cohort of 40 MoM THA patients. They suggested the use of US as the initial imaging modality for the screening of MoM THA patients (Garbuz et al., 2014). However, US is highly operator dependent, and the precise comparison of different imaging sessions can be difficult. US seems to be better at detecting joint effusions or tendinous pathologies than MARS-MRI in MoM hip arthroplasties, but worse at detecting pseudotumors or muscle atrophy (Siddiqui et al., 2014).

Both CT and MARS-MRI offer multi-planar cross-sectional images, which enable the evaluation of normal and abnormal anatomy in the presence of MoM hip arthroplasty. The availability of CT is often better than that of MARS-MRI (Anderson et al., 2011). CT is also an alternative in cases of claustrophobia or in the presence of a pacemaker or loose metal implants (Roth et al., 2012). Also, CT is better than MARS-MRI at detecting periprosthetic bony changes such as osteolysis (Robinson et al., 2014).

MARS-MRI is currently the gold standard for detecting soft tissue abnormalities in MoM hip arthroplasty patients. It enables the detailed description and grading of pseudotumors (SCENIHR, 2014). MARS-MRI provides a combination of minimized blurring of images, decent metal artefact suppression and relatively short scanning time, making the detection of asymptomatic pseudotumors possible (Hart et al., 2012; Sutphen et al., 2016).

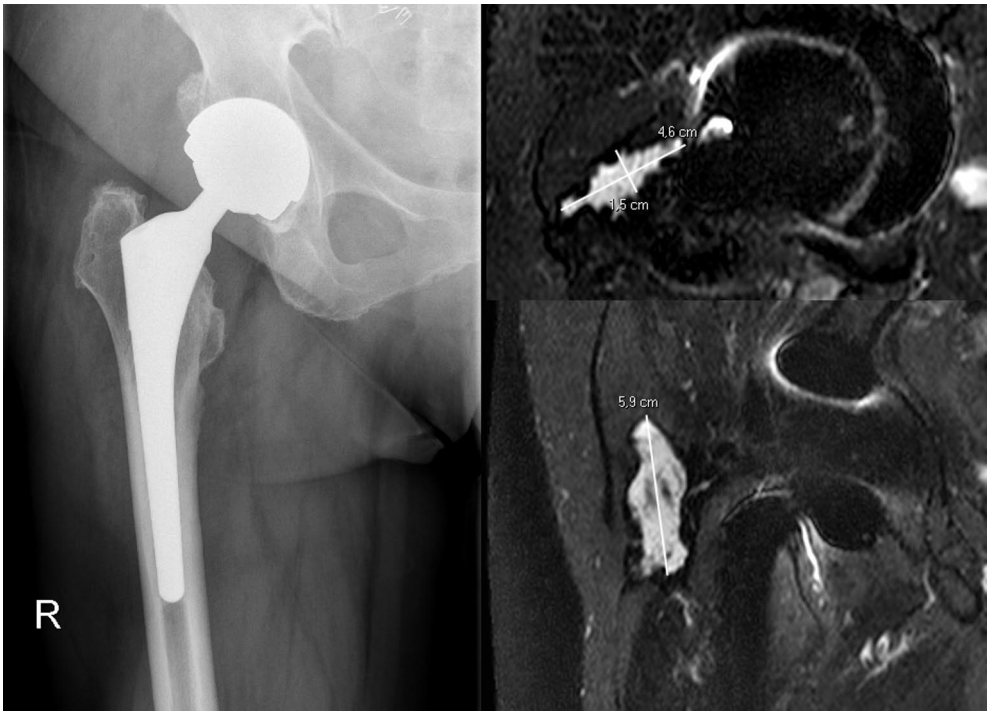

Figure 13. Normal X-ray (left) and MARS-MRI images of a pseudotumor in the same hip (right).

The size, location, and grade of pseudotumors and soft tissue destruction are important factors when considering revision surgery. The use of MRI in ARMD screening, however, is limited due to availability, cost, and patient compliance (Matharu et al., 2018b; Robinson et al., 2014). If MARS-MRI is not tolerated, is

unavailable or is contra-indicated, US should be considered as the initial imaging modality for soft tissue abnormalities (SCENIHR, 2014; Siddiqui et al., 2014).

2.6.4 Hip-specific outcome measurements

Patient-reported outcome measurement (PROM) questionnaires are commonly used in the evaluation of pre- or post-operative symptom state of an orthopedic patient. The Oxford Hip Score (OHS), Harris Hip Score (HHS) and Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) are examples of commonly used hip questionnaires.

Worldwide authorities such as the MHRA, TGA, FDA, Health Canada and the EFORT recommend stratifying the follow-up of MoM hip arthroplasty patients based on symptom state. The MHRA, FDA and Health Canada define the symptoms as abnormal gait and pain, while EFORT and TGA do not delineate symptoms (Matharu et al., 2015b). Pain is considered a common predictor of pseudotumor presence, typically in the groin. Also, clicking and clunking sensations or radicular thigh pain in a MoM hip arthroplasty can be caused by pseudotumors (Langton et al., 2011b). Health Canada and the FDA describe symptoms as noises from the hip, decreased ROM, dislocation, swelling, and local nerve palsy. None of these authorities recommend the use of hip-specific outcome measurements (Matharu et al., 2015b). In contrast, the Finnish Arthroplasty Society recommends the use of a hip-specific outcome measurements questionnaire in the follow-up of MoM hip arthroplasty patients, OHS being the most often used questionnaire in Finland (Finnish Arthroplasty Society, 2014).

The WOMAC consists of 24 questions related to pain, stiffness, and physical function. The maximum score from the WOMAC questionnaire is 96 points, fewer points reflecting better function and higher scores poorer function with stiffness and pain (Pulik et al., 2020).

Similarly, the OHS measures the functional outcome of the hip. The OHS has a scale of 0 to 48, with 48 being the best patient-reported outcome. A score below 26 is considered a poor outcome, 27–33 points a moderate outcome, 34–41 a good outcome, and 42–48 an excellent outcome (Murray et al., 2007).

The HHS was developed in 1969 and consists of 11 items regarding pain, everyday activities, and physical examination. It has a maximum of 100 points, a higher score indicating better function. The HHS is considered a valid measurement tool for pre- and postoperative function and is currently the most used hip outcome measurement questionnaire worldwide (Harris, 1969; Lovelock et al., 2018; Singh et al., 2016).

Other hip outcome measurement systems include the Rheumatoid and Arthritis Outcome Score (RAOS), the Mayo Hip Score (MHS), and the Hip Disability and Osteoarthritis Outcome Score (HOOS). The large number of scales makes it

somewhat difficult for a clinician to compare separate studies. Nevertheless, PROM questionnaires are valid tools for evaluating the effects of treatments (Pulik et al., 2020).

It has been suggested that HRA implants might provide better functional outcome than THA implants in young and active patients, at least in the short term (Lingard et al., 2009). However, based on more recent literature, there does not seem to be a difference in PROM scores between conventional THA, LD MoM THA, and HRA groups up to 5 years from the operation (Costa et al., 2018; Hersnaes et al., 2021).

Overall, good to excellent functional outcomes after MoM hip arthroplasty have been reported. Matharu et al. reported a postoperative median OHS of 45 after a follow-up of 5 years in a MoM THA cohort who had a median preoperative OHS of 16 (Matharu et al., 2014). Umar et al. reported a mean OHS of 43 after 10 years in a cohort of Corail-Pinnacle MoM THA patients (Umar et al., 2018). Gani et al. reported a mean OHS of 43 in a MoM HRA cohort with 15 years of follow-up (Gani et al., 2022). The mean preoperative OHS for all hip arthroplasty patients is currently 21 at our institution and the median is also 21, while the mean postoperative OHS is 41 and the median postoperative OHS 44. According to latest AOANJRR report the mean preoperative OHS was 20 and the mean postoperative OHS was 42 in Australian population (AOANJRR, 2021).

Similarly, excellent HHS outcomes after 10-year follow-up for MoM hip arthroplasties have been reported. Scholes reported an HHS of 97 after a minimum of 10 years (Scholes et al., 2019). Reito et al. reported a preoperative HHS of 56 and median postoperative HHS of 100 after 10 years of follow-up for a cohort of BHR patients (Reito et al., 2014). Van der Straeten reported a postoperative HHS of 97 after a mean follow-up of 11 years in a cohort of BHR patients (Van der Straeten et al., 2013b).

Even though hip-specific outcome measurement scores provide valuable information, they cannot be used as a sole screening tool for MoM hip arthroplasty patients, since a significant proportion of pseudotumors are asymptomatic (Fehring et al., 2014; Konan et al., 2017; Van der Weegen et al., 2013a).

2.7 Future aspects

2.7.1 Future aspects of MoM hip arthroplasty

According to estimates, approximately a million MoM bearings may still be in situ (Lainiala et al., 2021). The amount of MoM implantations worldwide decreased rapidly after the safety alert by MHRA in 2012 (MHRA, 2012). However, many of these patients were younger than conventional THA patients, especially with hip resurfacings (AOANJRR, 2021). Based on literature, a longer follow-up interval

may be sufficient for these patients in the future, but the screening of these patients continues to be imperative, and should not be discontinued at least in the nearby future (Matharu et al., 2015b; Reito et al., 2022; Van der Weegen et al., 2022).

Today, the number of annual HRA implantations is a fraction of what it used to be. Based on Australian registry data, primary HRA implantations represented only 1.2% of all hip replacements in 2020. ADEPT HRA was the most commonly implanted MoM HRA in Australia, with 296 implantations in 2019 and 316 in 2020 (Figure 14), followed by BHR with 145 implantations in 2019 and 152 in 2020 (AOANJRR, 2021).

ADEPT has a reasonably good revision rate of 5.4% at 10 years, while the 10-year revision rate for BHR is 6.6% in Australia (AOANJRR, 2021). In the U.S., there are currently two FDA approved HRA implants, BHR and the Corin Cormet Hip Resurfacing System. The usage of MoM THA implants is no longer recommended.

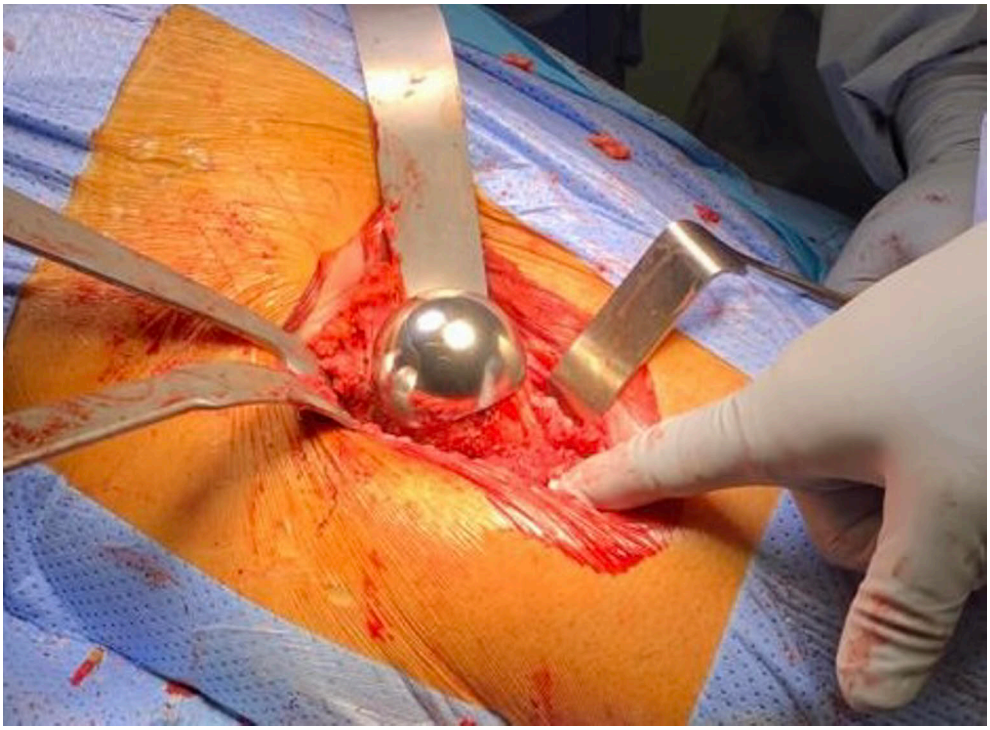

Figure 14. ADEPT HRA implanted via direct anterior approach in 2020

HRA implants are still considered a valid treatment for a carefully selected patient group in Australia, Belgium, Germany, the U.S., and the U.K. The theoretical advantages of HRA over conventional THA include lower risk of dislocation and possibly a return to high impact sports (Clough & Clough, 2021; FDA, 2019;

Matharu et al., 2015c). Target demographics for MoM HRA are male sex, age under 65 years, and femoral head size of 50mm or larger. However, based on registry data, MoM HRA implants have a higher rate of all-cause revisions even in this patient group compared to conventional THA (Stoney et al., 2020).

The theoretical advantages of MoM HRA implants do not seem to affect PROM scores, and the risk of revision with MoM HRA appears to be higher in all patient groups. Also, as MoM bearing surfaces predispose the patient to the harmful effects of Co and Cr ions and ARMD, the usage of MoM HRA may not be justified in the future (Costa et al., 2018; Hersnaes et al., 2021).

2.7.2 Future aspects of other resurfacings

ReCerf® hip resurfacing (MatOrtho Ltd., UK) is a relatively new HRA implant with a CoC bearing manufactured from BIOLOX® Delta Ceramic. Historically, CoC bearings in HRA implants were associated with inferior outcomes with older ceramic materials. Failures occurred due to ceramic fracture or loosening (Kmhr et al., 1981; Matharu et al., 2015a). BIOLOX® Delta ceramic is still clinically unproven in HRA implants. Longer follow-up results will clarify the future role of these devices (De Villiers et al., 2020).

Metal-on-HXLPE HRA is another fairly recent innovation with promising preliminary reports for patients who may benefit from HRA, but so far this can only be considered experimental surgery (Treacy et al., 2019).

Polyether-ether-ketone (PEEK) is a biocompatible polymer that has already been used in orthopedics. A potential bearing surface of PEEK on HXLPE might be an option in the future. In a mechanical in-vitro study, PEEK HRA implants had more beneficial strain distribution in the femur than harder materials. Still, there are concerns regarding the wear properties of PEEK, especially in large bearing surfaces. Further studies are required before PEEK articulating implants can be used in clinical practice (Fontalis et al., 2021; Merola & Affatato, 2019; Vogel et al., 2021).

3 Aims

The aim of this thesis was to examine WB metal ion changes and long-term outcomes of LD MoM hip arthroplasty patients. The specific aims of the studies were:

1. To evaluate how WB Co and Cr change in the mid-term follow-up of bilateral M2A-ReCap-Magnum THA patients, as their exposure to Co and Cr ions is double that of unilateral patients. The proportion of patients with WB metal ions above the SUL in repeated measurements was also determined.

2. To investigate whether there is any change in repeated WB Co and Cr measurements in the long-term follow-up of BHR HRA and BHR THA patients, and additionally to assess the clinical and imaging outcomes of these implants.

3. To determine the change of WB Co and Cr levels in Durom THA and MMC THA patients in repeated metal ion measurements, and to evaluate implant survival, clinical and radiological outcomes.

4. To assess metal ion changes in long-term follow-up of M2A-ReCap-Magnum THA patients and report clinical outcomes, survival, and radiological outcomes.

4 Patients and Methods

4.1 Patients

4.1.1 Study I

We identified 141 patients (282 THA) with bilateral ReCap-M2A-Magnum THA who had undergone surgery at Turku University hospital. Of these, 61 bilateral patients (122 hips) had had at least two WB Co and Cr ion measurements; 31 of them were females and 30 males. Mean age was 60 years (SD 9.7) at the first hip arthroplasty. The study period covering primary operations was from 2005 to 2012 and mean follow-up time 7 years. Mean time between the first and last metal ion measurement was 2 years.

4.1.2 Study II

For study II we identified a total of 233 patients (274 hips) with a BHR HRA implant. All operations were performed in the hospital district of Southwest Finland. Forty-one patients had bilateral BHR HRA. We further identified 38 patients who had a BHR-Synergy THA. There were no patients with bilateral BHR THA. BHR HRA operations were performed from 2003 to 2010 and BHR THA operations between 2007 and 2009. Median age of the patients was 53 years (interquartile range [IQR]=10); 89 (33%) of them were female. Patient and hip demographics are summarized in Table 4.

Median follow-up time for BHR HRA was 14 years (range 0.6–17) and for BHR THA 11 years (range: 4.7-13). Median time between the first and last metal ion measurement was 3 years. The number of deceased patients during follow-up was 23. In the cohort, 171 BHR HRA and 19 BHR THA patients had had two or more metal ion measurements, 192 had completed the OHS questionnaire postoperatively, and postoperative MARS-MRI images were available for 151.

Table 4. **Study II** Patient and hip characteristics in study II

OPERATIONS		**N=**	**312**	**PATIENTS**		**N=**	**271**
		N	**(%)**			**N**	**(%)**
AGE (YEARS)				**AGE (YEARS)**			
	18-49	96	(31)		18-49	83	(31)
	50-59	156	(50)		50-59	136	(50)
	60-	60	(19)		60-	52	(19)
SEX				**SEX**			
	Female	100	(32)		Female	89	(33)
	Male	212	(68)		Male	182	(67)
STEM				**BILATERAL**			
	BHR	274	(88)		No	230	(85)
	Synergy	38	(12)		Yes	41	(15)
BILATERAL (SIMULTANEOUS)				**OPERATION TYPE**			
	No	276	(88)		BHR HRA	233	(86)
	Yes	36	(12)		BHR THA	38	(14)
PRIOR OPERATION							
	No	289	(93)				
	Yes	23	(7)				
ANTEVERSION ANGLE							
	>0	274	(88)				
	≤0	26	(8)				
INCLINATION ANGLE							
	0-29	10	(3)				
	30-49	231	(74)				
	50-	62	(20)				

4.1.3 Study III

In study III we identified 227 patients (249 hips) with a Durom or MMC THA. All implantations were performed in the hospital district of Southwest Finland. Twenty-two of these patients (44 hips) had a bilateral THA (20 patients with Durom THA and two with MMC THA). Operations were performed between March 2005 and January 2011. Median age of the patients was 68 years (IQR=14) and 122 (49%) were women. The median follow-up time for Durom THA was 12 years and for MMC THA 9 years. Patient and hip characteristics are shown in Table 5.

A total of 83 Durom THA patients and 30 MMC THA patients had two or more metal ion measurements. Median time between the first and last metal ion measurement was 3 years. There were 167 patients who had postoperative OHS and 97 (109 hips) with postoperative MARS-MRI images of the hip.

Table 5. Study III. Patient and hip characteristics in study III.

OPERATIONS		**N=**	**249**	**PATIENTS**		**N=**	**227**
		N	**(%)**			**N**	**(%)**
AGE (YEARS)				**AGE (YEARS)**			
	18-59	60	(24)		18-59	51	(23)
	60-69	87	(35)		60-69	80	(35)
	70-	102	(41)		70-	96	(42)
SEX				**SEX**			
	Female	116	(47)		Female	108	(48)
	Male	133	(53)		Male	119	(52)
CUP				**BILATERAL**			
	Durom	200	(80)		No	205	(90)
	MMC	49	(20)		Yes	22	(10)
BILATERAL				**CUP**			
	No	205	(82)		Durom	180	(79)
	Yes	44	(18)		MMC	47	(21)
PRIOR OPERATION							
	No	235	(94)				
	Yes	14	(6)				
ANTEVERSION ANGLE							
	>0	236	(95)				
	≤0	13	(5)				
INCLINATION ANGLE							
	0-29	5	(2)				
	30-49	178	(71)				
	50-	66	(27)				

4.1.4 Study IV

In study IV we identified 1450 patients with a ReCap-M2a-Magnum THA (1624 hips, 174 bilateral) performed between August 2005 and April 2012. Median age of the patients was 65 years (IQR=12), 683 (47%) were male and 767 (53%) were female. Median follow-up was 10 years for unilateral implants and 11 years for bilateral implants. Patient and hip demographics are shown in Table 6.

A total of 991 patients had two or more metal ion measurements for metal ion change analysis; median time between the first and last measurement was 4 years. Postoperative OHS were available for 1252 hips in 1106 patients, and postoperative MARS-MRI images were found for 563 hips.

Table 6. Study IV. Patient and hip characteristics in study IV.

OPERATIONS		N=	1624	PATIENTS		N=	1450
AGE (YEARS)		**N**	**(%)**	**AGE (YEARS)**		**N**	**(%)**
	17-59	463	(29)		17-59	393	(27)
	60-69	655	(40)		60-69	593	(41)
	70-	506	(31)		70-	464	(32)
SEX				**SEX**			
	Female	852	(52)		Female	767	(53)
	Male	772	(48)		Male	683	(47)
BILATERAL				**BILATERAL**			
	No	1276	(79)		No	1276	(88)
	Yes	348	(21)		Yes	174	(12)
PRIOR OPERATION							
	No	1490	(92)				
	Yes	134	(8)				
ANTEVERSION ANGLE							
	>0	1580	(97)				
	≤0	41	(3)				
INCLINATION ANGLE							
	0-29	41	(3)				
	30-49	1253	(81)				
	50-	243	(16)				
HEAD DIAMETER							
	<46 mm	203	(12)				
	46-52 mm	1169	(72)				
	>52 mm	252	(16)				

4.2 Methods

When the problems with modern MoM articulations became evident in 2012, MoM hip arthroplasty implantations were discontinued in Finland. A systematic screening program for MoM hips was launched in 2012 at our institution to detect patients with ARMD. Before that, there were only hospital-specific follow-up schedules. The studied implants were not considered to be in a "run-in" phase when the first ion measurements were performed (Daniel et al., 2009; DeSouza et al., 2010). The screening program is based on the national follow-up protocol recommended by the Finnish Arthroplasty Society. The follow-up was planned to be continued until further notice based on e.g., new data available.

According to the screening program, all patients with MoM hip arthroplasty should undergo a clinical examination (orthopedic surgeon or physiotherapist) and/or symptom questionnaire, plain radiographs, and blood metal ion level measurements (Co and Cr levels) at least once. If these test results are considered normal, plain radiographs are repeated every fourth year and ion concentration measurements every second year.

Symptomatic patients and patients with metal ions above 5ppb undergo anteroposterior (AP) and shoot-through lateral radiographs of the hip every 2 years. In asymptomatic patients with low metal ion levels these radiographs are taken at a 4-year interval. Cr and Co ion measurements and OHS questionnaires are checked at a 1–2-year interval depending on the symptom state and previous metal ion levels.

If the patient had a symptomatic hip (poor or moderate postoperative OHS) or Cr and/or Co concentrations above 5ppb, they were scheduled for a MARS-MRI of the hip.

If the MARS-MRI is considered normal, these patients undergo clinical examination, a symptom questionnaire, and blood metal ion level measurements every year or every second year depending on the case. Plain radiographs are taken every second year. Repeated MARS-MRI is recommended if blood metal ion levels increase or there is progression of symptoms.

All participating patients had their blood samples taken from the antecubital vein using a 21-gauge BD Vacutainer® Eclipse™ blood collection needle (Becton, Dickinson and Company Franklin Lakes, NJ, USA). The first 10ml tube of blood was used for standard laboratory measurements such as C-reactive protein and erythrocyte sedimentation rate. 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 0.2ppb and for Co 0.2ppb. 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.

The median elapsed time from THA operation to the first metal ion measurement (initial measurement) was calculated. In staged bilateral patients the median time was calculated from the second hip replacement operation.

The median time from the first metal ion measurement (initial measurement) to the last (control measurement) was also assessed, with the time between measurements considered the measurement interval. If a patient had more than two consecutive measurements, the first and last were used for analysis.

We used SUL values of 4.6ppb for Cr and 4.0ppb for Co for unilateral patients and 7.4ppb and 5.0ppb, respectively, for bilateral patients, as suggested earlier by

Van der Straeten (Van der Straeten et al., 2013a). Patients with Co or Cr values above the SUL in both the initial and control measurement were counted. The proportion of patients with metal ion levels above the SUL at the initial and control measurement was compared using McNemar's test in Study IV.

4.2.1 Studies I, II, III, and IV

Studies I, II, III, and IV were retrospective cohort studies based on MoM hip screening data from Turku University Hospital and the Hospital District of Southwest Finland. Patients with a follow-up time of <6 months were not included in blood metal ion analyses. Cases where MoM implants were used as a revision implant after conventional THA or semi-endoprosthesis (SEP) failure were not included. However, if MoM implants were used to salvage a failed osteosynthesis, or if LD MoM THA was used to treat a fracture of the femoral neck, the patients were included. Revision operations and reasons for revision surgery were checked manually from patient records.

The follow-up data in study I was extracted from electronic patient records up to 2017. All operations were performed at Turku University Hospital. The data for studies II, III, and IV was extracted from the electronic data pool and electronic patient records of Turku University Hospital and the Hospital District of Southwest Finland. Follow-up data on revision surgery, radiological imaging, OHS, and metal ion measurements was collected up to the end of 2019.

4.2.2 Studies II, III, and IV

For studies II, III, and IV, all available postoperative MARS-MRI images were included. MARS-MRI images were evaluated by a musculoskeletal radiologist experienced in ARMD-associated pathologies. Fluid collections and soft tissue masses were graded with the Hart pseudotumor classification initially after imaging (Matthies et al., 2012). For these studies, all MARS-MRI reports were manually checked and pseudotumors were categorized accordingly. In cases of repeated MARS-MRI, the change between imaging sessions was reported and the highest pseudotumor grade was used in the study.

The cup anteversion and inclination were measured using a Carestream Vue PACS-software angle measurement tool from standard pelvic AP and lateral shoot-through radiographs. Because the measurement of the anteversion angle may be challenging from axial cross-table radiographs, we categorized the cups into "retroverted" and "not retroverted" subgroups for regression analysis (numbers and data distribution supported this). The measured cup anteversion was compared with the horizontal image plane. Cup inclination was measured from AP pelvis

radiographs by drawing a line tangential to the acetabular cup and another between the ischial tuberosities. The inclination angle subgroups were based on the long-held principle of a "safe zone" for acetabular implants (Lewinnek et al., 1978). An inclination of 30–49° was considered optimal (reference); angles below and above it were considered in separate subgroups.

The number of metal-related adverse events (pseudotumors, elevated metal ions above the SUL, or revision due to ARMD) were assessed. Identified postoperative OHS scores were analyzed in four outcome groups, a score below 26 being a poor outcome, 27–33 moderate, 34–41 good, and 41–48 excellent.

4.3 Statistics

4.3.1 Studies I, II, III, and IV

Individual differences in repeated WB metal ion measurements were modelled using a random coefficient model for the same patient. In the models, log-transformed metal ion levels were used because of the positively skewed dispersion of metal ion levels. Spaghetti plots were generated for naturally log-transformed ion levels to demonstrate the individual changes between initial and control measurements. Medians with range and geometric means were calculated at the initial and control measurements for better interpretability.

4.3.2 Studies II, III, and IV

The Kaplan-Meier estimator was used to analyze the survivorship function for overall survival (revision surgery for any reason as the endpoint), and separately for metal-related adverse events (pseudotumors, elevated metal ions above the SUL, or revision because of ARMD) as the endpoint with 95% confidence intervals (CI).

In studies II and III, the Wilcoxon rank sum test was used to compare the OHS scores and ion levels of patients with, and patients without, a radiologically diagnosed pseudotumor.

Hazard ratios (HR) with 95% CI for metal-related adverse events (pseudotumor, elevated metal ions above the SUL, or revision due to ARMD) were assessed using multivariable Cox proportional hazards regression analysis, adjusting for the potential contributory factors age, sex, bilateral surgery, inclination angle, anteversion angle, and femoral head size. The proportional hazards assumption for Cox analysis was evaluated with a statistical test based on scaled Schoenfeld residuals.

4.3.3 Studies III and IV

Both Kaplan-Meier analyses included all operated joints separately, i.e., all unilateral operations and both joints from bilateral patients. In survival analyses focusing on metal-related adverse events, the hips that were revised for reasons other than ARMD, either before or after the screening program was introduced, were censored at the time of revision. Furthermore, ion measurements performed after the revision were excluded from the analysis except for hips that had the same bearing surface even after revision. For these hips also the post-revision ion measurements were considered in the metal ion level analyses.

All models were stratified by MoM device. Additionally, multivariable analysis was done for variables with potential confounding bias by choosing the adjusting variables based on a directed acyclic graph (DAG) analysis. According to the DAG, the estimates for bilateral surgery were adjusted for age and the estimates for femoral head diameter were adjusted for sex. The PH assumption for all Cox models was assessed with a statistical test based on scaled Schoenfeld residuals (Grambsch and Therneau 1994). To fulfill the PH assumption for metal-related adverse events analysis, cup inclination angle outliers (<30° or ≥50°) were combined into a single outlier group.

In studies III and IV we constructed a directed acyclic graph (DAG) under the following assumptions (Figure 15):

1) Revision surgery or metal-related adverse events are dependent on age, sex, bilateral surgery, inclination angle, anteversion angle, and head diameter.

2) Bilateral surgery is dependent on age because both hips are seldom operated in the elderly.

3) Head diameter is dependent on sex because head diameter is on average smaller in women.

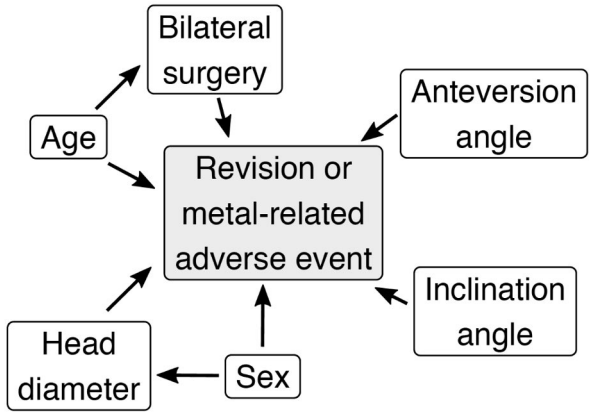

Figure 15. DAG demonstrating the direct causal effects of hip characteristics in studies III and IV.

In all analyses, p-values <0.05 in a 2-tailed test were considered statistically significant. All statistical analyses were carried out using the R statistical computing environment version 3.5.3. R packages survival (version 3.2-10) and ggplot2 (version 3.3.3) were used for survival analysis and visualizations, respectively.

4.4 Ethics

The study protocol was based on the national recommendation for systematic screening of MoM hip arthroplasty patients issued by the Finnish Arthroplasty Society (2014). The studies were retrospective and patients were not contacted. Therefore, approval by the local ethical committee was not needed.

5 Results

5.1 Changes in whole blood cobalt and chromium (Studies I, II, III, and IV)

In study I, the geometric mean of Co and Cr values decreased from 2.8ppb (range 0.6–25) to 2.2ppb (range 0.5–21) and from 2.8ppb (range 0.8-14) to 2.3ppb (range 0.5–18), respectively. Individual metal ion changes are shown in Figure 16.

Co values were below the SUL in 49 of the 61 patients (80%) at both metal ion assessments. Four patients (7%) had a Co value below the SUL at the first measurement and above the SUL at follow-up. Similarly, four (7%) patients had a Co value above the SUL at the first measurement and below the SUL at follow-up. Only four patients (7%) had Co ion values above the SUL at both assessments.

Cr values were below the SUL in 57 of the 61 (93%) patients at both assessments. Only two patients had a Cr value above the SUL on both occasions. One patient had a Cr value below the SUL at the first measurement and above the SUL at follow-up. Similarly, one patient had a Cr value above the SUL at the first assessment but below the SUL at follow-up.

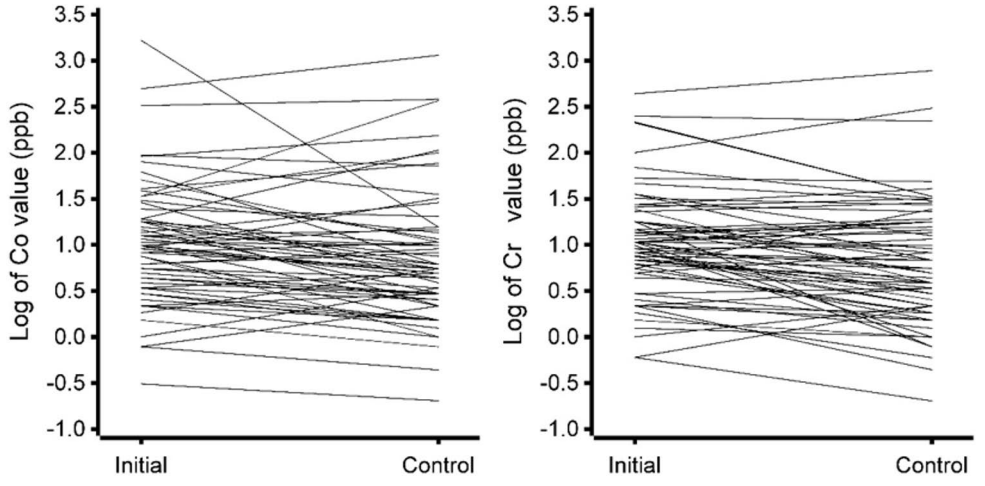

Figure 16, Study I. Spaghetti plots for patient-specific WB Co and WB Cr values at initial and follow-up measurements in bilateral ReCap-M2A-Magnum THA patients.

In study II, the geometric mean of Co dropped from 2.1ppb (range 0.2–122) to 1.6ppb (range 0.1–100, p<0.001) and similarly that of Cr from 2.4ppb (range 0.7–56) to 1.5ppb (range 0.2–63, p<0.001) during a measurement interval of 3.0 years in the BHR HRA group. Metal ion levels in the BHR THA group did not show a notable increase. Spaghetti plots for individual metal ion changes are shown in Figure 17.

Co values were above the SUL in 55 patients (25%) at the initial measurement and above the SUL in 41 patients (22%) at the control. Similarly, Cr values were above the SUL in 32 patients (14%) at the initial measurement and above the SUL in 21 patients (11%) at the control. Overall, 26 patients (12%) had ion levels above 10ppb during follow-up and 12 (6%) of them eventually had a revision (10 patients (5%) had a revision due to ARMD).

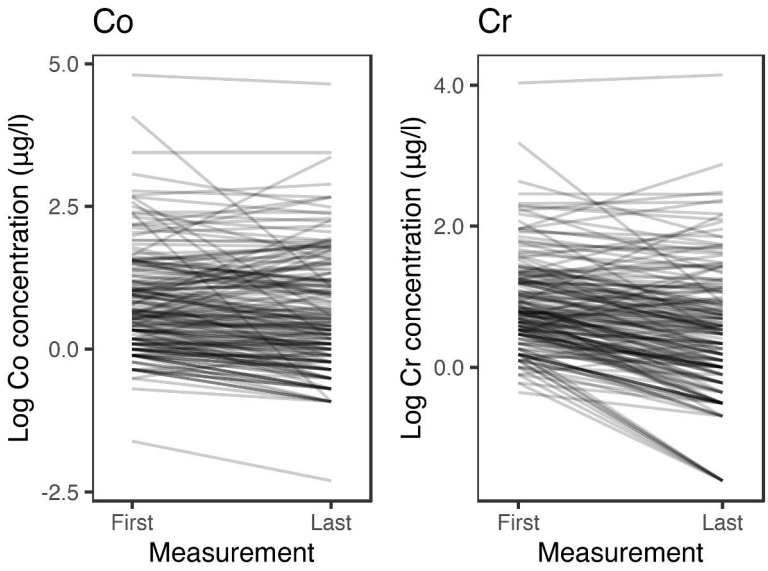

Figure 17. Study II: Change in individual Co and Cr values in BHR HRA and BHR THA patients.

In study III, the geometric mean of WB Cr (p<0.001) in Durom THA patients dropped from 2.2ppb (range 0.7–15) to 1.5ppb (range 0.2–17) and in MMC THA patients from 1.8ppb (range 0.9–24) to 1.1ppb (range 0.2–33, p=0.01). The geometric mean of WB Co remained unchanged in Durom THA patients, with 4.6ppb (range 0.5–32) at initial measurement and 4.9ppb (range 0.4–24, p=0.21) at the control. In MMC THA patients the geometric mean of Co was 2.2ppb (range 0.6–57) at initial measurement and 2.3ppb (range 0.4–88, p=0.56) at the control. The violin and spaghetti plots are shown in Figure 18.

Overall, 59 patients (53%) had a Co value above the SUL and 12 patients (11%) had a Cr value above the SUL at the first measurement. When the last metal ion

measurement was assessed, 65 patients (58%) had a Co value above the SUL and 10 patients (9%) had a Cr value above the SUL.

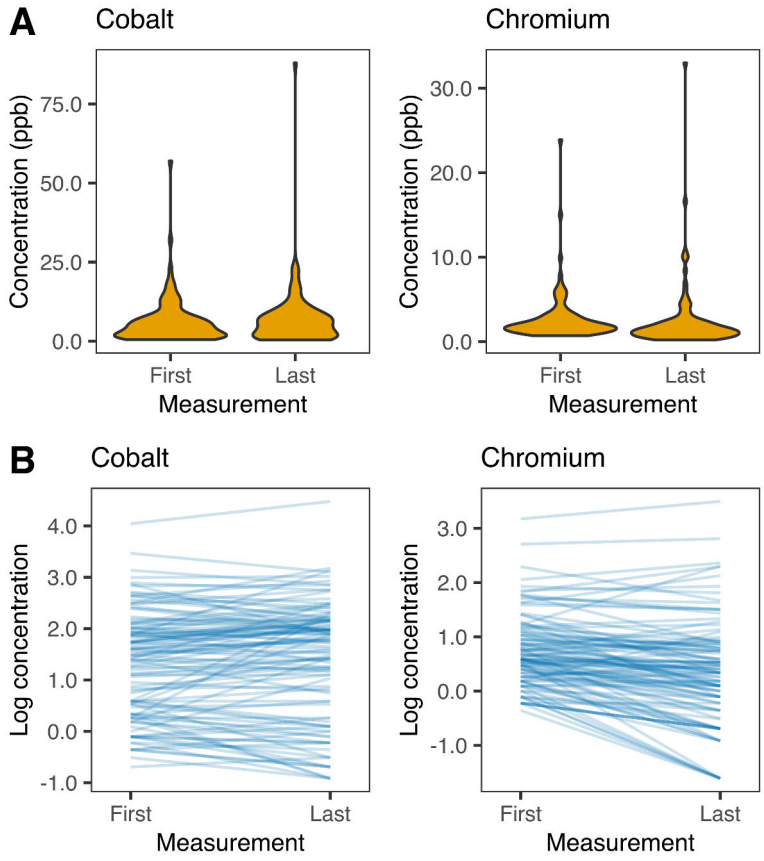

Figure 18. Study III: A: Violin plot figures for initial and control metal ion levels in Durom and MMC THA patients. **B:** Spagetti plots for individual cobalt and chromium values at initial and control measurements in Durom and MMC THA patients.

In study IV, the geometric mean of Cr decreased both in unilateral and bilateral patients from 1.8ppb (range 0.2–26) to 1.0ppb (range 0.1–43, $p<0.001$) and from 2.9ppb (range 0.7–45) to 1.7ppb (range 0.2–29, $p<0.001$), respectively. Co levels decreased both in unilateral and bilateral patients from 1.7 (range 0.2–89) to 1.4ppb (range 0.1–144, $p<0.001$) and from 3.1ppb (range 0.6–74) to 2.4ppb (range 0.5–70, $p<0.001$) respectively. Spaghetti plots for individual Cr and Co ion changes are shown in Figure 19.

In the whole cohort, 74 (7%) patients had Cr levels above the SUL and 135 (14%) had Co levels above the SUL at initial ion measurement, compared with 72 (7%) and

135 (14%) at the control, respectively. The proportion of patients above the SUL did not change during follow-up. Among unilateral patients only 63 (7%) had a Cr value above the SUL at initial measurement compared with 62 (7%) at the control (p=1.0); 110 (13%) had a Co value above the SUL at initial measurement compared with 115 (13%) at the control (p=0.6). Among bilateral patients, 11 (8%) had Cr above the SUL at initial measurement compared with 10 (8%) at the control (p=1.0); 25 (19%) had Co above the SUL at initial measurement compared with 20 (15%) at the control (p=0.3).

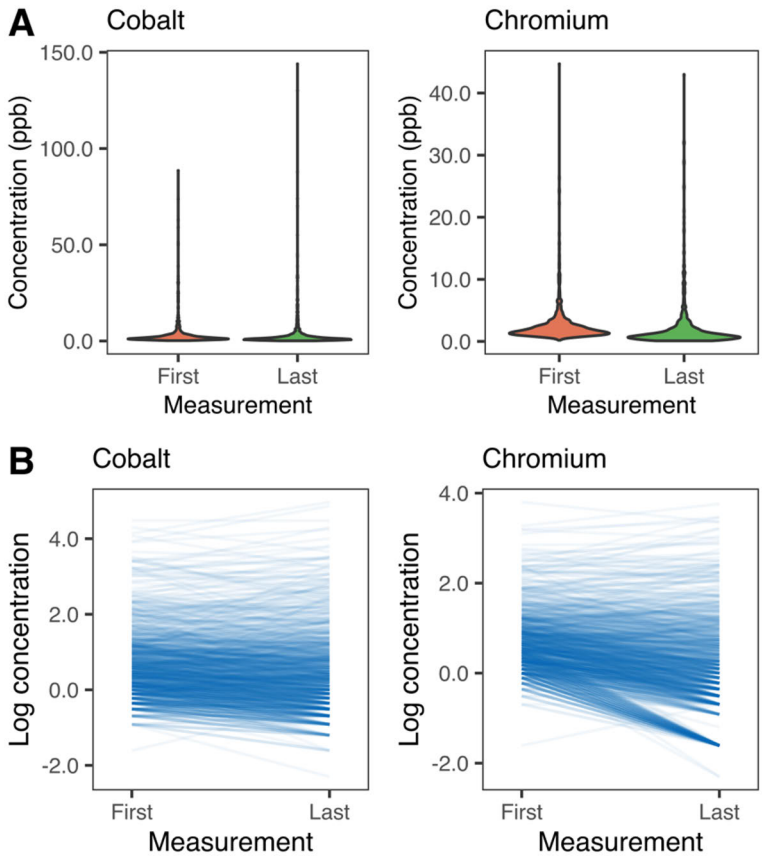

Figure 19. Study IV: A: Violin plots demonstrating the skewedness of metal ion values. **B:** Spaghetti plots for individual chromium and cobalt ion levels.

5.2 MARS-MRI results (Studies II, III, IV)

In study II, 151 patients had undergone postoperative MARS-MRI. We identified 62 hips (41%, 23% of all hips) with a radiologically diagnosed pseudotumor. Of these,

24 were Hart 1, 10 Hart 2A, 23 Hart 2B, and five Hart 3. If patients had undergone repeated MARS-MRI, we reported the imaging with the highest grade pseudotumor. Eighteen hips with a pseudotumor underwent more than one MARS-MRI. In eight hips the size and grading of the pseudotumor remained similar on repeated MARS-MRI; in one hip the pseudotumor was no longer visible, and in three hips the pseudotumors had shrunk. In five hips the pseudotumor had grown, and in one of these the grade of the pseudotumor was also higher. Additionally, 21 of 26 hips that had had normal initial MARS-MRI were still normal at follow-up while five showed the presence of a pseudotumor.

In study III we identified 97 patients (109 hips) with a postoperative MARS-MRI of the hip. A pseudotumor was found in 66 of these (61%, 30% of all hips), most of which (40) were Hart 2A or 2B pseudotumors. A Hart 3 pseudotumor was identified in eight hips and Hart 1 in 18. There were 29 hips with repeated MARS-MRI; most of them (29) had undergone two imaging sessions and two had undergone three. Ten patients had normal images at both the initial and repeated MARS-MRI. Five had a Hart 1 pseudotumor on the initial scan but no pseudotumor was visible at the repeat MARS-MRI. Three patients had a normal image initially but were diagnosed with a pseudotumor at the repeat MARS-MRI. Six pseudotumors had grown at the repeat MARS-MRI but the grade remained the same, and in one patient both the grade and size of the pseudotumor had increased. In contrast, in one patient the grade of the pseudotumor had decreased but the size had increased. Four patients had a similar pseudotumor on the repeat MARS-MRI, while one pseudotumor had shrunk.

In study IV, we evaluated 563 THAs with MARS-MRI. There was a pseudotumor in 338 hips (60%, 21% of all hips), and in 225 (40%) THAs the MARS-MRI was considered normal. A Hart 1 pseudotumor was diagnosed in 132 THAs, a Hart 2A pseudotumor in 71, and a Hart 2B pseudotumor in 107. A solid Hart 3 pseudotumor was identified in 28 hips.

In addition, we evaluated 161 hips with repeated MARS-MRI. In this cohort 39 patients had undergone three MARS-MRI sessions and six had undergone a total of four. Sixty-six patients had a normal initial MARS-MRI image, 46 of whom also had normal findings at the repeat scan. There was a new pseudotumor in 20 hips that had had a normal initial MARS-MRI. In 14 hips with an initially diagnosed pseudotumor, the repeat MARS-MRI was considered normal. Most of these (11) were Hart 1 pseudotumors, two were Hart 2A, and one was Hart 2B. In 47 hips with pseudotumors, the pseudotumors were evaluated to be similar in size and grade on the repeat scan. In 10 hips the pseudotumor was smaller but in 24 it had increased in size, and in four of those also the grade of the pseudotumor had increased.

5.3 OHS (Studies II, III, IV)

In study II, 175 of 192 patients (91%) had a good to excellent OHS postoperatively. In the BHR HRA group 161 patients of 175 reported a good to excellent outcome, while only six (4.9%) reported a poor outcome. In the BHR THA group 13 patients (77%) of 17 had an excellent outcome and three (20%) reported a bad outcome. Patients without a radiologically diagnosed pseudotumor (n=148) had a median OHS of 46 (IQR=7, range 2–48), while patients with a radiologically diagnosed pseudotumor (n=44) had a median OHS of 44 (IQR=9, range 3-48). The difference between the scores was statistically significant (p=0.03).

In study III, 199 patients completed the OHS questionnaire postoperatively. One-fourth of them reported a poor or moderate outcome (27 (14%) poor and 21 (11%) moderate) while the vast majority reported a good to excellent outcome (42 (21%) good, 109 (55%) excellent). Mean OHS was 39 (SD=10.4, median=43) and the score distribution was similar in both Durom and MMC patients.

In study IV, we reviewed postoperative OHS questionnaire data from 1252 hips. Median OHS was 43 (excellent outcome) and mean 40 (good outcome). Most (729, 58%) of the hips had an excellent functional outcome and 228 (18%) a good patient reported outcome. Further, 136 (11%) hips had a moderate functional outcome and 159 (13%) a poor functional outcome.

5.4 Survival (Studies II, III, IV)

5.4.1 Implant survival with revision for any reason as the endpoint

In study II, the overall implant survival was 83% at 16 years for BHR HRA and 87% at 12 years for BHR THA with revision for any reason as the endpoint (Figure 20). Forty hips out of 274 were revised in the BHR HRA group and five out of 38 in the BHR THA group. ARMD was the most common reason for revision in both these groups (10 (25%) and 3 hips (60%), respectively).

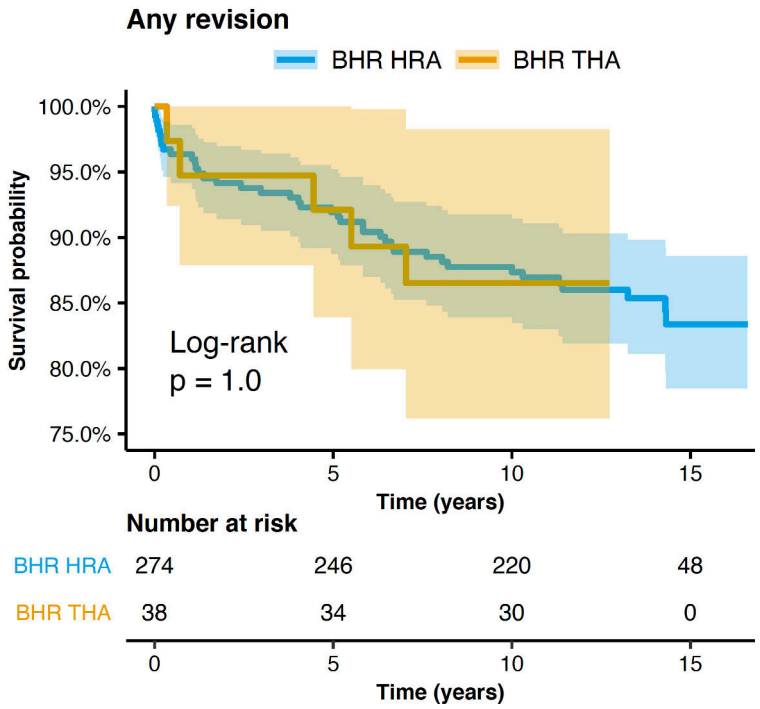

Figure 20. Study II. Kaplan-Meier estimator for both BHR HRA and BHR THA with revision surgery as the endpoint with 95% CI.

In study III, the overall 10-year survival of Durom THA was 82% with any reason for revision as the endpoint. The 10-year survival of MMC THA with any reason for revision as the endpoint was 89%. The survival of both Durom and MMC THA is shown in Figure 21. The total number of revised Durom THA was 44 (22%), and the most common reason for revision was ARMD (27 revisions). Five hips (9%) were revised in the MMC THA group and, again, ARMD was most often the reason for revision (3 revisions).

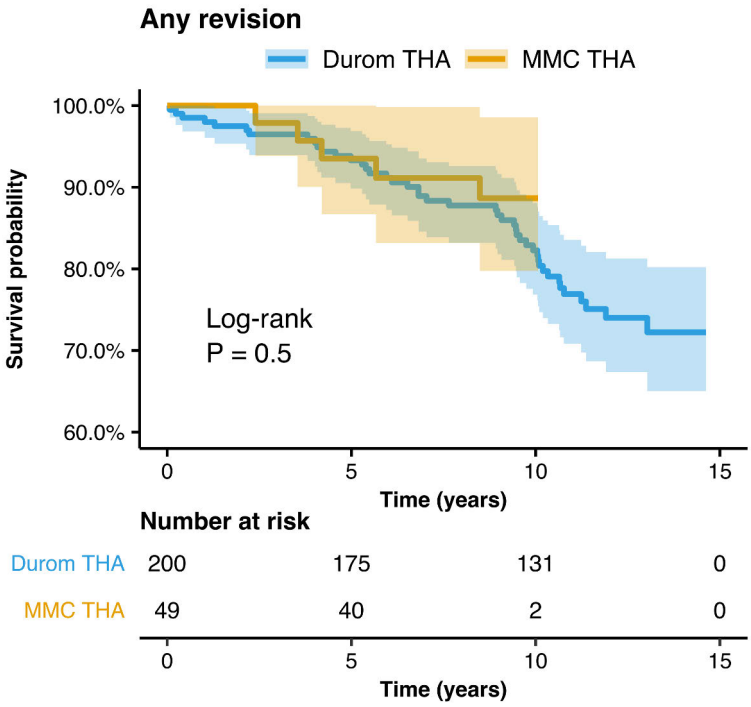

Figure 21. Study III. Kaplan-Meier survival curves for both Durom THA and MMC THA with revision for any reason as the endpoint with 95% CI.

In study IV, the 14-year implant survival for unilateral ReCap-M2a-Magnum THA implants was 85% (95% CI 0.83–0.88) and for bilateral implants 86% (95% CI 0.81–0.90). The overall implant survival is shown in Figure 22. The total number of revised hips during follow-up was 197 (12% of all hips), of which 121 were revised before two blood metal ion measurements. ARMD was most often the reason for revision; 80 unilateral and 20 bilateral implants were revised owing to ARMD.

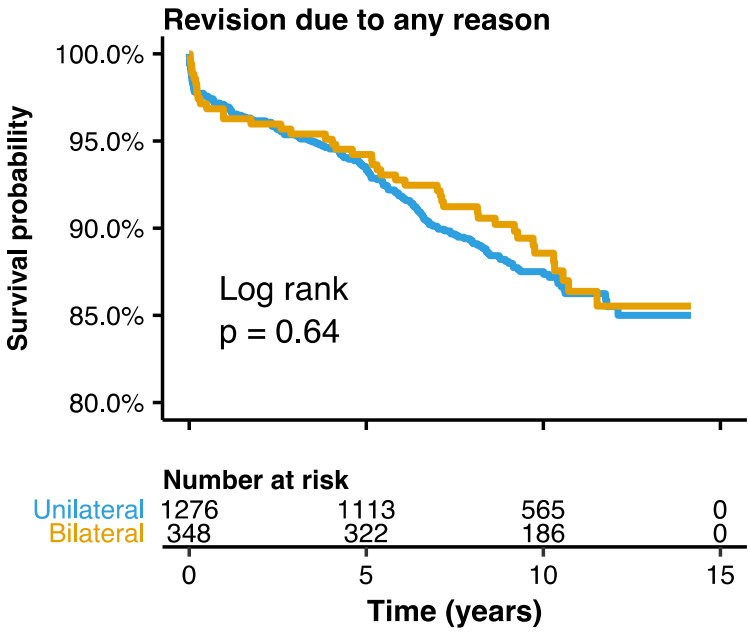

Figure 22. Study IV. Kaplan-Meier curves for unilateral and bilateral ReCap-M2a-Magnum implants.

5.4.2 Survival with any metal-related adverse event as the endpoint

In study II, the overall survival of hips in relation to metal-related adverse events was 63% at 16 years postoperatively. Separately, for BHR HRA it was 72% at 10 years and 66% at 16 years, and for BHR THA 55% at 10 years and 34% at 12 years (Figure 23). The total number of metal-related adverse events during our follow-up was 98.

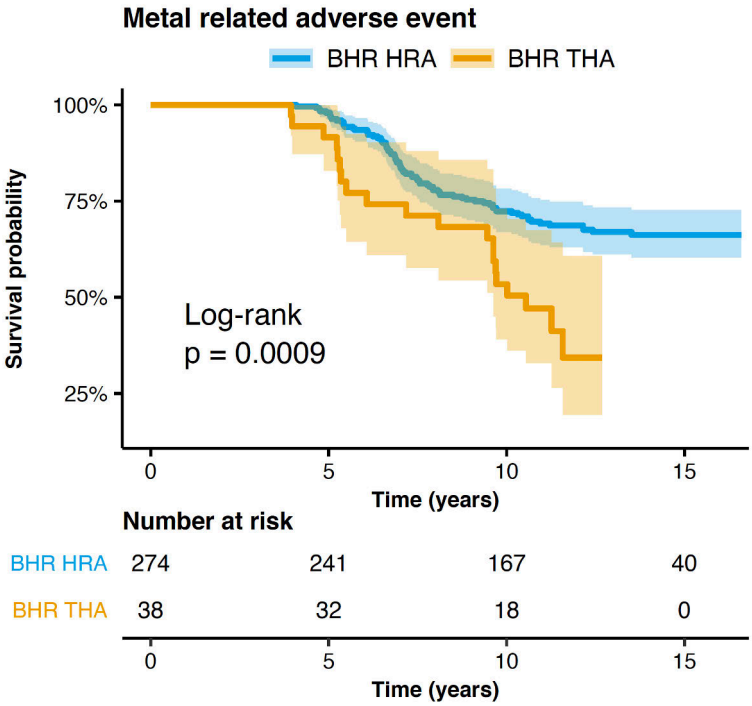

Figure 23. Study II. Kaplan-Meier estimator for BHR HRA and BHR THA with metal-related adverse events as the endpoint with 95% CI.

In study III, the 10-year hip survival with metal-related adverse event as the endpoint (with 95% CI) for Durom THA was 36% and the 14-year survival 18%. The 10-year hip survival for MMC THA was 58% (Figure 24). The total number of metal-related adverse events during follow-up was 151 (Durom=130, MMC=21) in 136 patients.

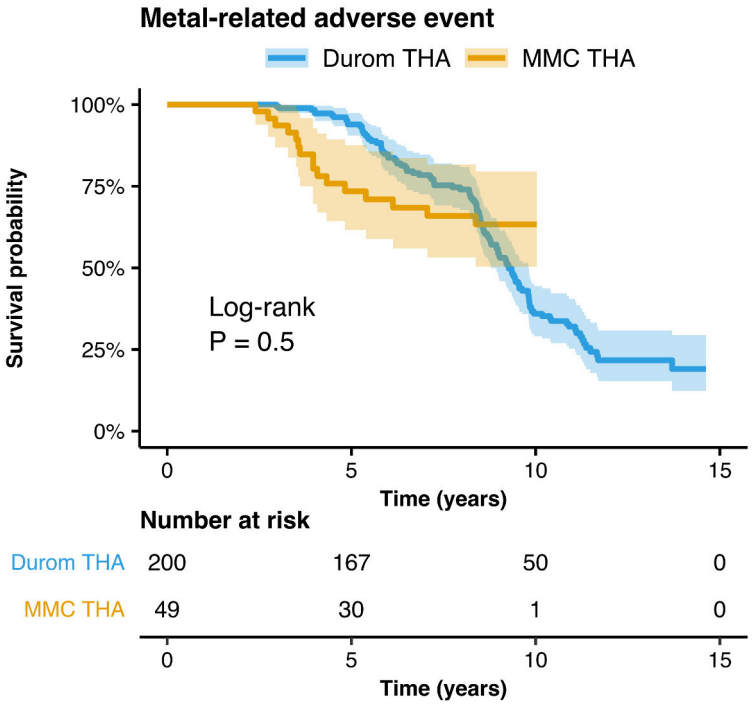

Figure 24. Study III. Kaplan-Meier survival analysis for Durom THA and MMC THA with metal-related adverse events as the endpoint with 95% CI.

In study IV, the 10-year hip survival in relation to metal-related adverse events (pseudotumor, metal ions above the SUL, or revision due to ARMD) was 71% and the 14-year survival 69% for unilateral implants. For bilateral implants the 10-year survival was 65% and the 14-year survival 60% (Figure 25). The total number of metal-related adverse events was 432 (314 unilateral and 118 bilateral hips).

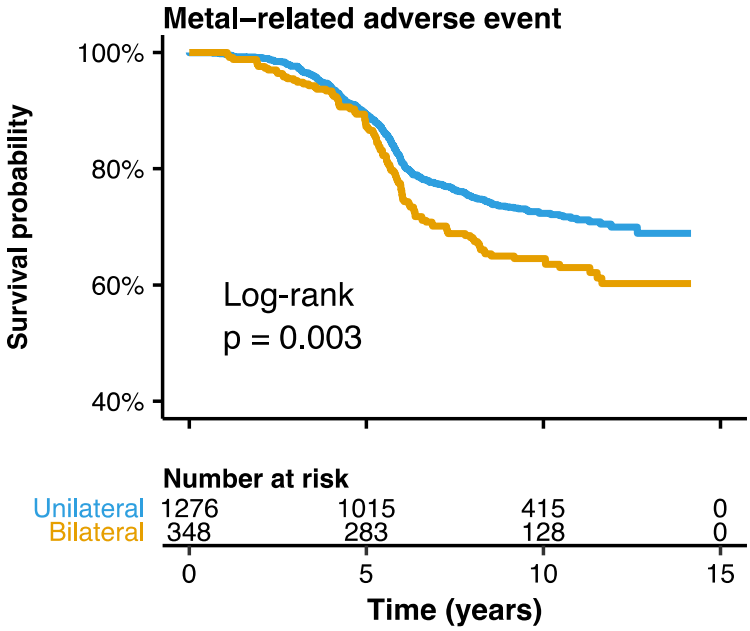

Figure 25. Study IV. Kaplan-Meier survival analysis for unilateral and bilateral implants with metal-related adverse events as the endpoint.

5.5 Risk factors (Studies II, III, IV)

In study II, female sex (HR=2.2) and cup retroversion (HR=4.0) were associated with a higher risk of revision. Additionally, cup retroversion was associated with increased risk of metal-related adverse events compared to cups that were in anteversion with a HR of 3.9, and the difference was statistically significant ($p<0.001$). These findings are presented in Tables 7 and 8.

Table 7. **Study II.** Cox regression analysis data with 95% CI for revision for any reason in BHR HRA and BHR THA patients.

		HAZARD RATIO	(95%CI)	P-VALUE
AGE (YEARS)				
	<50	Reference		-
	50-59	1.0	(0.5 - 1.8)	0.9
	≥60	0.4	(0.1 - 1.5)	0.2
SEX				
	Male	Reference		-
	Female	2.2	(1.1 - 4.3)	0.03
BILATERAL SURGERY				
	No	Reference		
	Yes	0.9	(0.3- 2.9)	0.9
INCLINATION ANGLE				
	<30	1.2	(0.3 - 5.7)	0.8
	30-49	Reference		
	≥50	1.8	(0.9 - 3.6)	0.1
ANTEVERSION ANGLE				
	≤0	4.0	(1.8 - 9.2)	0.001
	>0	Reference		

Table 8. **Study II.** Cox regression analysis data with 95% CI for Revision due to ARMD OR Pseudotumor OR Co>4.0 OR Co>4.6 at any point during follow-up in BHR HRA and BHR THA patients.

		HAZARD RATIO	(95% CI)	P-VALUE
AGE (YEARS)				
	<50	Reference		-
	50-59	1.4	(0.9 - 2.2)	0.2
	≥60	1.4	(0.8 - 2.6)	0.2
SEX				
	Male	Reference		-
	Female	1.5	(1,0 - 2.3)	0.07
BILATERAL SURGERY				
	No	Reference		
	Yes	1.2	(0.7 - 1.8)	0.5
INCLINATION ANGLE				
	<30	1.5	(0.5 - 5.1)	0.5
	30-49	Reference		
	≥50	1.0	(0.6 - 1.7)	0.9
ANTEVERSION ANGLE				
	≤0	4.0	(2.3 - 6.9)	<0.0001
	>0	Reference		

In study III, female sex was the only factor associated with increased risk of revision (HR=2.4, p=0.003), and with a higher risk of adverse metal-related events (HR=1.5, p=0.03). The Cox regression analysis data in Durom and MMC THA patients is shown in Tables 9 and 10.

Table 9. **Study III.** Cox regression analysis data with 95% CI for revision for any reason during follow-up of Durom and MMC THA patients.

		UNADJUSTED		
		Hazard ratio	**(95% CI)**	**p-value**
AGE (YEARS)				
	<60	Reference		
	60-69	1.1	(0.6-2.1)	0.8
	≥70	0.8	(0.4-1.7)	0.6
SEX				
	Male	Reference		-
	Female	2.4	(1.3-4.4)	0.003
BILATERAL SURGERY				
	No	Reference		
	Yes	1.0	(0.5-2.0)	0.9
INCLINATION ANGLE				
	<30	1.0	(0.1-7.5)	1.0
	30-49	Reference		
	≥50	0.9	(0.5-1.7)	0.8
ANTEVERSION ANGLE				
	≤0	1.4	(0.5-3.9)	0.5
	>0	Reference		
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	1.7	(0.6-4.8)	0.3
	<46mm	2.9	(0.9-8.8)	0.1
		ADJUSTED		
		Hazard ratio	**(95% CI)**	**p-value**
BILATERAL SURGERY				
	No	Reference		
	Yes	1.0	(0.5-2.0)	0.9
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	1.3	(0.4-3.8)	0.6
	<46mm	1.7	(0.5-5.5)	0.4

Table 10. Study III. Cox regression analysis data with 95% CI for revision due to ARMD, pseudotumor, Co>SUL or Cr>SUL at any point during follow-up of Durom and MMC THA patients.

		UNADJUSTED		
		Hazard ratio	**(95% CI)**	**p-value**
AGE (YEARS)				
	<60	Reference		-
	60-69	0.8	(0.5-1.2)	0.2
	≥70	0.9	(0.6-1.4)	0.7
SEX				
	Male	Reference		-
	Female	1.5	(1-2)	0.03
BILATERAL SURGERY				
	No	Reference		
	Yes	1.2	(0.8-1.8)	0.4
INCLINATION ANGLE				
	<30	1.5	(0.1-2.7)	0.6
	30-49	Reference		
	≥50	1.0	(0.7-1.4)	0.9
ANTEVERSION ANGLE				
	≤0	1.3	(0.7-2.6)	0.4
	>0	Reference		
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	1.2	(0.7-2)	0.5
	<46mm	1.6	(0.9-3)	0.1
		ADJUSTED		
		Hazard ratio	**(95% CI)**	**p-value**
BILATERAL SURGERY				
	No	Reference		
	Yes	1.1	(0.7-1.8)	0.6
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	1.1	(0.6-1.8)	0.8
	<46mm	1.3	(0.7-2.5)	0.5

In study IV, cup retroversion (HR=3.5, p<0.001), inclination angle above 50° (HR=2.2, p<0.001) and female sex (HR=1.9, p<0.001) were associated with a higher risk of revision in unilateral patients. Furthermore, retroversion of the cup (HR=2.3, p=0.006) was associated with a higher risk of metal-related adverse events. Femoral

head diameter of 46–52mm was associated with better implant survival than diameter >52mm (HR=0.5, p=0.004). Female sex (HR=1.8, p<0.001) was associated with a higher risk of metal-related adverse events in unilateral patients. The Cox regression data are shown in Tables 11 and 12.

Table 11. Study IV. Cox regression analysis results for revision for any reason in ReCap-M2A-Magnum THA patients.

UNILATERAL PATIENTS				
		Hazard ratio	**(95% CI)**	**p-value**
AGE (YEARS)				
	<60	Reference		-
	60-69	0.9	(0.6 - 1.3)	0.6
	≥70	1.0	(0.7 - 1.5)	0.9
SEX				
	Male	Reference		-
	Female	1.9	(1.4-2.7)	<0.001
INCLINATION ANGLE				
	<30	0.5	(0.1-2.1)	0.4
	30-49	Reference		
	≥50	2.2	(1.6-3.2)	<0.001
ANTEVERSION ANGLE				
	≤0	3.5	(1.9-6.6)	<0.001
	>0	Reference		
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	0.5	(0.3 - 0.8)	0.0
	<46mm	0.8	(0.4 - 1.4)	0.4
BILATERAL PATIENTS (BOTH HIPS)				
		Hazard ratio	**(95% CI)**	**p-value**
AGE (YEARS)				
	<60	Reference		-
	60-69	1.2	(0.6 - 2.3)	0.7
	≥70	1.3	(0.6 - 2.8)	0.5
SEX				
	Male	Reference		-
	Female	1.3	(0.7 - 2.3)	0.4
INCLINATION ANGLE				
	<30	3.6	(0.9 - 15)	0.1
	30-49	Reference		
	≥50	0.9	(0.4 - 2.2)	0.8
ANTEVERSION ANGLE				
	≤0	2.1	(0.5 - 8.7)	0.3
	>0	Reference		
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	1.0	(0.4 - 2.6)	1.0
	<46mm	2.3	(0.7 - 7.8)	0.2

Table 12. Study IV. Cox regression analysis results for metal-related adverse events in ReCap-M2A-Magnum THA patients.

UNILATERAL PATIENTS				
AGE (YEARS)		**Hazard ratio**	**(95% CI)**	**p-value**
	<60	Reference		-
	60-69	1.1	(0.8 - 1.4)	0.6
	≥70	0.9	(0.7 - 1.3)	0.7
SEX				
	Male	Reference		-
	Female	1.8	(1.4 - 2.3)	<0.001
INCLINATION ANGLE				
	<30	0.8	(0.4 - 1.7)	0.6
	30-49	Reference		
	≥50	1.2	(0.9 - 1.6)	0.2
ANTEVERSION ANGLE				
	≤0	2.3	(1.3 - 4)	0.0
	>0	Reference		
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	0.9	(0.6 - 1.3)	0.4
	<46mm	1.3	(0.8 - 2)	0.4
BILATERAL PATIENTS (BOTH HIPS)				
		Hazard ratio	**(95% CI)**	**p-value**
AGE (YEARS)				
	<60	Reference		-
	60-69	0.9	(0.6 - 1.4)	0.7
	≥70	0.8	(0.5 - 1.3)	0.4
SEX				
	Male	Reference		-
	Female	0.9	(0.6 - 1.3)	0.6
INCLINATION ANGLE				
	<30	2.1	(0.7 - 6.7)	0.2
	30-49	Reference		
	≥50	0.7	(0.4 - 1.3)	0.3
ANTEVERSION ANGLE				
	≤0	0.7	(0.2 - 2.7)	0.6
	>0	Reference		
HEAD DIAMETER				
	>52mm	Reference		
	46-52mm	0.7	(0.5 - 1.2)	0.2
	<46mm	0.5	(0.2 - 1.2)	0.1

6 Discussion

It is now more than a decade since the problems with modern LD MoM hip implants were recognized. The follow-up of MoM hip arthroplasties is currently changing from mid-term to long-term and most of the unrevised patients are doing well. On the other hand, the number of patients with a MoM hip who will eventually develop ARMD in the long-term is unclear (Lainiala et al., 2019, 2021; SCENIHR, 2014). The follow-up is important to detect the failing implants or imminent systemic metal toxicity early. These patients would benefit from updated, uniform, and more evidence based follow-up protocols worldwide to optimize the usage of limited health care resources in long-term follow-up.

While the survival of different MoM implants varies, it might be rational to have differing follow-up protocols for each brand. Due to trunnion corrosion the survival of MoM HRA is often better than MoM THA version on the same brand. It can be argued that HRA and THA implants should also have separate follow-up protocols from the cost-effective point of view.

Based on registry data the amount of ARMD revision is declining, and it will probably continue to decrease for the foreseeable future (AOANJRR, 2021; FAR, n.d.); NJR, 2021). Many of the future revisions in MoM hip implants will be related to normal wear and periprosthetic fractures. Identical follow-up protocols for both MoM HRA and MoM THA would probably be the most functional option for clinicians that perform the screening due to practical reasons.

6.1 Metal ion measurements

While metal ion measurements have a role in the screening of MoM THA patients (Finnish Arthroplasty Society, 2014; MHRA, 2017; TGA, 2012), there is no international consensus on what the most suitable measurement interval would be.

Current guidelines in Finland recommend repeated metal ion measurements every 2 years for all MoM hip devices. In contrast, the FDA does not recommend the routine usage of WB metal ion measurements at all in the screening of MoM patients (FDA, 2019). It has been suggested that WB Cr ion measurements could be omitted from the follow-up protocol of MoM hip arthroplasty patients, since Cr is

very rarely elevated without WB Co also being elevated, and Cr ion measurements rarely provide any additional value in clinical practice (Lainiala et al., 2021).

Based on our studies, if initial WB Cr or Co values are low, repeated metal ion measurement at a 4-year interval may not provide clinically useful information for patients with a well-functioning unilateral or bilateral M2A-ReCap-Magnum THA. Similarly, repeated metal ion measurements on patients with a well-functioning MoM BHR HRA, BHR THA, Durom THA, or MMC THA have not shown a notable increase during a measurement interval of 3 years.

Our results regarding decreasing ion level trends are in line with previous studies. Van der Straeten et al. studied WB Co and Cr changes in patients with well-functioning BHR implants. Overall Co and Cr levels dropped significantly in their cohort at 10 to 13 years in asymptomatic patients (Van der Straeten et al., 2013b). In some implants a longer "run-in" phase, or period of elevated metal ion release, has been observed. Sangaletti et al. found an increase of Co but not Cr ions 5 to 10 years after implantation in a cohort of 36mm Pinnacle-Ultamet MoM THA patients (Sangaletti et al., 2018). Bernstein et al. reported a "run-in" period that peaked 4 years after implantation but declined thereafter and stayed steady until 10 years from the operation. However, their implants were second generation Metasul implants and thus not directly comparable to our studies (Bernstein et al., 2012).

Matharu et al. considered that the current guidelines regarding the follow-up of MoM hip arthroplasty are not evidence based (Matharu et al., 2015b). The number of studies on long-term follow-up of MoM hip arthroplasty patients is limited, but the available literature and our results suggest that the appropriate follow-up interval should be longer than it currently is (Van der Weegen et al., 2022). Based on our results we suggest that the appropriate measurement interval would be 5 years for asymptomatic patients with the studied implants after 10 years from implantation.

6.2 MARS-MRI and OHS scores (Studies II, III, IV)

Of all MoM hip arthroplasty patients in our screening program, pseudotumor was diagnosed on MARS-MRI in 30% of Durom/MMC THA hips, 23% of BHR HRA or BHR THA hips, and 21% of ReCap-M2a-Magnum THA hips. However, MARS-MRI was performed only on patients with poor or moderate OHS, symptomatic hip, or elevated WB Co or Cr ion levels as suggested by our screening protocol.

MARS-MRI was most often performed on BHR HRA or BHR THA hips (55% of all hips). A total of 44% of Durom/MMC hips and only 35% of ReCap-M2a-Magnum THA hips were imaged with MARS-MRI. Ideally we would have had MARS-MRI images for all the patients. Because of the missing data, comparison with other studies is difficult.

Even though the amount of pseudotumors was relatively high in our study patients, most of the patients had mainly good to excellent functional outcomes, suggesting that a substantial proportion of the pseudotumors were asymptomatic. Up to 91% of BHR THA or BHR HRA patients, 78% of Durom/MMC THA patients, and 76% of ReCap-M2a-Magnum THA patients reported good to excellent outcomes.

The correlation between symptoms and pseudotumor incidence is not clear (Galea et al. 2019a). Kwon et al. found that asymptomatic MoM HRA patients with a pseudotumor may have lower OHS than patients without a pseudotumor (41 and 47 points, respectively) (Kwon et al., 2011). Kleeman et al reported a 53% incidence for pseudotumors, of which 40% were asymptomatic, but they had MRI images only as suggested by their screening protocol similarly to ours, so their incidence may be subject to bias. Their cohort included 92 patients with a Pinnacle MoM THA implant (Kleeman et al., 2018). In a study by Hart et al., 34 of the 58 (59%) patients had a pseudotumor visible on MARS-MRI and the prevalence of pseudotumors was not significantly different in the asymptomatic and symptomatic cohorts (Hart et al., 2012).

Sutphen and colleagues studied a cohort of Durom THA patients and reported a high prevalence of pseudotumors (82%) in symptomatic patients, and in asymptomatic patients as well (61%) (Sutphen et al., 2016). Fehring et al. reported an incidence of 31% for ARMD in asymptomatic MoM THA patients and 50% in symptomatic patients. Their cohort included 114 patients with mostly (97%) a Pinnacle (DePuy Orthopaedics, Warsaw, IN, USA) MoM THA implant (Fehring et al., 2014).

6.3 Implant survival (Studies II, III, IV)

The survival of BHR HRA was 88% at 10 years and 83% at 16 years. The 10-year survival of BHR THA was 88% in our hospital district, although the BHR THA cohort was small. This is in line with the Finnish Arthroplasty Register which reports a revision rate of 13% for BHR at 15 years (FAR, n.d.). The Australian registry reports a slightly better survival with BHR HRA, with a 7% revision rate at 10 years and 10% at 15 years (AOANJRR, 2021). The NJR reports a revision rate of 8% at 10 years and 11% at 15 years for BHR HRA (NJR, 2021).

The overall 10-year implant survival of Durom THA was 82% and of MMC THA 89% in our cohort. Seppänen et al. (2018) reported an overall 10-year survival of 81% for Durom/MMC THA based on FAR data (Seppänen et al., 2018). In the Australian population the 10-year revision rate for the Durom cup was 16% (AOANJRR, 2021). ARMD was the most common reason for revision in our cohort (13% of all patients, 59% of revisions), as expected based on previous registry data

(NJR, 2021). Inferior long-term survivorship of Durom/MMC THA owing to ARMD has been reported also in some clinical studies. Ridon et al. (2019) reported that ARMD was the reason for revision in 29% of Durom THA patients, with an overall 10-year survival of 67% (Ridon et al., 2019).

Our overall 10-year survival of ReCap-M2a-Magnum THA was 88%, which is also in line with previous literature. In our earlier report the 5-year survival of ReCap-M2a-Magnum THA was 93% for any reason for revision. 104 hips (8%) of 1329 hips were revised after a median follow-up of 5 years, and ARMD was reported as the reason for revision in 33 hips (32% of revisions) (Mäntymäki et al., 2017). In the present study 199 hips (12%) had been revised and ARMD was the reason for revision in 50% of these reoperations, at a median of 10 years from implantation. Lainiala and colleagues reported an almost similar 10-year survival of 89% for ReCap-M2a-Magnum THA in the Finnish population (Lainiala et al., 2019). Both the AOANJRR and FAR report a revision rate of 11% at 10 years and FAR has a 15-year revision rate of 14% for ReCap-M2a-Magnum THA (AOANJRR, 2021; FAR, n.d.).

As expected, ARMD was the most common reason for revision for all studied MoM implants in our hospital district. Still, we considered that the revision rate does not adequately represent the rate of functional failure in MoM THA or HRA implants. Therefore, we performed a separate survival analysis with metal-related adverse event as the endpoint (elevated metal ions above the SUL, revision due to ARMD, pseudotumor on MARS-MRI).

ReCap-M2a-Magnum THA and BHR HRA had slightly better survival than Durom/MMC THA and BHR THA implants. The amount of metal-related adverse events was rather high for all implants, but revision surgery was seldom required. Indications for revision surgery after MoM THA are severe symptoms caused by ARMD, large pseudotumors with tissue necrosis, and high levels of WB metal ions (Matharu et al., 2018a). In practice, many asymptomatic elderly patients with slightly elevated metal ions or small pseudotumors should not be revised. The revision decision is multifactorial, even though early revision may be associated with improved outcome (Van der Merwe, 2021).

6.4 Risk factors (Studies II, III, IV)

Based on the literature, male sex, younger age, and larger femoral head size decrease the risk of revision for MoM HRA implants (FDA, 2019; SCENIHR, 2014). On the other hand, MoM HRA devices are not recommended for patients with known moderate renal insufficiency, metal sensitivity, immunosuppression, corticosteroid treatment, or females of childbearing age (Finnish Arthroplasty Society, 2014; TGA, 2017; FDA, 2019).

6.4.1 Cup malposition

Cup positioning has been reported to be a risk factor for increased wear and metal bearing related complications. Excessive anteversion, insufficient anteversion, or increased cup inclination raise the risk of edge loading and impingement in MoM implants, which can lead to excess wear (Langton et al., 2011c; Matthies et al., 2011b).

In conventional THA, prosthesis dislocation is one of the most common reasons for revision (20% of all revisions) and the most common reason for revision during the first 5 years after implantation (AOANJRR, 2021). This is often caused by cup malposition. Lewinnek et al. described the optimal cup orientation for total hip arthroplasty in 1978. They found that cup anteversion of 15±10° and abduction of 40±10° would provide the lowest risk of THA dislocation, which was then referred to as the "Lewinnek Safe Zone" (Lewinnek et al., 1978). It has later been argued that this "safe zone" might not really exist, but surgeons should recognize the individual patient characteristics and functional position of the hip during postural changes to prevent impingement or dislocation rather than looking only at the cup position (Dorr & Callaghan, 2019).

LD MoM THA implants should theoretically tolerate a malposition of the acetabular component better than does conventional THA, since the jumping distance with LD femoral heads is greater (Sariali et al., 2009).

However, excess cup inclination (abduction) can cause impingement or edge loading which are associated with increased wear in LD MoM implants. A higher inclination angle seems to be associated with higher wear, regardless of femoral head size (Langton et al., 2011c; Leslie et al., 2009; Ollivere et al., 2009).

In study II, retroversion of the acetabular cup was associated with an increased risk of metal-related complications, although cup inclination did not have an effect. In study III, cup positioning had no effect on the risk of revision or metal-related adverse events.

In study IV, female sex, cup retroversion or cup abduction above 50° were associated with an increased risk of revision in unilateral but not in bilateral patients. Female sex and cup retroversion were associated with a higher risk of metal-related adverse events. The relationship between cup anteversion and excess wear is not as clear as with inclination and might be more implant specific (Haddad et al., 2011). Langton and colleagues noted that even slightly suboptimal cup anteversion (<10° and >20°) is associated with increased wear in LD BHR MoM acetabular implants, especially with smaller femoral heads (Langton et al., 2009). In a later study by Langton et al. they noted that increased wear in ASR implants is highly elevated in cups with excessively increased or decreased anteversion. In patients with a BHR cup, an anteversion angle above 30° was associated with increased wear, but not in patients with a femoral head diameter larger than 50mm (Langton et al., 2011c).

Laaksonen et al. found that this association between large head size or cup positioning and ARMD in ASR THA might not be as clear as previously thought (Laaksonen et al., 2017). Pseudotumors are commonly seen in well-positioned implants without any obvious problems that would predispose the hip to ARMD, which suggests that patient susceptibility has an important role (Donell et al., 2010; Matthies et al., 2012).

6.4.2 Femoral head size (Studies III and IV)

Smaller femoral head size is associated with a higher rate of wear in MoM HRA (Ollivere et al., 2009). According to AOANJRR, the rate of revision in HRA patients decreases with increasing femoral head size. Also, the risk of revision for smaller head sizes (below 50mm) is more than double that for larger head sizes (AOANJRR, 2021). In our cohort of BHR HRA patients, femoral head size was not associated with increased risk of revision or of metal-related adverse events.

In contrast to HRA implants, larger femoral head size may increase the risk of volumetric wear and of trunnionosis in MoM THA implants. In study III we did not find an association between femoral head size and risk of revision or metal-related adverse events. In study IV, head size >52mm was associated with a higher risk of metal-related adverse events.

Based on the literature, larger head size may be associated with a higher risk of failure in MoM THA implants in general (Cross et al., 2012; Jack et al., 2013; Smith et al., 2012). That said, some authors have not found this correlation (Bernstein et al., 2011; Cushnie et al., 2019). Larger femoral heads in THA increase the head-neck ratio, which theoretically increases the impingement-free ROM, but these advantages are mostly achieved already with 36mm or 40mm femoral heads. Kasparek et al. found that patients with a larger femoral head size had a higher Co/Cr ratio, meaning that larger head sizes tend to release more cobalt than chromium (Kasparek et al., 2018).

6.4.3 Bilateral surgery

Some case reports have described severe metal-related problems with bilateral HRA implants (Killampalli & Reading, 2009; Pandit et al., 2008b), but long-term reports have shown that the survival of bilateral HRA implants is comparable to unilateral implants in suitable patients (Daniel et al., 2014; Matharu et al., 2013). Both one-stage and two-stage HRA implantations can be performed for suitable patients (McBryde et al., 2007). Bilateral surgery was associated with an increased risk of metal-related adverse events in our data, but not with increased risk of revision.

The literature on bilateral MoM THA implants is limited. Madanat et al. studied a cohort of bilateral ASR THA patients and found that those with simultaneous implantations had a similar incidence of ARMD reactions in both hips, but patients with staged bilateral hip arthroplasty had a higher risk of developing a more severe pseudotumor in the later hip. Their cohort size, however, was small (Madanat et al., 2015). The follow-up of bilateral patients is also more challenging, because possibly elevated WB Co or Cr does not clarify which hip is failing. Patients with bilateral MoM HRA or THA implants often have higher levels of Co and Cr present than patients with a unilateral implant, which increases the risk of toxic metal ion levels (Van der Straeten et al., 2013a).

6.4.4 Age and gender

In study II, the risk of revision or metal-related adverse events was similar in males and females. In study III, female sex was associated with a higher risk of revision, and in study IV female sex was associated with a higher risk of metal-related adverse events. Based on registry data, female sex seems to be associated with a higher rate of wear, and female patients have a higher revision rate for both MoM HRA and MoM THA than men, even with the same femoral head size (Haughom et al., 2015; Smith et al., 2012).

According to the most recent AOANJRR report, the revision rate of HRA implants in females is more than double that in males (AOANJRR, 2021; Ollivere et al., 2009). The reason why females have worse survival is not clear.

As a consequence of sparing the native femoral neck, the mineral bone density of the proximal femur remains stronger, anatomical hip offset may be easier to achieve, and the risk of leg length discrepancy may be smaller in HRA implantations (Brown et al., 2013; Girard et al., 2006). On the other hand, preservation of the native femoral neck exposes the patient to the risk of femoral neck fracture due to the changed biomechanics in loading. Superior femoral cortex notching, varus malposition of the femoral component, or decreased femoral bone density also increase the risk of femoral neck fracture (Shimmin et al., 2005; Vail et al., 2008). Older age may increase the risk of periprosthetic femoral neck fracture further.

It has been suggested that women are at higher risk of a combination of poor prognostic factors, such as smaller femoral head size, increased risk of developmental dysplasia of the hip, or decreased bone mineral density, which would increase the risk of periprosthetic fracture (Clough & Clough, 2021). However, the results are slightly skewed by the lack of gender specific outcome reports (Haughom et al., 2015).

In our studies, age was not associated with increased risk of revision or metal-related adverse events. In HRA patients aged 65 years or more the risk of revision is higher than in younger patients during the first 6 months after implantation. Beyond this, the revision risk seems lower than in younger patients, in both sexes (AOANJRR, 2021). In a register study in which only male patients aged 65 years or younger were included, and BHR patients were compared to an age and sex matched cohort of conventional THA patients, the revision risk of BHR implants was higher at 17 years' follow-up (Stoney et al., 2020). Young age seems to increase the risk of pseudotumor related revisions in HRA patients (Matharu et al., 2016b). There is some evidence that older age is not associated with elevated metal ion levels in MoM THA patients, suggesting that age does not have a substantial effect on MoM THA implant wear (Kasparek et al., 2018; Vendittoli et al., 2010). Also, older age increases the risk of femoral neck fracture due to inferior bone quality with HRA implants, especially in females (Carrothers et al., 2011).

6.5 Strengths and limitations

We acknowledge that our studies had some limitations. Our study design was retrospective. The measurement interval in all our studies was relatively short. On the other hand, the total follow-up time was reasonably long. Another limitation of our study is that patients with intense hip symptoms or a pseudotumor on MRI may have been revised before any ion measurements, which may have caused some bias in our results. MARS-MRI was performed only on patients with poor or moderate OHS, symptomatic hip, or elevated WB Co or Cr ion levels as suggested by our screening protocol. We did not have preoperative OHS and not all patients completed the postoperative OHS questionnaire.

Since not all patients underwent metal ion measurements or MARS-MRI, the true amount of metal-related adverse events might be higher. It is possible that Cox proportional hazards regression analysis could provide slightly different hazard ratios without missing data.

The main aim of this thesis was to evaluate changes in blood metal ion concentrations over repeated measurements in MoM hip arthroplasty patients. The literature on long-term metal ion levels in MoM hip arthroplasty patients is scarce, and we were able to provide consistent evidence. Unfortunately, data on blood metal ion concentrations is not available in the national arthroplasty register. In practice, in Finland most revision operations are performed in the patient's own district area; thus we thought it unnecessary to try to link our data to that from the national register. We consider that this bias in our revision rates is minor. X-ray angle measurements followed standard procedure as described in the methods, but intra- or inter-class

variation was not separately assessed. However, we believe that this potential bias has only a minor effect on our results. We acknowledge that our results are implant specific and not generalizable to all MoM hip devices.

7 Conclusions

Based on our findings, the following conclusions can be drawn:

1. Our findings suggest that patients with a bilateral ReCap-M2A-Magnum THA do not benefit from routine metal ion measurements at 2 years' interval.

2. WB metal ion levels decrease during long-term follow-up in BHR patients. Patients with a well-functioning BHR hip do not seem to benefit from routine metal ion measurements at 2 years' interval. Patients were satisfied with the clinical results, even though the amount of metal-related adverse events was relatively high. Revision surgery was rarely required.

3. WB Cr decreased, and WB Co did not show any increase, in Durom and MMC MoM THA patients during a measurement interval of 3 years. The timespan of follow-up measurements could be longer than the median 3 years in the future. The amount of metal-related adverse events was high but revision surgery was seldom needed.

4. WB Co and Cr ion levels decreased during a median 10-year follow-up of ReCap-M2a-Magnum THA patients. The amount of metal-related adverse events was high, but patients reported good functional outcomes. The revision rate was relatively low. Based on our findings we suggest that the appropriate measurement interval for asymptomatic ReCap-M2a-Magnum THA patients should be longer, for example 5 years.

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Original Publications

Pietiläinen S, Mäntymäki H, Vahlberg T, Reito A, Eskelinen A, Lankinen P, Mäkelä K (2020)
Repeated cobalt and chromium ion measurements in patients with bilateral large-diameter head metal-on-metal ReCap-M2A-Magnum total hip replacement.
Acta Orthopaedica

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Repeated cobalt and chromium ion measurements in patients with bilateral large-diameter head metal-on-metal ReCap-M2A-Magnum total hip replacement

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Background and purpose — Whole-blood (WB) chromium (Cr) and cobalt (Co) measurements are vital in the follow-up of metal-on-metal total hip replacement (MoM THR) patients. We examined whether there is a substantial change in repeated WB, Co, and Cr levels in patients with bilateral ReCap-M2A-Magnum THR. We also specified the number of patients exceeding the safe upper limit (SUL) of WB Co and Cr in the repeated measurement.

Patients and methods — We identified 141 patients with bilateral ReCap-M2A-Magnum THR operated in our institution. 61 patients had repeated WB metal ion measurements with bilateral MoM implants still in situ in the second measurement. The mean time elapsing from the first measurement (initial measurement) to the second (control measurement) was 1.9 years (SD = 0.6, range 0.2–3.5). We used earlier established SUL levels for bilateral implants by Van Der Straeten et al. (2013).

Results — The median (range) Co and Cr values decreased in the repeated measurement from 2.7 (0.6–25) to 2.1 (0.5–21) and 2.6 (0.8–14) to 2.1 (0.5–18) respectively. In 13% of the patients Co levels exceeded the SUL in the initial measurement and the proportion remained constant, at 13%, in the repeated measurement. In 5% of the patients, Cr levels were above SUL in the initial measurement and an equal 5% in the control measurement.

Interpretation — Repeated WB metal ion levels did not increase in patients with bilateral ReCap-M2A-Magnum THR with a mean 1.9-year measurement interval. Long-term development of WB metal ion levels is still unclear in these patients.

More than 20,000 metal-on-metal (MoM) hip replacements were performed in Finland during 2000–2015 (Finnish Arthroplasty Register). Currently, there are still thousands of patients with a MoM THR in situ. Whole-blood (WB) metal ion measurements are an essential part of the follow-up of MoM patients, even though they do not solely identify failing implants alone (De Smet et al. 2008, Hart et al. 2014, Reito et al. 2016).

While there is no agreed universal WB metal ion level that indicates revision surgery or predicts the outcome, different health authorities have suggested diverse follow-up protocols for the monitoring of MoM patients (Hannemann et al. 2013, MHRA 2017, US Food and Drug Administration (FDA) 2019). Furthermore, some MoM implants have better survival rates than others, which makes risk evaluation even more difficult (Matharu et al. 2016, MHRA 2017, Kasparek et al. 2018, Donahue et al. 2019).

The evaluation of patients with bilateral MoM THR is even more challenging. Patients with bilateral MoM implants often present higher levels of Co and Cr than patients with a unilateral device (Van Der Straeten et al. 2013, Reito et al. 2014, 2016). Only a few studies have assessed blood metal ion levels in patients with bilateral MoM THR. Reito et al. (2016) evaluated ion level changes in bilateral ASR THR, and ASR (DePuy, Warsaw, IN, USA) hip resurfacing arthroplasty (HRA) patients. Both WB Co and Cr were substantially higher in the ASR THR cohort in the repeated measurement (Reito et al. 2016). However, metal ion levels were not able to distinguish failing MoM components from well-functioning hips in patients with bilateral ASR THR (Reito et al. 2016, Donahue et al. 2019).

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ReCap-M2A-Magnum was the most common MoM THR in Finland (Finnish Arthroplasty Register). We have previously reported that repeated metal ion measurements in unilateral ReCap-M2A-Magnum patients at a mean 2-year time interval did not show any increase (Mäntymäki et al. 2019).

We performed a retrospective comparative study to further investigate the role of repeated WB metal ion measurements in patients with bilateral M2A-ReCap-Magnum THR. Our main objectives were to investigate:

1. Is there a substantial change in the WB Co and Cr level during a follow-up period?
2. How large proportion of patients' measurements exceed the safe upper limits (SUL) of WB Co and Cr levels in the repeated measurement (thresholds WB Co 5.0 µg/L and Cr 7.4 µg/L) (Van Der Straeten et al. 2013).

Patients and methods

A screening program for MoM hips was launched at our institution to detect patients with adverse reactions to metal debris (ARMD). The screening was performed in consensus with the follow-up protocol recommended by the Finnish Arthroplasty Society (Finnish Arthroplasty Society 2015). The screening included anteroposterior and lateral radiographs of the hip, WB Cr and Co ion measurements, and Oxford Hip Score (OHS) questionnaire. Furthermore, if patients had poor or moderate OHS score, or elevated Cr or Co WB concentration (beyond 5 ppb), they were referred for MARS (magnetic artefact reduction sequence) MRI.

Patients with poor or moderate OHS or elevated WB ion measurements were also clinically evaluated by a senior orthopedic surgeon in an outpatient clinic. If patients had severe hip symptoms (pain, clicking, swelling) or if a pseudotumor was detected in MRI, revision surgery was considered. In addition to this, if an asymptomatic patient had WB metal ion levels above 10 ppb, revision surgery was considered to minimize the risk of Co poisoning. Patients who were not admitted for revision surgery were scheduled for annual or biannual visits in our outpatient clinic.

A ReCap-M2A-Magnum THR was used in 1,329 operations (1,188 patients) at our institution from 2005 to 2012. For this study we identified patients with bilateral ReCap-M2A-Magnum THR. Overall 141 patients (282 hips) had bilateral M2A-ReCap-Magnum THR. Of these 141 patients we identified 62 patients with at least 2 WB Co and Cr ion measurements. Of these, 3 patients had unilateral revision surgery during the follow-up period. 1 patient was revised due to aseptic loosening of the femoral component, and another for acute-onset infection. However, both patients still had both MoM bearing surfaces in situ after the revision surgery, and they remained in our study group. One patient was excluded because of unilateral revision surgery, where MoM bearing surfaces were converted to conventional ones. After this exclusion we had 61 bilateral (31 females) ReCap-M2A Magnum THR patients (122 hips) in our study group. The mean age of patients was 60 years (SD 9.7) at the time of the first hip arthroplasty. The mean femoral head size was 50 mm (SD = 3.4) and the mean acetabular inclination 44 degrees (SD = 6.3). The study period concerning primary operations was from 2005 to 2012. The follow-up data concerning ion measurements were collected from the patients until 2017.

All participating patients had their blood samples taken from the antecubital vein using a 21-gauge BD Vacutainer® Eclipse™ blood collection needle (Becton, Dickinson & 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 Vacuette® NH trace elements tube (Greiner Bio-One GmbH, Kremsmünster, Austria) containing sodium heparin. Cobalt and chromium analyses from whole blood were performed using an accredited method with inductively coupled plasma mass spectrometry (ICP-MS, VITA Laboratory, Helsinki, Finland in collaboration with 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 were 2.2% and 2.7% and inter-assay variation were 6.7% and 7.9%, respectively.

Statistics

61 patients with bilateral ReCap-M2a-Magnum THR met the criteria with at least 2 repeated metal ion measurements. The mean time elapsing from the first metal ion assessment (initial measurement) to the second (control measurement) was 1.9 years (SD 0.6, range 0.2–3.5). The time elapsing from the second hip replacement to the first (initial) metal ion measurement was considered as the follow-up time. Mean follow-up time from the second operation to the initial measurement was 4.7 years (1.9–9.0). Patients were divided into follow-up time interval groups according to the time elapsing from the second operation to the first metal ion assessment.

The individual change in 2 consecutive metal ion measurements from the same patient was modelled using a random coefficient model. Log-transformed ion values were used in conditional models due to positively skewed distribution of ion levels. Results are expressed as geometric means for better interpretability. SUL values for WB Co were 5.0 ppb and WB Cr 7.4 ppb as reported earlier (Van Der Straeten et al. 2013). P-values lower than 0.05 in a 2-tailed test were considered statistically significant.

The change over a 1.9-year measurement interval was calculated and plotted as frequency distributions for both metal ions separately.

Ethics, funding, and potential conflicts of interest

The study was based on the national recommendation for systematic screening of MoM THR patients given by the Finnish Arthroplasty Society (2015). It was a register study, and

Differences in WB Co and Cr levels (ppb)

	Initial	Control	p-value
WB Co, n = 61			
geometric mean	2.8	2.2	< 0.007
median (range)	2.7 (0.60–25)	2.1 (0.50–21)	
WB Cr, n = 61			
geometric mean	2.8	2.3	
median (range)	2.6 (0.80–14)	2.1 (0.50–18)	< 0.001

There was a statistically significant decrease in repeated WB Co and Cr ion values.

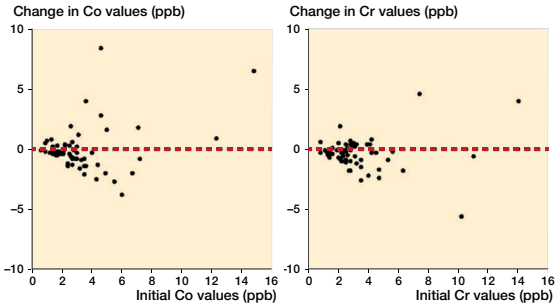

Figure 2. Changes in Cobalt (Co) and Chromium (Cr) ion levels compared to initial measurement

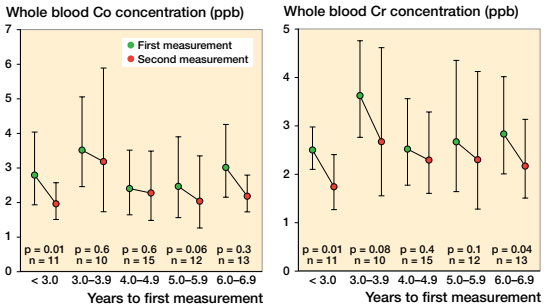

Figure 1. Geometric mean whole blood Co values (left) and Cr levels (right) divided across the follow-up time before initial measurement.

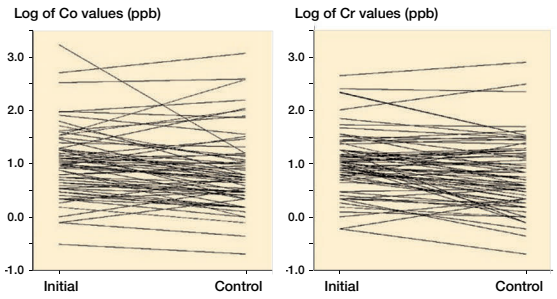

Figure 3. Spagetti plots for Co and Cr values at initial and control measurements. Values are naturally log-transformed.

the patients were not directly contacted. Therefore, approval by the local ethical committee was not needed. Data sharing is not possible. No benefits in any form have been received related directly or indirectly to this article. Outside this study, HM has received travel/accommodation expenses from DePuy Synthes. AE received research funding from Zimmer Biomet and DePuy Synthes and consultancy fees from Zimmer Biomet. AR reports personal fees from a paid lecture. SP, PL, KTM, and TV have nothing to disclose.

Results (Table)

The geometric mean of WB Cr level decreased in the < 3-year and ≥ 6-year follow-up groups. The geometric mean of WB Co level decreased in the < 3-year group (Figure 1).

Co values were below the SUL in 49 of the 61 patients in both metal ion measurements. 4 patients (6.6%) had their Co value below the SUL in the first measurement and above the SUL in repeated measurement. Similarly, 4 patients had their Co value above the SUL in the first measurement and below the SUL in the repeated measurement. Only 4 patients had Co ion values above SUL in both measurements.

Cr values were below the SUL in 57 of the 61 patients in both metal ion measurements. Only 2 patients had their Cr value above the SUL in both measurements. 1 patient had his Cr value below the SUL in the first measurement and above the SUL in the repeated measurement. In a similar manner, 1 patient had his Cr value above the SUL in the first measurement, but below the SUL in the repeated measurement.

The Co and Cr levels decreased over time and stayed mostly below the SUL if the initial value was low. The exceptions were those with high values already in the initial measurements (Figure 2). Spaghetti plots for individual Co and Cr values at initial and control measurements are presented in Figure 3. Values are naturally log-transformed.

Discussion

The motivation for performing this study was the lack of evidence of progress of metal ion levels in bilateral ReCap Magnum THR patients.

We found that median or geometric mean WB Co and Cr levels in repeated metal ion measurements in bilateral ReCap-M2A-Magnum patients at a mean 1.9-year time interval did not show notable increase. However, our results cannot be applied to other MoM THR brands.

Data concerning ion levels of patients with a ReCap Magnum THR are scarce. A strength of our study is that we

are able to present novel information, which can be used in modifying follow-up schedules worldwide. We are not aware of any other studies concerning ion levels of bilateral ReCap Magnum THRs.

A limitation of our study is that the follow-up time was short. Long-term WB ion levels in patients with bilateral ReCap-M2A-Magnum are not yet known. It is possible that a longer time range between the measurements such as 10 years might give different results. Also, the mean time interval between the WB ion measurements was only 1.9 years. Another limitation of our study is that patients with intense hip symptoms or a pseudotumor in the MRI may have been revised before any ion measurements. In addition, some of the patients who had substantially elevated WB Co or Cr levels after the initial measurement could have been admitted for revision surgery to decrease the risk of toxic effects of the metal ion levels.

The literature concerning patients with bilateral MoM hip arthroplasty is limited. Van Der Straeten et al. (2013) studied a group of 453 patients with unilateral, and 139 patients with bilateral MoM hip arthroplasty. They compared WB Co and Cr levels in patients with a well-functioning MoM hip with those who had a poorly functioning MoM hip. They suggested a SUL value of 4.6 µg/L for Cr, and 4.0 µg/L for Co in patients with unilateral MoM hip. Accordingly, they suggested SUL values of 7.4 µg/L for Cr and 5.0 µg/L for Co in bilateral patients. They stated that WB ion values above this predicted problems in metal-on-metal resurfacings. Donahue et al. (2019) proposed an even lower SUL of 4.0 µg/L for both Co and Cr for patients with bilateral ASR HRA (DePuy, Warsaw, IN, USA). The lower SUL was supposedly because ASR HRA has inferior survival to other HRA models. In their study, a SUL of 4.0 µg/L was able to successfully differentiate well-functioning implants from poorly functioning implants with a sensitivity of 42% and specificity of 90%. However, they were unable to present reliable general SUL for MoM THA due to the inadequate cohort size. In our study we used SUL values suggested by Van Der Straeten et al. (2013), because their study included also other brands in addition to ASR hip prosthesis.

The Finnish Arthroplasty Society recommends biannual metal ion measurements of MoM THA patients (Finnish Arthroplasty Society 2015). However, there are no clear guidelines on how to interpret ion concentrations and how high levels justify revision surgery. It seems that further research is needed to elucidate implant-specific WB metal ion level thresholds (Matharu et al. 2015).

Sidaginamale et al. (2013) found that metal ion concentrations are reliable indicators of abnormal wear processes in MoM implants and the Co concentration threshold of 4.5 µg/L provided good sensitivity and specificity.

Metal ion levels that should raise concern vary in different countries. In the UK, Canada and Europe values that cause alarm are between 2 ppb and 7 ppb (EFORT 2012, Health Canada 2012, MHRA 2017).

Reito et al. (2016) assessed a cohort of 76 patients with bilateral (ASR) hip resurfacings or with bilateral ASR XL THR with repeated WB ion measurements and with a median follow-up of 3.6 years. They reported no substantial difference in the HRA cohort (38 patients). However, patients with bilateral THR had a statistically significant increase in their WB Co and CR ion levels during this follow-up period (Co 8.3 µg/L vs. 12.6 µg/L, Cr 3.15 µg/L vs. 3.4 µg/L, both $p < 0.001$) between the 2 measurements. They therefore suggested that annual blood metal ion measurements on patients with bilateral high-risk MoM THR could be beneficial (Reito et al. 2016). We were not able to confirm this finding in patients with bilateral ReCap-M2A-Magnum THR. The poorer performance of the ASR device may explain the difference in WB ion level development compared with the ReCap Magnum THR (Seppanen et al. 2018). Matharu et al. (2017) recommended the use of different whole-blood (WB) metal ion thresholds for different implants in the follow-up MoM patients. Our current findings support this recommendation.

Mäntymäki et al. (2019) studied a group of 319 patients with unilateral ReCap-M2A-Magnum THR with repeated metal ion measurements. They had a mean follow-up time of 5.5 years (1.8–9.3) and the mean time between the measurements was 2 years. A statistically significant decrease in both Co and Cr values was detected. Both Co and Cr concentrations remained within ± 1 ppb of their initial value in the majority of patients (86% for Co, 81% for Cr). They concluded that repeated metal ion measurements may not be necessary for patients with unilateral M2A-ReCap-Magnum THR patients with WB metal ion levels below the SUL. It seems that the same may hold true even in patients with bilateral devices.

In summary, it is not necessary that patients with asymptomatic bilateral ReCap Magnum THR undergo metal ion level measurements at 2-year intervals. The optimal measurement interval is not yet known. Long-term metal ion level progression is not known either. Therefore, further research on the subject is needed.

AR and AE designed the protocol and methods. KTM performed the surgery and recorded the intraoperative data. AR and TV analyzed the data and did the statistics. SP, KTM, and TV collected the data. SP, HM, PL, KTM, and TV wrote the manuscript. All authors contributed to the revision of the manuscript.

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Abstract

Background and objective: Our aim was to assess long-term metal ion level changes and clinical outcome in patients with a Birmingham hip arthroplasty.

Methods: For the purpose of this study, we identified all BHR hip resurfacing arthroplasty (HRA) and total hip arthroplasty (THA) operations performed in Turku University Hospital. A random coefficient model was used to compare the change between the first and last metal ion measurement. A Kaplan–Meier estimator was used to assess the survivorship of the BHR HRA and BHR THA with metal related adverse events (pseudotumor, elevated metal ions above the safe upper limit, revision due to metallosis), or revision due to any reason as endpoints with 95% confidence intervals (CIs).

Results: BHR HRA was used in 274 hips (233 patients). In addition, we identified 38 BHR-Synergy THAs (38 patients). Operations were performed between 2003 and 2010. Median follow-up time was 14 years for BHR HRA (range: 0.6–17) and 11 years for BHR THA (range: 4.7–13). In the BHR HRA group, geometric means of Cr and Co levels decreased from 2.1 to 1.6 ppb and 2.4 to 1.5 ppb, respectively, during a 3.0-year measurement interval. Metal ion levels in the BHR THA group did not show notable increase. The survivorship of BHR HRA was 66% in 16 years and 34% for BHR THA at 12 years for any metal-related adverse event.

Conclusions: Patients with a Birmingham hip device do not seem to benefit from frequent repeated metal ion measurements. The amount of patients with metal-related adverse events was relatively high, but many of them did not require surgery.

Keywords

BHR, Birmingham hip resurfacing, arthroplasty, metal-on-metal, hip

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Introduction

The usage of metal-on-metal (MoM) hip implants has decreased substantially due to high revision rates. Nevertheless, approximately 1.5 million MoM hip implants have been implanted worldwide.[1] Despite of the high revision rates associated with metal bearing, majority of these implants are still *in situ*, and concerns remain regarding the adverse reaction to metal debris (ARMD) and blood metal ion levels in longterm.[2]

As for MoM total hip arthroplasties (THAs), implant survival of most MoM hip resurfacing

arthroplasty (HRA) brands have been poor compared to conventional bearing surfaces.[3] However, the Birmingham hip resurfacing (BHR HRA, Smith & Nephew, London, United Kingdom) device is still in scarce use especially in England and Australia[4,5] due to satisfying outcome compared to other HRA brands.[6,7] The 10-year overall survival rate for all HRA has been 86% while BHR HRA has 91% 10-year survival in Finland.[8]

Regulatory authorities worldwide have recommended regular follow-up for MoM hip arthroplasty patients to detect metal bearing–related complications. Screening tools to detect ARMD consist of blood metal ion level measurements, hip imaging, and patient-reported outcome measure questionnaires. Soft tissue imaging (ultrasound, computed tomography (CT), metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI)) have good sensitivity in detecting ARMD, but they are often too expensive and resource consuming to be used as a sole screening tool. Various safe upper limit (SUL) values for blood metal ion levels have been suggested to detect the failing MoM implants.[9–13] However, recently SUL thresholds have been suggested to be implant specific.[14,15]

Our primary aim was to investigate if there is substantial change in the whole blood (WB) metal ion levels in long term after BHR HRA or BHR THA. Furthermore, we assessed clinical and imaging outcome for these implants and risk factors for revision surgery to optimize the follow-up.

Methods

We performed a retrospective cohort study to assess long-term blood cobalt (Co) and chromium (Cr) levels and clinical outcome in BHR HRA and BHR THA patients operated at our institution. BHR HRA consists of a trimmed femoral head, capped with a large-diameter modular BHR head covering and a BHR monoblock acetabular cup. BHR THA consists of a large-diameter modular BHR head, a large-diameter BHR monoblock acetabular cup and a Synergy femoral stem.

A routine screening program for MoM hips was used at our institution to detect patients with ARMD. The screening was performed in consensus with the follow-up protocol recommended by the Finnish Arthroplasty Society.[12] The screening included anteroposterior and lateral radiographs of the hip, WB Cr, and Co measurements and the Oxford Hip Score (OHS).[16] Furthermore, if patients had poor or moderate OHS score (below 33 points), or elevated WB Cr or Co concentration (above 5 ppb), they were referred to MARS-MRI. Patients with poor or moderate OHS or elevated WB ion measurements were also clinically evaluated by a senior orthopedic surgeon at our outpatient clinic. If patients had severe hip symptoms (pain, clicking, and swelling) or if a pseudotumor was detected in MRI, revision surgery was considered. In addition, if an asymptomatic patient had WB metal ion levels above 10 ppb, revision surgery was considered to minimize the risk of Co poisoning. Patients who were not admitted to revision surgery were scheduled for annual or biannual visits in our outpatient clinic. Blood samples from all participating patients were collected and analyzed using the same methods that we have described earlier in our previous publications.[17,18]

All data were obtained from the Turku University Hospital data lake and electronic medical records.

In this study, SULs of 4.6 ppb for Cr and of 4.0 ppb for Co were used based on earlier study by Van Der Straeten.[13] The proportion of patients exceeding the SUL values of Cr and Co in the repeated measurements were reported.

Standard anteroposterior and shoot through lateral radiographs were used to assess anteversion and inclination angles of the cup. MARS-MRI images were evaluated by a musculoskeletal radiologist experienced in ARMD-related MRI diagnostics. Special attention was given to soft-tissue masses and periarticular fluid collections. Findings were graded using Hart pseudotumor classification.[19]

We used the OHS—questionnaire to measure the functional outcomes of patients with BHR HRA or BHR THA during the follow-up. OHS has a scale of 0–48, with 48 being the best patient-reported outcome. A score below 26 was considered as a bad outcome, 27–33 points was considered to as a moderate outcome, 34–41 was considered as a good outcome, and 42–48 was considered as an excellent outcome. In addition, revision operations and reasons for revision surgery were checked manually from the patient records.

Ethics

The study was based on the national recommendation for systematic screening of MoM hip arthroplasty patients given by the Finnish Arthroplasty Society (2014). It was a register study, and the patients were not directly contacted. Therefore, approval by the local ethical committee was not needed.

Statistics

The individual change between two consecutive metal ion measurements from the same patient was modeled using a random coefficient model. Log-transformed ion values were used in conditional models due to positively skewed distribution of ion levels. Results were reported as geometric means and medians with range at the initial and control measurements for better interpretation. Spaghetti plots for naturally log-transformed ion values were generated to visualize individual changes in ion levels. A Kaplan–Meier estimator was used to analyze the overall survivorship function, with revision surgery as the endpoint with 95% confidence interval (CI). A separate Kaplan–Meier analysis was performed to assess the survivorship of the BHR HRA and BHR THA patients with metal-related adverse events (pseudotumor, elevated metal ions above the SUL, or revision due to ARMD) as endpoints with 95% CI. Wilcoxon rank sum test was used to compare the OHS scores and ion levels of patients with a radiologically diagnosed pseudotumor and patients without a radiologically diagnosed pseudotumor.

Hazard ratios (HRs) with 95% CI for metal-related adverse events (pseudotumor, elevated metal ions above the SUL, or revision due to ARMD) were assessed using multivariable Cox regression analysis, adjusting for potential contributory factors age, sex, bilateral surgery, inclination angle, and anteversion angle. None of these variables were considered to be along causal pathway from exposure to outcome but were considered as confounders. The proportional hazards assumption for Cox analysis was evaluated with a statistical test based on scaled Schoenfeld residuals.[20]

P-values lower than 0.05 in a two-tailed test were considered statistically significant in all analyses. All statistical analyses were carried out using the R statistical computing environment version 3.5.3.[21]

R packages *survival* (version 3.2-10) and *ggplot2* (version 3.3.3) were used for survival analysis and visualizations, respectively.

Results

BHR was the most common HRA device at our institution with 233 patients (274 hips). Fourty one patients had bilateral operation. In addition, we identified 38 patients who had a BHR-Synergy THA. There were no patients with bilateral BHR THA. BHR HRA operations were performed from 2003 to 2010 and BHR THA operations between 2007 and 2009. Median age of the patients was 53 years (interquartile range (IQR) = 10 years, range: 18–76). Eighty nine (33%) were female. The follow-up data from the patients were collected until November 2019 or eventual death. The number of deceased patients during the follow-up was 23. Median follow-up time for BHR HRA and BHR THA was 14 years (range: 0.6–17) and 11 years (range: 4.7–13), respectively. Patient characteristics are presented in Table 1.

A total of 223 patients (193 BHR HRA and 30 BHR THA) with one or more metal ion measurements during the follow-up were identified. One hundred and seventy one BHR HRA and 19 BHR THA patients had two or more metal ion measurements (BHR HRA: median = 2 (range: 2–6), BHR THA: median = 3 (range: 2–5)). If a patient had more than two consecutive metal ion measurements, the first and the last of the measurements were used to assess change. The median time from the first metal ion measurement (initial measurement) to the last (control measurement) was 3.0 years (range: 0.8–6.8 years), and it was considered as the measurement interval. The mean time from the index operation to the initial metal ion measurement was 7.5 years (range: 3.9–14). For staged bilateral patients, this was calculated from the date when the second hip was operated. The follow-up data were collected until 28.10.2019. Twelve patients with BHR HRA did not have inclination or anteversion angle data. Furthermore, 151 hips had been imaged using MARS-MRI, and 192 patients (175 BHR HRA and 17 had BHR THA) had completed the OHS questionnaire postoperatively.

Table 1. Patient characteristics hipwise and patientwise.

Operations	N total = 312		Patients	N total = 271	
	N	(%)		N	(%)
Age			Age		
18–49	96	(31)	18–49	83	(31)
50–59	156	(50)	50–59	136	(50)
60+	60	(19)	60+	52	(19)
Sex			Sex		
Female	100	(32)	Female	89	(33)
Male	212	(68)	Male	182	(67)
Stem			Bilateral (all)		
BHR	274	(88)	No	230	(85)
Synergy	38	(12)	Yes	41	(15)
Bilateral (simultaneous)			Operation type		
No	276	(88)	BHR HRA	233	(86)
Yes	36	(12)	BHR THA	38	(14)
Prior operation					
No	289	(93)			
Yes	23	(7)			
Anteversion angle (°)					
>0	274	(88)			
≤0	26	(8)			
Inclination angle (°)					
0–29	10	(3)			
30–49	231	(74)			
50+	62	(20)			

BHR: Birmingham hip resurfacing; HRA: hip resurfacing arthroplasty; THA: total hip arthroplasty.

Geometric mean of Co decreased from 2.1 ppb (range: 0.2–122) to 1.6 ppb (range: 0.1–100, $p < 0.001$) and similarly the geometric mean of Cr decreased from 2.4 ppb (range: 0.7–56) to 1.5 ppb (range: 0.2–63, $p < 0.001$) during the 3.0 years measurement interval in the BHR HRA group. Metal ion levels in the BHR THA group did not show notable increase. Differences in metal ion levels and p values are demonstrated in Table 2.

In the whole cohort, Co values were above the SUL in 55 patients (25%) in the first measurement and above the SUL in 41 patients (22%) in the last measurement. In a similar manner, Cr values were above the SUL in 32 patients (14%) in the first measurement and above the SUL in 21 patients (11%) in the last measurement. Overall, 26 patients had ion levels above 10 ppb during follow-up and 12 of them eventually had a revision (10 patients had a revision due to ARMD). Change of individual Co and Cr values are presented in Fig. 1.

Out of the 151 hips with MARS-MRI imaging, we identified 62 hips (41%) with radiologically diagnosed pseudotumor. Of these, 24 were Hart 1, 10 Hart 2A, 23 Hart 2B, and 5 Hart 3. If patients had repeated MARS-MRI imaging, we

Table 2. Differences in Co and Cr ion levels (ppb).

	Initial	Control	P value
BHR HRA			
Co			
Median	1.8	1.4	
Geometric mean (range)	2.1 (0.2–120)	1.6 (0.1–100)	<0.001
Cr			
Median	2.2	1.4	
Geometric mean (range)	2.4 (0.7–56)	1.5 (0.2–63)	<0.001
BHR THA			
Co			
Median	3.6	4.9	
Geometric mean (range)	4.5 (0.9–59)	4.2 (0.4–31)	0.58
Cr			
Median	2.5	1.8	
Geometric mean (range)	2.7 (0.9–24)	2.0 (0.6–12)	0.05

BHR: Birmingham hip resurfacing; HRA: hip resurfacing arthroplasty; THA: total hip arthroplasty.

reported the one with the highest grade pseudotumor. Eighteen hips with a pseudotumor had more than one MARS-MRI done. In eight hips, the size and grading of the pseudotumor remained similar. In one hip, the pseudotumor was no longer visible in the repeated MARS-MRI. In three hips, pseudotumors had decreased in size in the repeated MARS-MRI. On the other hand, in five hips, the pseudotumor had increased in size in the repeated MRI, and in one of these hips, the grade of the pseudotumor was higher in the repeated MARS-MRI. In addition, 26 hips had repeated MARS-MRI with normal initial MARS-MRI images. New pseudotumor was detected in five hips, while the repeated MARS-MRI was normal in 21 hips. Patients with a radiologically diagnosed pseudotumor presented with significantly higher maximum Co ($p < 0.001$) and Cr values ($p < 0.001$) than patients without a pseudotumor. Patients without a radiologically diagnosed pseudotumor had a median Co of 1.8 ppb (IQR and median Cr of 2.2 ppb (IQR = 1.8)) while patients with a radiologically diagnosed pseudotumor had median Co of 5.8 ppb (IQR = 10.5) and median Cr of 4.2 ppb (IQR = 4.7).

Implant survival with revision for any reason as the endpoint

We had an overall implant survival of 83% in 16 years for BHR HRA and 87% for BHR THA at 12 years with revision for any reason as the endpoint. Fourty hips of 274 were revised in the BHR HRA group, and 5 of 38 hips were revised in the BHR THA group (Fig. 2). ARMD was the most common reasons for revision in both BHR HRA and BHR THA groups (10 (25%) and 3 hips (60%), respectively). Other reasons for revision in BHR HRA group were: periprosthetic fracture (7 hips), loosening of the cup (7 hips), loosening of the femoral component (5 hips), mechanical impingement (4 hips), infection (2 hips), implant mal-alignment (2 hips), pain (1 hip), grossly elevated metal ions (1 hip), and leg length discrepancy (1 hip). Other reasons for revision in BHR THA group were infection and pain (1 hip each).

Survival with any metal-related adverse event (pseudotumor in MARS MRI, elevated metal ions above the SUL, or revision due to ARMD) as the endpoint

The overall survival of the hips in terms of metal-related adverse events (pseudotumor, elevated metal ions above the SUL, or revision due to ARMD) was 63% at 16 years. For BHR HRA separately, it was 66% in 16 years and for BHR THA, it was 34% at 12 years from the operation (Fig. 3). The total number of metal-related adverse events during our follow-up was 98.

Overall, 175 out of 192 patients (91%) had good to excellent OHS scores postoperatively. In BHR HRA group, 161 patients out of 175 reported a good to excellent outcomes, while only 6 patients (4.9%) reported having a bad outcome. In BHR THA group, 13 patients (77%) out of 17 had an excellent outcome, and 3 patients (20%) reported a bad outcome. Patients without a radiologically diagnosed pseudotumor (n = 148) had a median OHS score of 46 (IQR = 7, range: 2–48), while patients with a radiologically diagnosed pseudotumor (n = 44) had a median OHS score of 44 (IQR = 9, range: 3–48). The difference between OHS scores was statistically significant ($p = 0.03$).

In Cox multivariable regression analysis, cup retroversion was associated with increased risk of adverse events when compared to cups that were in anteversion with an HR of 3.9, and the difference was statistically significant ($p < 0.0001$). Cox multivariable regression analysis data with 95% CI is presented in Table 3.

Discussion

The aim of this study was to assess long-term blood Co and Cr levels and clinical outcome for patients with BHR HRA or BHR THA. WB Co and Cr levels in BHR patients stayed mostly below the SUL. Furthermore, we noted a statistically significant decrease in both Co and Cr levels during median follow-up time of 14 years in BHR HRA group. Metal ion levels in BHR THA group did not show notable increase during a follow-up of 11 years. The amount of patients with metal-related adverse events was relatively high, but many of them did not require surgery.

Our results regarding decreasing ion level trends are in line with previous studies. Van der Straeten et al. studied WB Co and Cr change in patients with well-functioning BHR

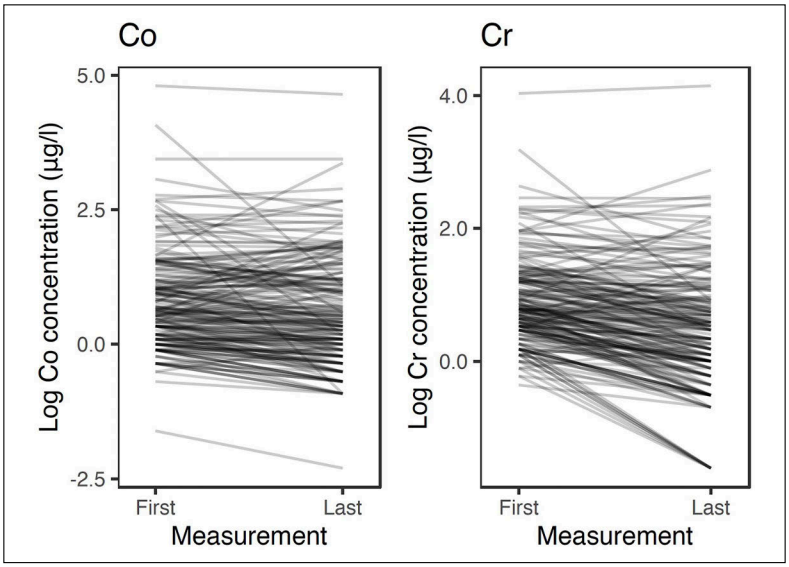

Fig. 1. Naturally log-transformed spaghetti plots for individual Co and Cr values for all patients.

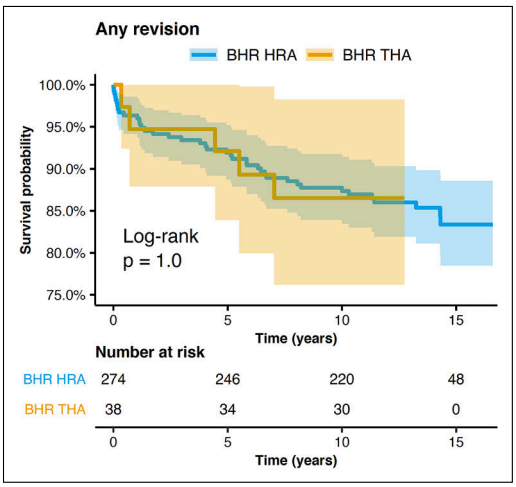

Fig. 2. A Kaplan–Meier estimator for both BHR HRA and BHR THA with revision surgery as the endpoint with 95% CI.

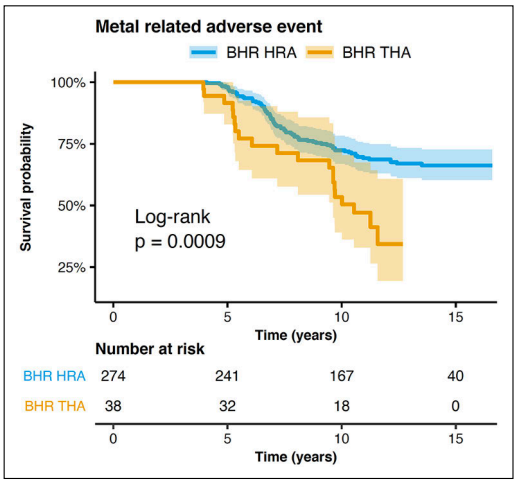

Fig. 3. A Kaplan–Meier estimator for both BHR HRA and BHR THA with metal-related adverse events as the endpoint with 95% CI.

implants. Overall, Co and Cr levels decreased significantly in their cohort at 10–13 years in asymptomatic patients.[22] Also, patients with unilateral or bilateral ReCap-M2A-Magnum MoM THA had decreasing ion levels in long-term follow-up. Authors discussed that these patients might not benefit from repeated metal ion measurements on as short as a 2-year interval.[17,18] Even when the high-risk articular surface replacement (ASR) implants were assessed, Reito et al. reported that patients with a unilateral ASR HRA might not benefit from repeated metal ion measurements on a 1-year interval. However, high-risk ASR XL THA patients did benefit from repeated metal ion measurements in order to detect patients with ARMD.[9] National guidelines recommend regular WB metal ion measurements in the follow-up of patients treated with MoM implants. However, performing regular

Table 3. Cox multivariate regression analysis data with 95% CI.

OUTCOME: Revision due to ARMD OR Pseudotumor OR Co > 4.0 OR Co > 4.6 at any point during follow-up			
	Hazard ratio	**(95% CI)**	**P value**
Age			
<50	Reference		
50–59	1.4	(0.9–2.2)	0.2
⩾60	1.4	(0.8–2.6)	0.2
Sex			
Male	Reference		
Female	1.5	(1.0–2.3)	0.07
Bilateral surgery			
No	Reference		
Yes	1.2	(0.7–1.8)	0.5
Inclination angle (°)			
<30	1.5	(0.5–5.1)	0.4
30-49	Reference		
⩾50	1.0	(0.6–1.7)	0.9
Anteversion angle			
⩽0	4.0	(2.3–6.9)	<0.0001
>0	Reference		
Table information			
Number of operations		300	
Number of patients		261	
Number of events		98	
Number of observations deleted due to missingness		12	
Number of BHR HRA		262	
Number of BHR THA		38	

ARMD: adverse reaction to metal debris; BHR: Birmingham hip resurfacing; HRA: hip resurfacing arthroplasty; THA: total hip arthroplasty.

metal ion measurements for all MoM hip patients is both expensive and resource consuming.[12,23] Based on our study and earlier literature, 2-year interval seems rather short for repeated ion measurements in patients with BHR HRA or BHR THA device. For long-term follow-up, for example, 5-year interval might be more appropriate.

MARS-MRI in our study was performed only to patients with poor or moderate OHS scores, symptomatic hip, or elevated WB Co or Cr ion levels. Thus, the reported high prevalence of pseudotumor in MARS-MRI does not represent the whole cohort of patients. Ideally, we would have had MARS-MRI images from all the patients with a BHR hip implant. As expected, levels of both Co and Cr were higher in patients with a radiologically diagnosed pseudotumor. Only 3 out of 17 pseudotumors increased in size in repeated MRI. Relatively high prevalence of pseudotumors in MARS-MRI of BHR patients have been reported previously, but the data concerning the subject is scarce.[19] Bisschop et al. reported a prevalence of 28% for pseudotumors in CT scans of BHR HRA patients, and majority of these (72.5%) were asymptomatic.[24]

Regarding to the OHS score, majority of the patients in our study reported good to excellent scores after the BHR implantation. Comparably, Matharu and colleagues reported a total of 1394 OHS questionnaires with excellent outcomes, pre-operative OHS score improving from pre-operative 19–46 at the latest visit.[25] In our study, patients with a radiologically diagnosed pseudotumor reported inferior OHS scores when compared to patients without a radiologically diagnosed pseudotumor, although the difference was not necessarily clinically significant. Unfortunately, our patients do not have pre-operative OHS values. Kwon et al. found out that asymptomatic MoM HRA patients with a pseudotumor may have even lower OHS scores than patients without a pseudotumor (41 and 47 points, respectively).[26] However, this correlation between symptoms and pseudotumor incidence is not clear.[27]

The survival of BHR HRA was 83% at 16 years and that of BHR THA 87% at 12 years in our material. This is in line with Finnish Arthroplasty Register which reports a revision rate of 13% for BHR at 15 years.[7] The Australian registry reports a slightly better survival with BHR HRA with 7% revision rate at 10 years and 10% at 15 years.[28] In a similar manner, NJR reports a revision rate of 8% at 10 years and 11% at 15 years for BHR HRA.[6]

In the short- to mid-term follow-up, BHR HRA and BHR THA seemed to have equally good survival rates with 95% and 97% at 6 years, respectively.[29] However, in the long-term follow-up BHR THAs revision rates increase to 18% at 10 years, which is higher than for majority of the other MoM THA or HRA brands.[7,28] We did not notice this increased revision rate compared to BHR HRA in this study. The amount of BHR THA was rather small, though. Due to the previously reported high risk of ARMD and revision surgery, the implantation of BHR THA is no longer recommended.[30]

Sole revision rate might not tell the whole truth about adverse events or functional failure. Therefore, we assessed separately survival with any metal-related adverse event (pseudotumor in MARS-MRI, elevated metal ions above the SUL, or revision due to ARMD) as the endpoint. It seems that we had considerable amount of metal-related adverse events, although most of them did not require revision surgery. This is especially true with the BHR THA.

Cup positioning has been reported to be a risk factor for increased wear and metal bearing–related complications. Excessive anteversion, insufficient anteversion or increased cup inclination increase the risk of posterior edge loading and impingement in MoM implants, which can lead to excess wear.[31,32] In our study, only the retroversion of the acetabular cup was associated with an increased risk for metal-related complications, although bilateral surgery or cup inclination did not have an effect. There is some evidence that pseudotumors do not have to necessarily be associated with high wear or increased metal ion levels, and they can occur in well-positioned implants,

suggesting that patient susceptibility has an important role in the development of pseudotumors.[33]

We acknowledge that our study had several limitations. First, the measurement interval was relatively short. Longer follow-up might change the course. Another limitation was that some patients with poor clinical outcome may have been revised before any metal ion measurements were done. Furthermore, all patients did not go through MARS-MRI or fill in OHS questionnaire which might have skewed the results. Our results are implant specific, and therefore not generalizable to other MoM devices. In this study, we used SUL values suggested by Van Der Straeten et al. (2013) for unilateral HRA implants. We used this SUL value for both unilateral and bilateral BHR HRA and unilateral BHR THA patients for better interpretability.

Conclusion

We found that WB metal ion levels decrease during the long-term follow-up in BHR patients. Patients with a well-functioning BHR hip may not necessarily benefit from routine metal ion measurements on a 2-year interval. The amount of patients with a metal-related adverse events was relatively high, although revision surgery was not always needed.

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Authors contributions

K.T.M. and M.S.V. designed the protocol and methods. K.T.M. performed the surgery, recorded the intraoperative data, and arranged the follow-up of the patients. M.S.V. analyzed the data and did the statistics. S.P., K.T.M., and M.L. collected the data. S.P., M.L., I.L., P.L., and K.T.M. wrote the manuscript. All authors contributed to the revision of the manuscript.

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Repeated metal ion measurements and long-term outcome of Durom/MMC total hip arthroplasty.
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III

Repeated metal ion measurements and long-term outcome of Durom/MMC total hip arthroplasty

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Background and purpose — Data regarding long-term behavior of metal ion levels in metal-on-metal total hip arthroplasty (MoM THA) patients is scarce. Therefore, we assessed whether there is any change in whole blood (WB) chromium (Cr), and cobalt (Co) ion measurements in Durom and MMC MoM THA patients over time. The secondary aim was to report the clinical outcomes using these devices in a single district.

Patients and methods — Durom and MMC cups were used in 249 MoM THAs from 2005 to 2011 in our district. Median follow-up time was 12 years for Durom THA (interquartile range [IQR] = 3) and 9 years for MMC THA (IQR = 1). A random coefficient model was used to compare individual differences in repeated WB Cr and Co ion measurements. The Kaplan–Meier estimator was used to analyze implant survival with any reason for revision as the endpoint.

Results — Geometric means of Cr in Durom THA and MMC THA patients decreased from 2.2 ppb (geometric standard deviation [SD] = 1.9) to 1.5 ppb (geometric SD = 2.5, $p < 0.001$) and from 1.8 ppb (geometric SD = 1.8) to 1.1 ppb (geometric SD = 2.8, $p = 0.01$) respectively. The geometric means of Co values remained unchanged. The 10-year survival of Durom THA was 82%, and that of MMC THA 89% for any revision reason as endpoint.

Interpretation — WB Cr levels decreased over time, and Co levels remained unchanged at long-term follow-up. Despite this we recommend continuing the follow-up of these devices due to relatively low implant survival.

The Durom Metasul large-diameter head (LDH) MoM acetabular device (Zimmer, Warsaw, IN, USA) was introduced in 2003. Overall, there were at least 3,000 implantations in Australia, England, and Finland (1-3). The Durom cup was found to have a high incidence of failure due to lack of osseointegration, and it was recalled in 2008 (4). The Zimmer MMC cup for LDH MoM THA was released in 2009 to address the problems of the Durom cup (5).

After concerns regarding adverse reaction to metal debris (ARMD) emerged, the usage of MMC cups was ceased in 2012 (6). While the revision rate of MoM THA has been relatively high there are still a large number of patients with a MoM device in situ requiring surveillance (2,7). Because ARMD may be asymptomatic, patient-reported outcome measurement (PROM) questionnaires, such as the Oxford Hip Score (OHS), are often not sufficient used alone to detect failing implants (8). Metal artefact reduction sequence magnetic resonance imaging (MARS-MRI) is a reliable tool to detect ARMD, but its utility in screening is limited due to availability, cost, and patient compliance (9,10). Whole blood (WB) metal ions, chromium (Cr), and cobalt (Co), have a fundamental role in the screening of MoM THA patients, although low WB metal ion levels do not exclude ARMD (11,12).

We assessed whether there is any change in the WB metal ion levels in the long term in Durom/MMC THA patients. We also assessed clinical outcomes, risk factors for revision surgery and radiological outcomes of Durom/MMC THA patients. We hypothesized that WB metal ion levels are not increasing during the long-term follow-up of these patients.

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Patients and methods

We conducted a retrospective cohort study to assess long-term WB Co and Cr level changes and clinical outcomes in Durom and MMC THA patients. Turku University Hospital electronic data pool was used as a data source. We identified all Durom and MMC THAs operated on in our district from March 2005 to January 2011. Unilateral Durom/MMC patients who had a different brand of MoM hip arthroplasty on the contralateral hip were excluded. The patients were followed until revision operation, death, or by the date of October 28, 2019.

We started the systematic screening of MoM hips in 2012, when the ARMD problems became evident. Before that there were only hospital-specific follow-up schedules. The studied implants were not considered to be in a "run in" period when the first ion measurements were performed (13). The screening program is based on the national follow-up protocol recommended by the Finnish Arthroplasty Society. The follow-up was planned to continue until further notice, based on, e.g., new data available.

According to the screening program all patients with MoM hip arthroplasty should go through clinical examination and/or a symptom questionnaire, plain radiographs, and WB Co and Cr ion measurements at least once. If these tests are considered normal, plain radiographs are repeated every 4th year and ion levels every 2nd year.

Symptomatic patients, and patients with metal ions above 5 ppb, undergo anteroposterior and shoot-through lateral radiographs of the hip every 2 years. In asymptomatic patients with low metal ions these radiographs are taken at a 4-year interval. Cr and Co ion measurements and Oxford Hip Score (OHS) questionnaires are checked on a 1- to 2-year interval depending on the symptom state and previous metal ion levels. The OHS questionnaire scale has been presented previously (14). If the patient had a symptomatic hip (poor or moderate postoperative OHS scores), or Cr and/or Co concentrations above 5 ppb, they were scheduled for MARS-MRI imaging of the hip. OHS results of the current study are presented as Supplementary data.

If MARS-MRI is considered normal, these patients undergo clinical examination, symptom questionnaire, and blood metal ion level measurements every year or every 2nd year depending on the case. Plain radiographs are taken every 2nd year. Repeated MARS-MRI is recommended if blood metal ion levels increase or there is progression in symptoms.

The details of WB Co and Cr laboratory analyses have been described previously (15,16).

We used safe upper limit (SUL) values of 4.6 ppb for Cr and of 4.0 ppb for Co for unilateral implants. For bilateral implants we used SUL values of 7.4 ppb for Cr and 5.0 ppb for Co as suggested earlier by Van Der Straeten et al. (17). The number of patients who had Co or Cr ions above the SUL in the repeated measurement were reported.

Table 1. Patient characteristics. Values are n (%)

	Operations n = 249	Patients n = 227
Age		
18–59	60 (24)	51 (23)
60–69	87 (35)	80 (35)
≥ 70	102 (41)	96 (42)
Sex		
Female	116 (47)	108 (48)
Male	133 (53)	119 (52)
Cup		
Durom	200 (80)	180 (79)
MMC	49 (20)	47 (21)
Bilateral		
No	205 (82)	205 (90)
Yes	44 (18)	22 (10)
Prior operation		
No	235 (94)	
Yes	14 (6)	
Anteversion angle		
> 0°	236 (95)	
≤ 0°	13 (5)	
Inclination angle		
0°–29°	5 (2)	
30°–49°	178 (71)	
≥ 50°	66 (27)	

All MARS-MRI images available were evaluated by a musculoskeletal radiologist experienced with ARMD-associated pathologies (see Supplementary data). Fluid collections and soft tissue masses were graded by the Hart pseudotumor classification (18). Operative data such as femoral head size and reasons for revision were collected manually from the medical records. The number of metal-related adverse events (pseudotumors, elevated metal ions above the SUL, or revision due to ARMD) were assessed separately for Durom and MMC THAs (see Supplementary data).

Patients

We identified 227 patients (249 hips) with a Durom or MMC THA. 22 of these patients (44 hips) had a bilateral THA (20 patients with Durom THA and 2 MMC THA). From the 249 hips, there were 126 Durom—CLS, 70 Durom—M/L Taper and 53 MMC—M/L Taper THAs. Median age of the patients was 68 years (IQR 14) and 108 (48%) were women. The median follow-up time for Durom THA was 12 years (IQR 3) and 9 years (IQR 1) for MMC THA (Table 1). 12 patients were revised before metal ion measurements started and 58 patients died during the follow-up.

There were 114 patients with less than 2 repeated metal ion measurements (Durom THA: median 1 [IQR 2], MMC THA: median 2 [IQR 1]). 113 patients had 2 or more metal ion measurements (83 Durom THA patients, 30 MMC THA). The median time elapsing from the index THA to the first metal ion measurement (initial measurement) was 6 years (IQR 4). In staged bilateral patients the median time was calculated from the 2nd hip replacement operation. The median time from the

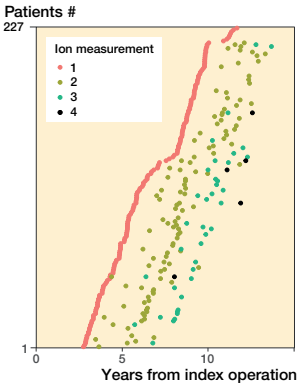

Figure 1. Repeated metal ion measurements by time from operation.

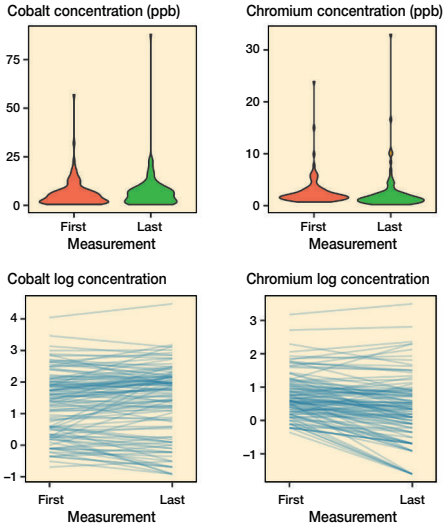

Figure 2. Boxplot figures for initial and control metal ion levels (upper panels). Spaghetti plots for individual cobalt and chromium values at initial and control measurements (lower panels). Values are naturally log-transformed.

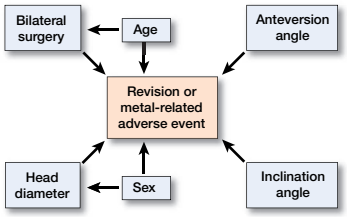

Figure 3. DAG demonstrating the direct causal effects of hip characteristics.

initial metal ion measurement to the last metal ion measurement (control measurement) was 3 years (IQR 1) and was considered as the measurement interval. The change between the first and the last metal ion measurement was assessed. The individual metal ion measurement time points with respect to the index operation are presented in Figure 1. The radiological measurements methods are reported in Supplementary data.

Statistics

The individual differences in repeated WB metal ion measurements were modelled using a random coefficient model for the same patient. In the models, log-transformed metal ion levels were used because of the positively skewed dispersion of ion levels. Spaghetti plots for naturally log-transformed ion levels were generated to demonstrate the individual changes between initial and control metal ion measurements (Figure 2). Medians with interquartile range (IQR), range, and geometric means with geometric standard deviation (GSD) were calculated at the initial and control measurements for better interpretability. The maximum ion values between patients with and without pseudotumors were compared using Wilcoxon's rank sum test. The Kaplan–Meier estimator was used to analyze the survivorship function for overall survival (revision surgery for any reason as the endpoint), and separately for metal-related adverse events (pseudotumors, elevated metal ions above the SUL, or revision because of ARMD) (see Supplementary data) as the endpoint with 95% confidence intervals (CI). Both Kaplan–Meier analyses included all operated joints separately, i.e., all unilateral operations and both joints from bilateral patients. All revisions were manually checked from medical records.

In survival analyses focusing on metal-related adverse events, the hips that were revised for reasons other than ARMD, either before or after the screening program was introduced, were censored at the time of revision. Furthermore, ion measurements taking place after the revision were excluded from the analysis except for hips that had the same bearing surface even after the revision. For these hips the post-revision ion measurements were also considered in the metal ion level analyses.

Univariable Cox proportional hazards (PH) regression analysis was used to calculate hazard ratios (HR) with 95% CI for revision for any reason, and separately for any metal-related adverse event (pseudotumor, metal ions above SUL, or revision due to ARMD) (see Supplementary data).

All models were stratified by MoM device. Additionally, we performed multivariable analysis for variables with potential confounding bias by choosing the adjusting variables based on a directed acyclic graph (DAG) analysis.

DAG (Figure 3) was constructed under the following assumptions:

1. Revision surgery or metal-related adverse events are dependent on age, sex, bilateral surgery, inclination angle, anteversion angle, and head diameter.
2. Bilateral surgery is dependent on age because both hips are seldom operated on in the elderly.
3. Head diameter is dependent on sex because head diameter is on average smaller in women.

According to DAG, the estimates for bilateral surgery were adjusted for age and the estimates for head diameter were adjusted for sex. The PH assumption for all Cox models was assessed by a statistical test based on scaled Schoenfeld residuals (19). To achieve the PH function assumption for metal-related adverse events analysis, cup inclination angle outliers ($< 30°$ or $\geq 50°$) were combined to a single outlier group.

P-values below 0.05 were considered statistically significant. Data analysis was performed using the R statistical com-

Table 2. Metal ion changes with p-values for patients with 2 or more metal ion measurements

Factor		Initial	Control	p-value
Durom THA (n = 82)				
Co	Median (IQR)	5.6 (5.5)	6.6 (5.4)	
	Geometric mean (GSD)	4.6 (2.6)	4.9 (2.84)	0.2
	Minimum–maximum	0.5–32	0.4–24	
Cr	Median (IQR)	2.0 (1.9)	1.5 (1.5)	
	Geometric mean (GSD)	2.2 (1.9)	1.5 (2.5)	< 0.001
	Minimum–maximum	0.7–15	0.2–17	
MMC THA (n = 30)				
Co	Median (IQR)	1.8 (2.2)	2.1 (4.8)	
	Geometric mean (GSD)	2.2 (2.6)	2.3 (3.6)	0.6
	Minimum–maximum	0.6–57	0.4–88	
Cr	Median (IQR)	1.6 (0.9)	1.1 (1.3)	
	Geometric mean (GSD)	1.8 (1.8)	1.1 (2.8)	0.01
	Minimum–maximum	0.9–24	0.2–33	

GSD – geometric standard deviation
Values are presented in ppb, which is equal to µg/L.
To convert ppb of Cr to nmol/L it is necessary to divide by 0.052.
To convert ppb of Co to nmol/L it is necessary to divide by 0.059.

puting environment version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria. R packages survival (version 3.2-10) and ggplot2 (version 3.3.3) were used for survival analysis and visualizations, respectively.

Ethics, funding, and potential conflicts of interest

The study protocol was based on the national recommendation for systematic screening of MoM THA patients given by the Finnish Arthroplasty Society (20). It was a register study, and the patients were not directly contacted. Therefore, approval by the local ethical committee was not needed. Data sharing is not possible. SP has received research funding from Turku University regarding the follow-up of MoM hip arthroplasty patients. MSV reports funding from the Academy of Finland (grant no. 322123). ES, IL, PL ,and KTM have nothing to disclose.

Results

The geometric mean of WB Cr decreased ($p < 0.001$) in Durom THA patients from 2.2 ppb (GSD 1.9) to 1.5 ppb (GSD 2.5) and in MMC THA patients from 1.8 ppb (GSD 1.8) to 1.1 ppb (GSD 2.8, $p = 0.01$). The geometric mean of WB Co remained unchanged in Durom THA patients with 4.6 ppb (GSD 2.6) at the initial measurement and 4.9 ppb (GSD 2.8, $p = 0.2$) at the control measurement. In MMC THA patients the geometric mean of Co was 2.2 ppb (GSD 2.6) at the initial measurement and 2.3 ppb (GSD 3.6, $p = 0.6$) at the control measurement (Table 2 and Figure 2).

Among patients with at least two ion measurements available, 59 patients (53%, 52 unilateral, 7 bilateral patients) had a Co value above the SUL and 12 patients (11%, all unilateral) had Cr value above the SUL in the first measurement. When the last metal ion measurement was assessed, 65 patients (58%, 57 unilateral, 8 bilateral patients) had a Co value above the SUL and 10 patients (9%, all unilateral) had a Cr value above the SUL. Spaghetti plots for individual WB Co and Cr changes at initial and control measurement are shown in Figure 2.

Table 3. Reasons for revision for both study devices

Reasons for revision	Durom THA	MMC THA
ARMD	27	3
Periprosthetic fracture	2	
Loosening of the cup	6	
Loosening of the femoral component	2	
Osteolysis	2	
Infection	3	1
Pain	2	1
Total	44	5

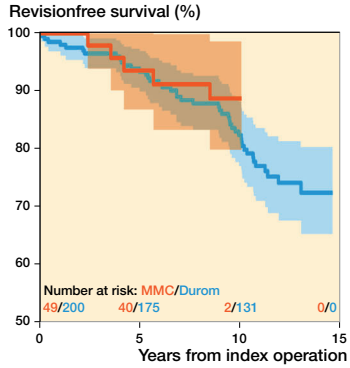

Figure 4. Kaplan–Meier survival curves for both Durom THA and MMC THA with revision for any reason as the endpoint with 95% CI.

44 (22%) Durom THAs were revised, and the most common reason was ARMD (27 revisions). 5 hips (9%) were revised in the MMC THA group and similarly ARMD was most often the reason for revision (3 revisions) (Table 3). The 10-year survival of Durom THA was 82% (CI 0.77–0.88) with any reason for revision as the endpoint. The 10-year survival of MMC THA with any reason for revision as the endpoint was 89% (CI 0.80–0.99) (Figure 4). Female sex was the only factor that was associated with increased risk of revision (HR = 2.4, $p = 0.003$) (Table 4).

Discussion

The main aim of the study was to assess whether there is any change in WB Cr and Co levels in Durom and MMC MoM THA patients over time. WB Cr levels decreased and Co ions

Table 4. Cox regression analysis data with 95% CI for revision for any reason

Factor	Hazard ratio (95% CI)	p-value
Unadjusted Hazard ratio		
Age (ref. < 60)		
60–69	1.1 (0.55–2.1)	0.8
≥ 70	0.81 (0.38–1.7)	0.6
Female sex (ref. male sex)	2.4 (1.3–4.4)	0.003
Bilateral surgery (ref. "no")	0.96 (0.46–2.0)	0.9
Inclination angle (ref. 30°–49°)		
< 30°	1.0 (0.14–7.5)	1.0
≥ 50°	0.90 (0.47–1.7)	0.8
Anteversion angle ≤ 0° (ref. > 0°)	1.4 (0.49–3.9)	0.5
Head diameter (ref. > 52 mm)		
46–52 mm	1.7 (0.60–4.8)	0.3
< 46 mm	2.9 (0.94–8.8)	0.06
Adjusted Hazard ratio		
Bilateral surgery (ref. "no")	0.95 (0.46–2.0)	0.9
Head diameter (ref. > 52 mm)		
46–52 mm	1.3 (0.44–3.8)	0.6
< 46 mm	1.7 (0.49–5.5)	0.4

In the multivariable analysis bilateral surgery was adjusted for age and head diameter was adjusted for sex. All models were stratified according to MoM THA device.

remained unchanged during the follow-up. The proportion of patients with metal ions above the SUL did not increase during the follow-up. The number of metal-related adverse events was high, but most of these patients did not require revision operation.

While metal ion measurements have a role in the screening of MoM THA patients, there is no international consensus on optimal measurement interval (12). Normal WB metal ion values do not exclude ARMD and elevated metal ion levels do not solely dictate the need for revision surgery. However, elevated metal ion levels are associated with increased wear and further examinations might reveal a failing hip that otherwise might have been missed (11,12). The decision to perform a revision operation is also affected, besides ion levels, by the patient's subjective feelings regarding the hip. If the patient is satisfied with the hip, revision surgery is often not needed. Many patients in our study had a surprisingly high OHS score (see Supplementary data). Current guidelines in Finland recommend repeated metal ion measurements every 2 years for all MoM hip devices. Conversely, the FDA does not recommend the routine usage of WB metal ion measurements at all in the screening of MoM patients (21). While the survival of different MoM hip implants varies (2,3), it might also be reasonable to have differing follow-up protocols for each brand from the cost-effective point of view. We have previously stated that if initial WB Cr or Co values are low, repeated metal ion measurement at 2-year intervals does not necessarily provide clinically useful information for patients with unilateral or bilateral M2A-ReCap-Magnum MoM THA (15,16). Also, Kiran and colleagues have previously suggested that large-head MoM THA patients might not benefit from annual metal ion measurements if they were asymptomatic (22). We are not aware of any previous reports regarding the repeated metal ion measurements of Durom or MMC MoM THA patients. Our findings advocate that Durom or MMC THA patients do not necessarily benefit from repeated metal ion measurements at 3-year intervals if WB metal ions are initially below the SUL. Our results do not explain why the number of patients with Cr ion levels above the SUL differs from the number of patients with Co ion levels above the SUL. Further studies are required to explain this discrepancy.

The overall implant survival of Durom and MMC THA in our series was in conformity with previous studies. Seppänen et al. reported in 2018 an overall 10-year survival of 81% for Durom/MMC THA based on the Finnish Arthroplasty Register (FAR) (23). In an Australian population the 10-year revision rate for the Durom cup was 16% (2). ARMD was the most common reason for revision in our cohort (13% of all patients, 59% of revisions), as expected based on previous registry data (1). Inferior long-term survivorship for Durom/MMC THA due to ARMD has been reported also in some clinical studies. Ridon et al. reported in 2019 that ARMD was the reason for revision in 29% of Durom THA patients, with an overall 10-year survival of 67% (24). Lainiala et al. reported a survivorship of 92% for Durom THA at 7 years with ARMD as the most common reason for revision (83% of all revisions), although they did not separate the Durom and MMC THAs (25). Our data suggests that MMC THA performs slightly better than the Durom THA, although the numbers were small. The 10-year revision rate of Durom—CLS THA is somewhat higher (25%) than that of Durom—M/L Taper (12%) or MMC M/L Taper combination (8.8%) based on the FAR data. The 10-year revision rate for the M/L Taper stem in conventional THA combinations varies from 5% to 9% (3). The better performance of the M/L Taper stem compared with the CLS stem may cause some minor bias to our results.

Inferior survivorship of MoM hip implants in female patients has been reported previously (21). Bilateral surgery, femoral head size, or older age were not associated with an increased risk of revision in our study. Naal et al. have previously reported that femoral head size is not necessarily associated with increased revision risk in Durom HRA patients. Similar to our study, women had a higher revision rate than men (26).

We acknowledge that our study has several limitations. First, our study design was retrospective. Not all the study patients underwent WB metal ion measurements. However, we were also interested in variables and outcomes other than ion levels (such as revision rate). Therefore, we decided to present data of the whole Durom/MMC-group as such, although missing data exists. MARS-MRI was performed only on patients with a symptomatic hip or elevated WB metal ions (above 5 ppb), and the incidence of pseudotumors in the MRI does not represent the whole cohort. Some of the patients with poor functional outcome may have been revised before participating in metal ion measurements.

The main aim of our study was to evaluate the change in metal ion levels in repeated measurements. Unfortunately, metal ion level data are not available in the national arthroplasty register. In Finland, most of the revision operations are usually performed in the same hospital district area where the primary implantations were performed. Therefore, we considered that linking our data with the national register would not have altered our results substantially. We think that this bias on our revision rates is minor. We did not have preoperative OHS scores and not all patients filled in a postoperative OHS questionnaire. The radiographic angle measurements were performed in a standard way as described in the Supplementary data, but intra- or inter-class variation was not separately assessed. However, we think this potential bias has only a minor effect on our results.

In conclusion, WB Cr decreased and WB Co remained unchanged in Durom and MMC MoM THA patients. The number of metal-related adverse events was high, but most of them did not require revision.

KTM and MSV designed the protocol and methods. KTM arranged the follow-up of the patients. MSV analyzed the data and did the statistics. SP, ES and KTM collected the data. SP, ES, IL, PL, and KTM wrote the manuscript. All authors contributed to the revision of the manuscript.

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Supplementary data

Supplementary methods (radiological measurements)

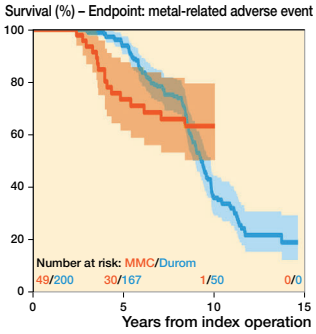
The cup anteversion and inclination were measured using Carestream Vue PACS software angle measurement tool from standard pelvic AP and lateral shoot-through radiographs. Because the measurement of the anteversion angle may be challenging from lateral radiographs, we categorized the cups into two subgroups, "retroverted" and "not retroverted," for the purpose of regression analysis (numbers and distribution of the data supported this). The measured cup anteversion was compared with the horizontal image plane. Cup inclination was measured from AP pelvis radiographs by drawing a line tangential to the acetabular cup, and another line between the ischial tuberosities. For 18 patients this angle was estimated from AP radiographs of the hip because pelvic radiographs were missing.

The inclination angle subgroups were based on the long-held principle of a "safe zone" for acetabular implants (1). 30°–49° was considered as the optimal inclination (reference). Inclination angles below and above this angle were considered as their own subgroups. There were 97 patients (109 hips) with MARS-MRI imaging of the hip. Postoperative OHS scores were available for 167 patients (183 hips).

Supplementary results

We identified 97 patients (109 hips) with a postoperative MARS-MRI of the hip. A pseudotumor was found in 66 hips (61%). The majority (40) were Hart 2A or 2B pseudotumors. Hart 3 pseudotumor was identified in eight hips, and Hart 1 pseudotumor was diagnosed in 18 hips. There were 29 hips with repeated MARS-MRI imaging. Most hips (n = 29) with repeated MRI imaging had undergone 2 MRI imaging sessions, while 2 hips had 3 MRI imaging sessions. 10 patients had normal MRI images in both the initial and repeated MARS-MRI. There were 5 patients with Hart 1 pseudotumor in the initial MRI, but no visible pseudotumor in the repeated MARS-MRI. 3 patients had normal MRI initially but were diagnosed with a pseudotumor in the repeated MRI. 6 pseudotumors increased in size in the repeated MRI but the grade remained the same, and in 1 patient both the grade and size of the pseudotumor increased. 4 patients had a similar pseudotumor on the repeated MRI.

The maximum metal ion values of patients with a MARS-MRI were assessed in a subgroup analysis. In cases where MARS-MRI was considered normal, the geometric mean of Co was 7.5 ppb (GSD 2.2). If pseudotumor was diagnosed the geometric mean of Co was 8.9 (GSD 2.5, p = 0.06). Similarly, the geometric mean of Cr in patients with normal MARS-MRI was 2.5 ppb (GSD 2.1) while patients with a diagnosed pseudotumor had a geometric mean of 3.0 ppb (GSD 2.2, p = 0.2).



Supplementary Figure. Kaplan–Meier survival analysis for both Durom THA and MMC THA with metal related adverse events as the endpoint with 95% CI.

The number of metal-related adverse events (pseudotumor, metal ions above SUL, or revision due to ARMD) was 233 in 120 patients (133 hips: Durom 117, MMC 16). A total of 56 patients had one metal-related adverse event, while 30 patients had two metal-related adverse events. Additionally, 34 patients had 3 or more metal-related adverse events. The 10-year survivorship in terms of metal-related adverse event as the endpoint (with 95% CI) for Durom THA was 36% (CI 0.29–0.44), while the 10-year survivorship of MMC THA in terms of metal-related adverse event as the endpoint was 63% (CI 0.50–0.80) (Supplementary Figure).

167 patients completed the OHS questionnaire postoperatively for 183 hips. One-fourth of the patients reported poor or moderate outcomes (19 [10%] bad and 20 [11%] moderate) while the vast majority of the patients had good to excellent outcomes (41 [22%] good, 103 [56%] excellent). The mean OHS was 40 (SD 9.8) and the median OHS was 44 (IQR 12). The distribution of OHS scores was similar in both Durom and MMC patients.

Female sex was the only factor that was associated with a higher risk of adverse metal-related events (HR 1.5, p = 0.03) (Supplementary Table).

Supplementary discussion

Durom and MMC metal-on-metal (MoM) devices as well as other MoM hip brands were developed to avoid problems with polyethylene wear. Larger head sizes were also associated with

Supplementary Table. Cox regression analysis data with 95% CI for revision due to adverse reaction to metal debris (ARMD), pseudotumor, Co > SUL or Cr > SUL at any point during follow-up

Factor	Hazard ratio (95% CI)	p-value
Unadjusted Hazard ratio		
Age (ref. < 60)		
60–69	0.77 (0.50–1.2)	0.2
≥ 70	0.92 (0.60–1.4)	0.7
Female sex (ref. male sex)	1.5 (1.0–2.1)	0.03
Bilateral surgery (ref. "no")	1.2 (0.77–1.8)	0.4
Inclination angle (ref. 30°–49°)		
< 30°	1.5 (0.16–2.7)	0.6
≥ 50°	1.0 (0.66–1.4)	0.9
Anteversion angle ≤ 0° (ref. > 0°)	1.3 (0.67–2.6)	0.4
Head diameter (ref. > 52 mm)		
46–52 mm	1.2 (0.72–2.0)	0.5
< 46 mm	1.6 (0.88–2.9)	0.1
Adjusted Hazard ratio		
Bilateral surgery (ref. "no")	1.1 (0.73–1.8)	0.6
Head diameter (ref. > 52 mm)		
46–52 mm	1.1 (0.63–1.8)	0.8
< 46 mm	1.3 (0.66-2.5)	0.5

In the multivariable analysis bilateral surgery was adjusted for age and head diameter was adjusted for sex. All models were stratified according to MoM THA device.

decreased dislocation revision risk. Both implants were used especially in the young and active population. The Durom cup has a high carbon content and forged chrome-cobalt (Cr-Co) alloy structure with optimized clearance. One theory behind the inferior results of the Durom cup was that the rim may cause poor contact with the prepared acetabular bone, which may lead to poor osseointegration and early failure.

We considered that revision rate alone may not adequately represent the rate of functional failure. Therefore, we performed a separate survival analysis in terms of metal-related adverse event as the endpoint (elevated metal ions above the SUL, revision due to ARMD, pseudotumor in MARS-MRI). The 10-year survival of Durom hips was only 36% while the 10-year survival of MMC hips was 63%.

Even though the amount of metal-related adverse events was high, the majority of the patients reported good to excellent OHS scores postoperatively. All OHS data was collected postoperatively as part of the screening in our study, so we do not have preoperative data. OHS data from all patients at a certain timepoint, e.g., 7 years after operation, is not available. However, the vast majority of the patients reported good to excellent outcomes after Durom/MMC THA implantation, which suggests that patients were mainly satisfied with their total hip.

Since not all patients underwent metal ion measurements or MARS-MRI imaging the true amount of metal-related adverse events might be higher. It is possible that Cox proportional hazards regression analysis could provide slightly different hazard ratios without missing data. Bilateral surgery was associated with an increased risk of metal-related adverse events based on our data, whereas femoral head size or older age were not. The higher rate of aseptic loosening in Durom cups might cause unexpected movement of the cup predisposing implants to edge loading and ARMD (2,3). Cup position was not associated with an increased risk of metal-related adverse events in our study, although the total numbers were small.

In our study, 75 out of 125 (60%) patients with MARS-MRI had pseudotumor, but direct comparison with other studies is not possible as we performed MARS-MRI only if suggested by the screening protocol. Repeated MARS-MRI changed to normal in many of the initial Hart 1 pseudotumor cases, and the normal finding remained so in most cases. There was no difference in the metal ion levels of patients with a pseudotumor in MARS-MRI and patients with a normal MARS-MRI in the subgroup analysis. However, MARS-MRI was performed only for patients who had symptoms or elevated metal ion levels, which might cause selection bias.

There are 2 previous reports we are aware of concerning incidence of pseudotumors in Durom THA patients. 70 patients of the 102 (68%) in the study of Sutphen et al. (4) and 34 of the 58 (59%) in the study of Hart et al. (5) had pseudotumor visible in MARS-MRI. The study of Sutphen et al. (4) had mostly Durom patients in their cohort, but the exact number was not reported. Similarly, Hart et al. (5) had also other MoM THA brands than Durom THA included in their study.

Both studied implants (Durom/MMC) have a modular large diameter head that consists of CoCr alloy. Both stems are monoblock stems that are manufactured from titanium alloy with a similar taper size of 12/14. Modularity of the head provides flexibility for the surgeon, but it creates an additional metal-on-metal interface, where corrosion and wear may occur. Trunnionosis, which refers to corrosion occurring at the head–neck junction in poorly functioning THA implants, can increase the risk of ARMD further. As the head-taper junctions are similar in both implants, we do not believe that trunnionosis causes bias to our study.

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Median 10-year whole blood metal ion levels and clinical outcome of ReCap-M2a-Magnum metal-on-metal total hip arthroplasty.
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IV

Median 10-year whole blood metal ion levels and clinical outcome of ReCap-M2a-Magnum metal-on-metal total hip arthroplasty

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Background and purpose — We have previously reported that the whole blood (WB) chromium (Cr) and cobalt (Co) ion levels decrease in the short term after ReCap-M2a-Magnum large-diameter head (LDH) metal-on-metal (MoM) total hip arthroplasty (THA). This study reports long-term metal ion levels and clinical outcomes after ReCap-Magnum THA.

Patients and methods — ReCap-M2a-Magnum LDH THA was used in 1,450 patients in our hospital district from 2005 to 2012. Median follow-up time was 10 years. 991 patients had 2 or more metal ion measurements. The median measurement interval was 4 years. Individual metal ion change was assessed using logarithmic metal ion values in a random coefficient model. Kaplan–Meier survival estimates were calculated for revision surgery for any reason for revision, and separately for metal-related adverse events (metal ions above safe upper limit [SUL], revision due to ARMD, or pseudotumor).

Results — Geometric mean of Cr decreased from 1.8 ppb (geometric standard deviation [GSD] 1.8) to 1.0 ppb (GSD 2.8, $p < 0.001$). The Co levels decreased from 1.7 ppb (GSD 2.4) to 1.4 ppb (GSD 2.8, $p < 0.001$). The hip-specific survival was 85% for revision due to any reason at 14 years and the hip-specific survival for any metal-related adverse event was 69% at 14 years.

Interpretation — WB Cr and Co levels continued to decrease in the long-term follow-up of ReCap-M2a-Magnum THA patients. The amount of metal-related adverse events was rather high, but revision surgery was seldom required. We suggest that after 10 years from the implantation a 5-year measurement interval may be sufficient for asymptomatic ReCap-M2a-Magnum patients.

In well-functioning metal-on-metal (MoM) total hip arthroplasty (THA), patients' whole blood (WB) chromium (Cr) and cobalt (Co) metal ion levels peak in the first years after the implantation and usually decrease thereafter (1). Data concerning long-term metal ion changes in MoM THA patients is scarce (2). Most MoM THAs have been performed over a decade ago, and many patients are doing relatively well without the need for revision surgery (3). The follow-up of these patients is important to recognise the failing implants, and also to identify and prevent systemic cobalt toxicity. Additionally, the long-term follow-up guidelines need to be updated to optimize the usage of limited healthcare resources (1,4,5).

ReCap-M2a-Magnum (ZimmerBiomet, Warsaw, IN, USA) large-diameter head (LDH) MoM THA was commonly used in Finland from 2005 to 2012 (6). In our previous reports regarding both unilateral and bilateral ReCap-M2a-Magnum LDH MOM THA patients in Turku University Hospital, 2.5% of the hips required a revision operation due to adverse reaction to metal debris (ARMD) and 12% had a definite ARMD, but revision was not performed during follow-up of 5 years. The WB Cr and Co ion levels decreased, and stayed mostly below the safe upper limit (SUL) if the initial values were low (7-9). SUL value describes the edge of acceptable metal ion levels, but there is no universally accepted SUL value for all MoM implants and normal metal ion levels do not exclude ARMD. Bosker et al. found a 4 times higher incidence of ARMD in ReCap-M2a-Magnum THA patients with metal ion levels above 5 ppb (10,11). High cobalt levels can cause pathological effects, such as cardiomyopathy, thyroid, hepatic, and hematology disorders, and neurological symptoms. High Cr levels can be both carcinogenetic and genotoxic (1). In the current study the ReCap-M2a-Magnum acetabular component and

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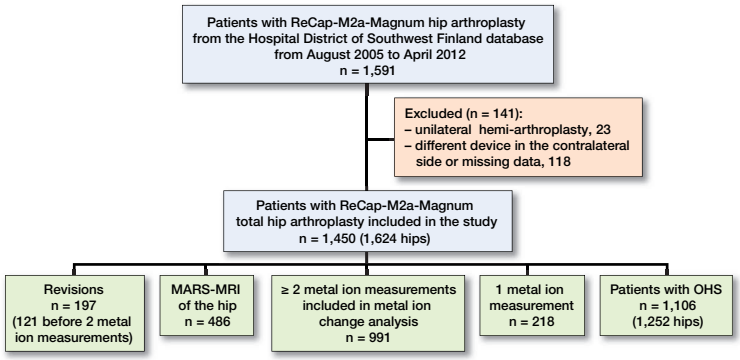

Figure 1. Flowchart demonstrating the inclusion criteria.

Table 1. Hip and patient demographics. Values are count (%)

	Operations n = 1,624	Patients n = 1,450
Age		
17–59	463 (29)	393 (27)
60–69	655 (40)	593(41)
≥ 70	506 (31)	464 (32)
Female sex	852 (53)	767 (53)
Bilateral	348 (21)	174 (12)
Prior operation	134 (8)	
Anteversion angle		
> 0°	1,580 (98)	
Inclination angle (°)		
0–29	41 (3)	
30–49	1,253 (81)	
≥ 50	243 (16)	
Head diameter, mm		
< 46	203 (13)	
46–52	1,169 (72)	
> 52	252 (15)	

femoral head were paired with either uncemented Bi-Metric or Reach stems (ZimmerBiomet, Warsaw, IN, USA). Measurement interval, i.e., the time between the first and last metal ion measurement, was 2 years in our previous publications. We have previously stated that based on the Turku University Hospital data at the mean follow-up time of 5.2 years, 14.3 % of all ReCap-M2a-Magnum hips exhibited adverse reaction to metal debris (9).

This study analyzed metal ion levels of ReCap-M2a-Magnum LDH MoM THA patients' change in the long term. We also assessed the clinical and imaging outcomes after ReCap-M2a-Magnum THA, and risk factors for revision surgery.

Patients and methods

We performed a retrospective cohort study to determine WB Cr and Co ion level changes in the long term. We have now analyzed WB Cr and Co ion level data in the Hospital District of Southwest Finland level with median follow-up of 10 years. We have also assessed the clinical outcome of ReCap-M2a-Magnum patients. All patients who had ReCap-M2a-Magnum LDH MOM THA from the Hospital District of Southwest Finland database from August 2005 to April 2012 were included. The patients were followed until revision surgery, death, or by the end of 2019. Patients with a unilateral Recap-M2a-Magnum THA and a different brand of MoM THA implant on the contralateral side were excluded from the analyses. A screening program for all MoM THA patients was started in 2012 at our institution.

We used previously established SUL values of 4.6 ppb for Cr and of 4.0 ppb for Co for unilateral implants, and 7.4 ppb for Cr and 5.0ppb for Co for bilateral implants (10). Patients with Co or Cr ions above 5 ppb or poor functional outcome in Oxford Hip Score (OHS) questionnaire were scheduled to MARS-MRI. The inclination angle of the cup was measured from straight anteroposterior pelvis radiographs, and the angle between ischial tuberosities and cup ring was measured. Further, the anteversion of the cup was assessed from lateral shoot-through radiographs measuring the angle between horizontal image plane and cup rim. Measurements were performed using the angle measurement tool of Carestream Vue PACS software (www.carestream.com/en/ca/). The details of this screening program have been explained in our previous publications (9,12,13). Data was obtained from the Hospital District of Southwest Finland data pool and electronic medical records. MARS-MRI images were performed in Turku University Hospital and were assessed by a radiologist consultant experienced in ARMD related pathologies. Pseudotumors were graded using the previously described classification system by Hart et al. (14).

Patients

1,450 patients (1,624 hips) were included in this study (Figure 1). 174 patients had bilateral ReCap-M2a-Magnum THA. 1,412 patients (1585 hips) had a Bimetric femoral stem while 38 patients (39 hips) had a Reach stem.

The median follow-up time for unilateral hips was 10 years (0.6–14) and 11 years (1–14) for bilateral hip implants. 313 patients died during follow-up. Median age of the patients was 65 years (interquartile range [IQR] 12), and 683 (47%) patients were male (Table 1)

We identified 991 patients with at least 2 WB metal ion measurements and evaluated the change between the first and the last measurement. The median time interval from THA to the index metal ion measurement was 5 years (0.5–11). The median time between the initial and the last metal ion measurement was considered as the measurement interval. The individual measurement time points with respect to the (later) THA operation are shown in Figure 2.

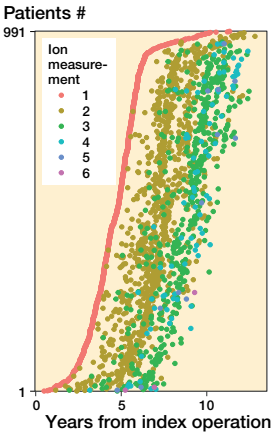

Figure 2. Individual metal ion measurement time points.

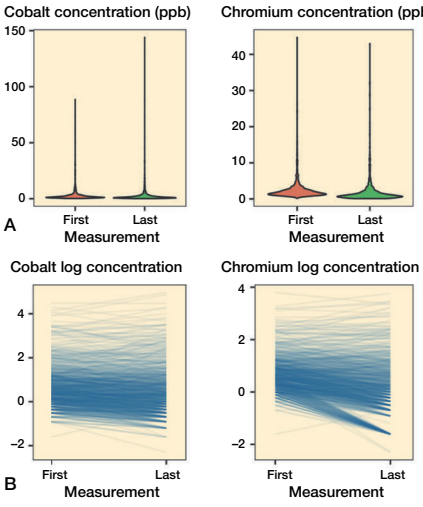

Figure 3. A. Violin plots demonstrating the skewedness of metal ion values. B. Spaghetti plots for individual chromium and cobalt ion levels.

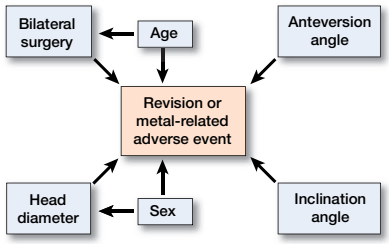

Figure 4. DAG demonstrating the direct causal effects of hip characteristics.

1,106 patients had completed a postoperative OHS questionnaire for 1,252 hips. Preoperative OHS scores were not available. Concerning radiographic data, 2 patients (3 hips) did not have anteversion angle data and 84 patients (87 hips) did not have inclination angle data due to missing radiographs.

486 patients (563 THA) had undergone MARS-MRI imaging of the hip, of which 161 hips had had more than 1 MARS-MRI imaging sessions.

Statistics

We used a random coefficient model to assess the individual change between repeated metal ion levels. Due to the positively skewed distribution of metal ion levels, metal ion levels were log transformed in conditional models. The individual change in metal ion levels was presented with spaghetti plots for natural log transformed metal ion values (Figure 3). We used medians with interquartile range (IQR) and geometric means with geometric standard deviation (GSD) were used at both the initial and control measurements for improved interpretability. McNemar's test was used to determine differences in proportions of patients with metal ion levels above the SUL between the first and the last measurements.

The overall survivorship for unilateral and bilateral ReCap-M2a-Magnum THA implants with 95% confidence intervals (CI) was calculated using the Kaplan–Meier estimator (revision surgery for any reason as the endpoint). Additionally, separate Kaplan–Meier analysis (with CI) was performed to assess the survivorship of ReCap-M2a-Magnum THA in terms of metal-related adverse events (metal ions above SUL, revision due to ARMD, pseudotumor visible in MARS-MRI) as endpoint. Regarding this metal-related adverse event analysis, the hips that were revised for reasons other than ARMD previously were censored at the time of revision. Kaplan–Meier analyses were hip-specific considering both implants from bilateral patients.

We manually checked all revisions from the electronic medical records of Hospital District of Southwest Finland. Metal ion measurements that were taken after revision were excluded, also in bilateral patients, unless the THA had the same bearing surface after the revision, as in many periprosthetic femoral fracture revisions. In these patients, metal ion measurements after revision were included in metal ion level analysis.

A directed acyclic graph (DAG) was constructed under these assumptions:

1. Metal-related adverse events and revision surgery are dependent on age, sex, bilateral surgery, anteversion angle, inclination angle, and head diameter.
2. Bilateral surgery is dependent on age, as both hips are not as commonly operated on in older patients.
3. Head diameter is dependent on sex, as head diameter is on average larger in men.

We used Cox proportional hazards (PH) regression analysis to estimate hazard ratios (HR) and their CI for each potential risk factor for metal-related adverse events and revision surgery. As suggested by the DAG analysis (Figure 4), the HR for head diameter was adjusted for confounding from sex whereas the estimates for other variables remained unadjusted. PH assumption for all Cox analyses was evaluated with visual inspection of Kaplan–Meier plots, and using a statistical analysis based on weighted Schoenfeld residuals. The HR estimates for metal-related events in different age groups showed minor violation of the PH assumption but the estimates were left as is, without dividing follow-up time into intervals, after inspection of corresponding Kaplan–Meier survival plots. All Cox PH models were stratified by THA brand.

A p-value of less than 0.05 was considered to be statistically significant. R statistical computing environment version 4.0.3 was used to execute data analysis (15). We used R packages ggplot2 (version 3.3.3) and survival (version 3.2-10) for visualizations and survival analysis.

Table 2. Metal ion changes with p-values for unilateral and bilateral ReCap-M2a-Magnum THA patients

Factor		Initial	Control	p–value
Unilateral patients, n		859	859	
Co	Median (IQR)	1.5 (1.7)	1.1 (1.6)	
	Geometric mean (GSD)	1.7 (2.4)	1.4 (2.8)	< 0.001
	range	0.2–89	0.1–144	
Cr	Median (IQR)	1.7 (1.3)	0.9 (1.3)	
	Geometric mean (GSD)	1.8 (1.8)	1.0 (2.8)	< 0.001
	range	0.2–26	0.1–43	
Bilateral patients, n		132	32	
Co	Median (IQR)	2.7 (2.6)	2.1 (2.2)	
	Geometric mean (GSD)	3.1 (2.2)	2.4 (2.5)	< 0.001
	range	0.6–74	0.5–70	
Cr	Median (IQR)	2.6 (1.9)	1.5 (2.0)	
	Geometric mean (GSD)	2.9 (1.9)	1.7 (2.4)	< 0.001
	range	0.7–45	0.2–29	

Table 3. Reasons for revision Unilateral and Bilateral Recap Magnum hips

	Reasons for revision		
	unilateral	bilateral	combined
ARMD	80	20	100
Periprosthetic fracture femur	20	6	26
Infection	19	6	25
Loosening of the cup	13	4	17
Loosening of the femoral component	10	2	12
Postoperative hematoma	4	1	5
Cup malposition	2	1	3
Unclear pain	4	–	4
Recurring luxation	1	2	3
Periprosthetic fracture acetabulum	1	–	1
Component breakage	1	–	1
Total	155	42	197

Ethics, funding, and potential conflicts of interest

This study was based on the national recommendations for MoM THA patient screening in Finland. Study data was gathered from register and electronic patient records. Patients were not contacted directly. For these reasons approval by the local ethical committee was not required. Data sharing is not possible. SP reports funding from Turku University and MSV has received funding from the Academy of Finland (grant no. 322123). AL, HM, IL, PL, and KTM have nothing to disclose.

Results

The geometric mean of WB Cr decreased from 1.8 ppb (GSD 1.8) to 1.0 ppb (GSD 2.8, $p < 0.001$) and the geometric mean of Co decreased from 1.7 ppb (GSD = 2.4) to 1.4 ppb (GSD 2.8, $p < 0.001$) in unilateral ReCap-M2a-Magnum patients. In bilateral patients WB Cr decreased from 2.9 ppb (GSD 1.9) to 1.7 ppb (GSD 2.4, $p < 0.001$) and WB Co decreased from 3.1 ppb (GSD 2.2) to 2.4 ppb (GSD 2.5, $p < 0.001$). The median measurement interval was 4 years (IQR 1.6) in unilateral patients and 4 years (IQR 1.9) in bilateral patients. Metal ion changes with p-values are given in Table 2.

In the whole cohort, 74 (7%) patients had Cr levels above the SUL and 135 (14%) patients had Co levels above the SUL in the first metal ion measurement, while 72 (7%) patients had their Cr levels above the SUL and 135 (14%) patients had their Co levels above the SUL in the last metal ion measurement. The proportion of patients above the SUL did not change during the follow-up. In unilateral patients, only 63 (7%) had a Cr value above the SUL in the first measurement while 62 (7%) had Cr values above the SUL in the last measurement. 110 (13%) unilateral patients had their Co value above the SUL in the first measurement and 115 (13%) had Co above the SUL in the last measurement ($p = 0.6$). In bilateral patients, 11 (8%) had Cr above the SUL in the first measurement and 10 (8%) had a Cr value above the SUL in the last measurement. 25 (19%) bilateral patients had Co above the SUL in the first measurement and 20 (15%) had Co above the SUL in the last measurement ($p = 0.3$). Individual metal ion change is demonstrated in Figure 2.

The combined implant survival for ReCap-M2a-Magnum THA with revision for any reason as the endpoint was 88% (CI 86–89) at 10 years and 85% (CI 83–88) at 14 years. For unilateral implants specifically, the 14-year survival was 85% (CI 83–88) and for bilateral implants it was almost similar, 86% (CI 81–90) at 14 years. The total number of revised hips during the follow-up time was 197 (12% of all hips), of which 121 were revised before two blood metal ion measurements. ARMD was the reason for revision in 100 hips (6% of all hips, 50% of revisions). Median time for revision due to ARMD was 6.4 years (IQR 3.2), infection 1.6 years (IQR 3.2), and for any other reason 0.8 years (IQR 5.0) from the implantation.

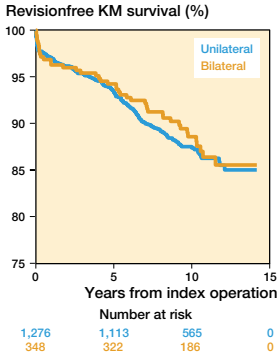

Figure 5. Kaplan–Meier curve for unilateral and bilateral implants separately with revision due to any reason as endpoint.

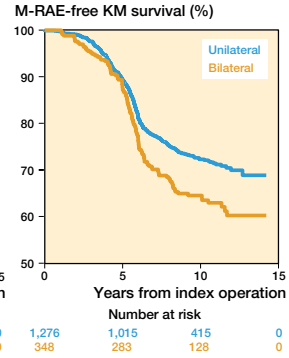

Figure 6. Kaplan–Meier estimates for unilateral and bilateral implants, with metal-related adverse events (M-RAE) as endpoints.

Table 4. Cox regression analysis results for metal-related adverse events

	Unilateral patients		Bilateral patients	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (ref. < 60)				
60–69	1.1 (0.8–1.4)	0.6	0.9 (0.6–1.4)	0.7
≥ 70	0.9 (0.7–1.3)	0.7	0.8 (0.5–1.3)	0.4
Sex (ref. male)				
Female	1.8 (1.4–2.3)	< 0.001	0.9 (0.6–1.3)	0.6
Inclination angle (ref. 30–49°)				
< 30°	0.8 (0.4–1.7)	0.6	2.1 (0.7–6.7)	0.2
≥ 50°	1.2 (0.9–1.6)	0.2	0.7 (0.4–1.3)	0.3
Anteversion angle (ref. > 0°)				
≤ 0°	2.3 (1.3–4.0)	0.006	0.7 (0.2–2.7)	0.6
Head diameter, mm (ref. > 52)				
46–52	0.9 (0.6–1.3)	0.4	0.7 (0.5–1.2)	0.2
< 46	1.3 (0.8–2.0)	0.4	0.5 (0.2–1.2)	0.1

HR = Hazard ratio
All effect estimates were derived from separate Cox proportional hazards regression models. As suggested by the directed acyclic graph (DAG) analysis, the effect estimates for all variables, except head diameter, were obtained from unadjusted univariable models. The effect estimates for head diameter were obtained using multivariable models with adjustment for sex.

Table 5. Cox regression analysis results for revision due to any reason

	Unilateral patients		Bilateral patients	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (ref. < 60)				
60–69	0.9 (0.6–1.3)	0.6	1.2 (0.6–2.3)	0.7
≥ 70	1.0 (0.7–1.5)	0.9	1.3 (0.6–2.1)	0.5
Sex (ref. male)				
Female	1.9 (1.4–2.7)	< 0.001	1.3 (0.7–2.3)	0.4
Inclination angle (ref. 30–49°)				
< 30°	0.5 (0.1–2.1)	0.4	3.6 (0.9–15)	0.08
≥ 50°	2.2 (1.5–3.2)	< 0.001	0.9 (0.4–2.2)	0.8
Anteversion angle (ref. > 0°)				
≤ 0°	3.5 (1.9–6.6)	< 0.001	2.1 (0.5–8.7)	0.3
Head diameter, mm (ref. > 52)				
46–52	0.5 (0.3–0.8)	0.004	1.0 (0.4–2.6)	1.0
< 46	0.8 (0.4–1.4)	0.4	2.3 (0.7–7.8)	0.2

For footnotes, see Table 4.

Kaplan–Meier results for implant survival for any reason of revision are presented in Figure 5, and reasons for revision in Table 3.

The 14-year survival for metal-related adverse events (pseudotumor, metal ions above the SUL, or revision due to ARMD) was 69% (CI 65–73) for unilateral implants and 60% (CI 55–67) for bilateral implants. The number of metal-related adverse events was 433 (314 unilateral and 118 bilateral hips). Kaplan–Meier survival curves are shown in Figure 6.

In Cox proportional hazards regression analysis, cup retroversion (HR 3.5, $p < 0.001$), inclination angle above 50 degrees (HR 2.2, $p < 0.001$), and female sex (HR 1.9, $p < 0.001$) were associated with higher risk of revision in unilateral patients. Furthermore, retroversion of the cup (HR 2.3, $p = 0.006$) was associated with a higher risk of metal-related adverse events. Femoral head diameter of 46–52 mm was associated with better implant survival as compared with head diameter of > 52 mm (HR 0.5, $p = 0.004$). Female sex (HR 1.8, $p < 0.001$) was associated with a higher risk of metal-related adverse events in unilateral patients. Cox regression analysis data is given in Tables 4 and 5.

Of the 563 THAs with MARS-MRI there was a pseudotumor in 338 hips (60%, 21% of all hips), and in 225 (40%) THAs the MRI was considered normal. Hart 1 pseudotumor was diagnosed in 132 THAs, Hart 2A pseudotumor in 71 THAs, and Hart 2B was seen in 107 THAs. Solid Hart 3 pseudotumor was identified in 28 hips.

In addition to this, we evaluated 161 hips with repeated MARS-MRI imaging. 39 patients did undergo 3 MARS-MRI imaging sessions and 6 patients had 4 MARS-MRI. Of these, 66 patients had normal initial MARS-MRI and 46 of these were normal in the repeated imaging. There was a new pseudotumor in 20 hips that had normal initial MRI. In 14 hips with initially diagnosed pseudotumor, the repeated MARS-MRI was considered normal. 11 were Hart 1 pseudotumors, 2 were Hart 2A pseudotumors, and 1 was Hart 2B pseudotumor. 47 hips with pseudotumors were evaluated to be similar in size and grade in the repeated MRI. In 10 hips the pseudotumor was smaller in the repeated MARS-MRI. However, in 24 hips the pseudotumor had increased in size and in 4 of these the grade of the pseudotumor had also increased.

We reviewed postoperative OHS questionnaire data regarding 1,252 hips. Median OHS score was 43 (excellent outcome) and mean was 40 (good outcome). The majority, 729 (58%), of hips had excellent functional outcome, while 228 (18%) hips had a good patient-reported outcome. Further, 136 (11%) hips had a moderate functional outcome and 159 (13%) hips had a poor functional outcome.

Discussion

We found that WB Cr and Co levels decreased during median 10-year follow-up. 14-year survival was 85% for any reason for revision, and 69% for metal-related adverse events.

Our previous mid-term metal ion report was based on 319 unilateral ReCap-Magnum patients who were operated on in Turku University Hospital with a mean follow-up time of 7 years. A decrease in both WB Cr and Co ion levels with time was noted. Metal ion levels stayed mostly below the SUL if the values were initially low. The same trend was seen in 61 bilateral ReCap-Magnum patients with repeated measurements (7,8).

In the current study we have included all ReCap-M2a-Magnum THA patients operated on in the Hospital District of Southwest Finland. 859 unilateral and 132 bilateral ReCap-Magnum

patients with at least 2 metal ion level measurements and a median follow-up of 10 years demonstrated a decreasing trend in WB metal ion levels. Compared with the previous studies, our results demonstrate that the decrease in WB Cr and Co ion levels continues further in long-term follow-up (7,8). The number of patients with metal ion levels above the SUL did not increase during this longer follow-up period either. This is the largest study of repeated WB Cr and Co ion measurements of ReCap-Magnum THA patients that we are aware of.

The decreasing trend of metal-ion levels in well-functioning MoM hip patients has been reported also in other studies (12,16,17). In some implants a longer "run-in" phase, or phase of elevated metal ion release, has been observed. Sangaletti et al. found an increase of Co but not Cr ions from 5 to 10 years after implantation in a cohort of 36 mm Pinnacle-Ultamet MoM THA patients (18). Bernstein et al. reported a "run-in" period that peaked 4 years after implantation but declined thereafter and stayed steady until 10 years from the operation. However, their implants were 2nd-generation Metasul implants and thus not directly comparable to our study (19). It has been suggested that beyond 10 years from surgery the appropriate follow-up interval for MoM hip resurfacing patients could be 5 years (4). Based on our data and these previous data we suggest that 5-year measurement interval for asymptomatic ReCap-M2a-Magnum patients may be sufficient in the future.

Our overall 10-year survival of 88% is in line with previous literature. In our previous report the 5-year survival of ReCap-M2a-Magnum THA was 93% for any reason for revision. 104 (8%) of 1,329 hips were revised after a median follow-up of 5 years, and ARMD was reported as the reason for revision in 33 hips (32% of revisions) (9). In the present study 197 hips (12%) had been revised and ARMD was the reason for revision in 50% of these reoperations at median of 10 years from the implantation. Lainiala et al. reported almost similar 10-year survival of 89% for ReCap-M2a-Magnum THA in a Finnish population (20). Both AOANJRR and FAR report a revision rate of 11% at 10 years and FAR has a 15-year revision rate of 14% for ReCap-M2a-Magnum THA (6,21). In a study based on the Finnish Arthroplasty Register the 10-year survivorship was 88% (22).

The Kaplan–Meier survival for metal-related adverse events was a proxy for functional failure of ReCap-M2a-Magnum THA implants. Even though the amount of metal-related adverse events was rather high, patients were mainly satisfied with their hip and revision surgery was relatively rarely required. Indications for revision surgery after MoM THA are severe symptoms caused by ARMD, large pseudotumors with tissue necrosis, and high WB metal ions (23). The revision decision is multifactorial, even though early revision may be associated with improved outcome (1).

We found pseudotumors in 338 hips (60%) of 563 hips undergoing MARS-MRI. However, MARS-MRI was performed only on patients with metal ions above 5 ppb, and/or those patients with a symptomatic hip. Therefore, the relatively high proportion of patients with a pseudotumor in MARS-MRI does not represent the whole cohort. Nevertheless, 338 of 1,624 hips (21% of all hips) were diagnosed with a pseudotumor, and the true incidence of pseudotumors would probably be higher. For preference, we would have had MARS-MRI images of all the hips. On the other hand, patients reported mainly good to excellent OHS scores postoperatively, suggesting that a substantial number of pseudotumors were asymptomatic. Similarly, Borgwardt et al. reported good to excellent functional outcomes up to 7 years after ReCap-M2a-Magnum THA implantation (24). In our study, repeated MARS-MRI images were normal most of the time if the initial MARS-MRI was considered normal, and the grade of the pseudotumors rarely changed. Reito et al. have previously reported similar findings in their study of 154 ASR patients (25). It has been suggested that routine MARS-MRI imaging after 10 years of MoM hip implantation might not be beneficial (4).

Female sex was associated with an increased revision risk and also an increased risk of metal-related adverse events. It has also been stated previously that female patients have a higher revision rate associated with MoM THA implants than men, even with the same head size (1). Cup retroversion was associated with a higher incidence of metal-related adverse events and higher revision rate in unilateral patients in the current study. High inclination angle was associated with an increased risk of metal-related adverse events in unilateral implants. Cup malposition in ReCap-M2a-Magnum THA patients has also been associated with elevated metal ion levels in an earlier publication (26). The ability to tolerate implant malposition is clearly decreased using the ReCap-Magnum device, which is a major weakness.

Our study has several limitations. First, the study setting was retrospective. Our results may be prone to selection bias. The worst ARMD hips were revised relatively early on, and therefore they did not undergo repeated metal ion measurements. Many of these revised patients would probably have had elevated whole-blood metal ion levels without the early revision to conventional THA. Also, some of the patients were reoperated on early due to fracture or infection and were not involved in metal ion measurements. MARS-MRI was performed only on patients with elevated metal ions above 5 ppb, or a symptomatic hip. Even though the angle measurements were performed using a standardized method, the intraclass correlation was not separately assessed. Further, our findings are implant specific, and not generalizable to other MoM THA brands.

In conclusion, WB Cr and Co ion levels decreased in median 10-year follow-up in the largest ReCap-Magnum series of repeated measurements we are aware of. Based on our findings, we suggest that after 10 years from the implantation the appropriate measurement interval for asymptomatic ReCap-M2a-Magnum THA patients might be longer, e.g., 5 years in the future. The amount of metal-related adverse events was relatively high, but patient satisfaction was acceptable.

KTM, MV, and SP designed the study protocol and methods. KTM organized the systematic screening. MV analyzed the data and performed the statistics. All authors contributed to the writing and revision of the manuscript.

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