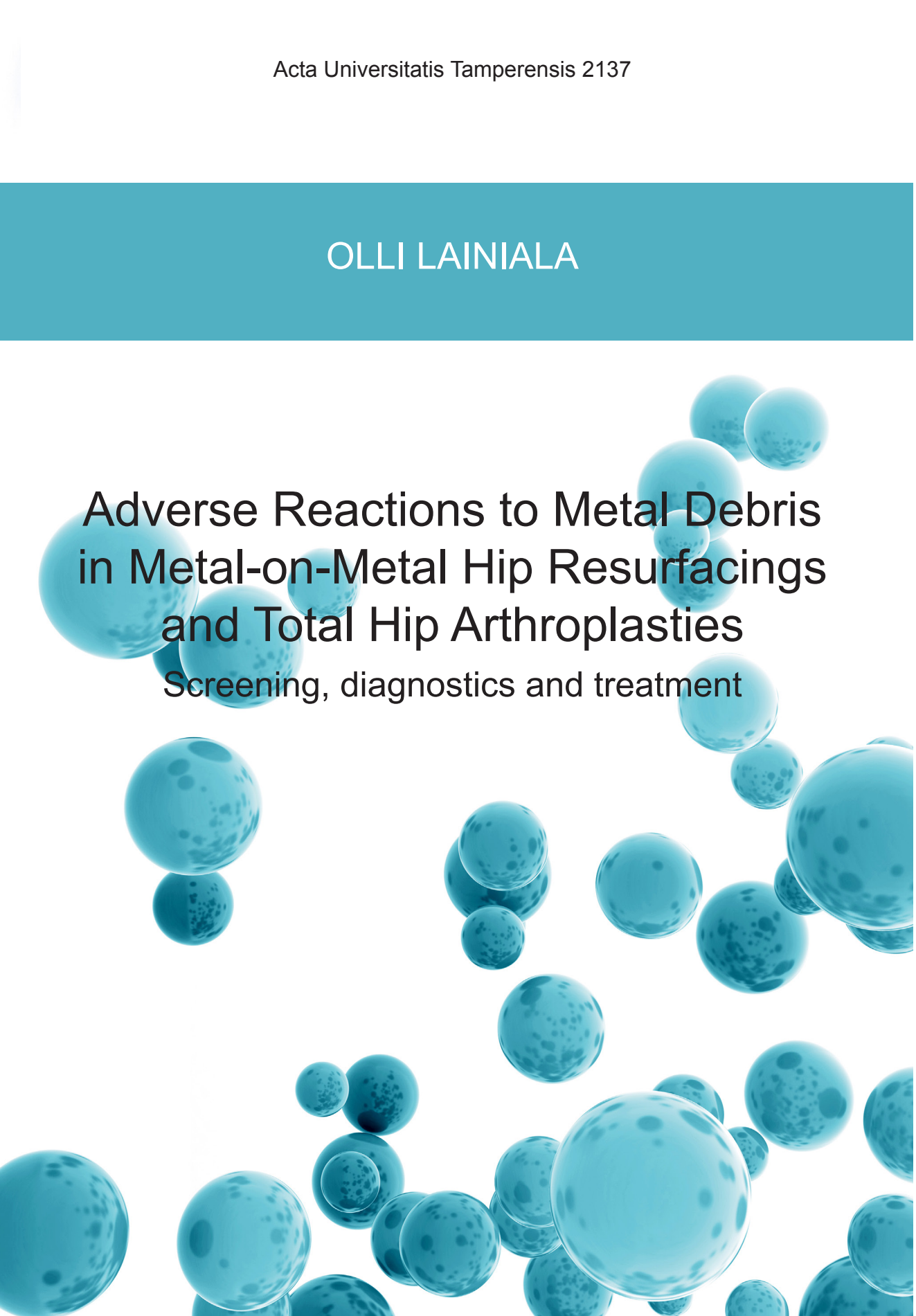


OLLI LAINIALA



Adverse Reactions to Metal Debris in Metal-on-Metal Hip Resurfacings and Total Hip Arthroplasties

Screening, diagnostics and treatment



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and Total Hip Arthroplasties

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ACADEMIC DISSERTATION

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the Board of the School of Medicine of the University of Tampere,
for public discussion in the small auditorium of building B,
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UNIVERSITY OF TAMPERE

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Contents

List of Original Communications	8
Abbreviations	9
Abstract.....	10
Tiivistelmä	12
1 Introduction	15
2 Review of the literature	17
2.1 Concept of hip replacement.....	17
2.2 History	18
2.2.1 Total hip arthroplasty and metal-on-metal bearings	18
2.2.2 Hip resurfacing	19
2.2.3 Emerging problems with metal-on-metal hips	20
2.3 Reasons and risk factors for failure.....	21
2.4 Adverse Reactions to Metal Debris	24
2.4.1 Histopathology.....	27
2.4.2 Risk factors for Adverse Reaction to Metal Debris	31
2.4.3 Risk factors for pseudotumors	32

2.4.4	Differential diagnosis	33
2.5	Systemic effects of implant metals	33
2.5.1	Risk for cancer	37
2.6	Screening protocols	38
2.7	Blood and serum metal ion concentrations	39
2.7.1	Rationale for blood Co and Cr measurements	39
2.7.2	Methods of measurement	39
2.7.3	Units of measurement	40
2.7.4	Normal versus elevated wear and metal ion levels.....	40
2.7.5	Effect of implant type on blood cobalt and chromium levels	41
2.7.6	Taper wear	42
2.7.7	Implant orientation	43
2.7.8	Other implant-related factors affecting blood cobalt and chromium.....	44
2.7.9	Patient-related factors affecting blood cobalt and chromium.....	45
2.8	Imaging of Adverse Reactions to Metal Debris.....	46
2.8.1	Imaging findings	46
2.8.2	Plain radiographs	47
2.8.3	Magnetic resonance imaging.....	48
2.8.4	Ultrasound	51

2.8.5	Computed tomography	52
2.8.6	Accuracy of cross-sectional imaging	53
2.8.7	When to image and to re-image?	54
2.9	Revision surgery of metal-on-metal hip	56
2.9.1	Indications	56
2.9.2	Revision procedure.....	57
2.9.3	Post-revision follow-up	58
2.9.4	Results of revision surgery	59
2.10	The current role of metal-on-metal hip replacements	63
2.10.1	Guidelines by authorities	63
2.10.2	MoM hip resurfacings	64
2.10.3	MoM total hip arthroplasties.....	65
2.10.4	Comparison to NICE criteria	66
3	Aims of the Study.....	67
4	Patients and methods.....	68
4.1	Patients.....	68
4.2	Methods.....	72
4.2.1	Primary surgeries and implants used	72
4.2.2	Screening protocol.....	73

4.2.3	Blood metal ion concentration measurements	73
4.2.4	Imaging.....	74
4.2.5	Revision surgery.....	76
4.2.6	Definition of Adverse Reaction to Metal Debris	77
4.2.7	Post-revision follow-up.....	78
4.3	Statistical methods	78
4.4	Ethical considerations	80
5	Results.....	81
5.1	Blood cobalt and chromium concentrations (Study I).....	81
5.2	MRI and ultrasound (Studies II and III).....	84
5.3	The effect of systematic screening (Study IV).....	87
5.4	Results of revisions for ARMD (Study V).....	90
6	Discussion	94
6.1	Blood metal ion concentrations.....	94
6.1.1	Limitations of the blood metal ion study	96
6.2	Imaging of pseudotumors.....	97
6.2.1	Limitations of the imaging studies.....	98
6.3	Effect of systematic screening	99
6.3.1	Screening of ARMD and World Health Organization criteria	100

6.3.2	Considerations about screening of ARMD.....	100
6.3.3	Limitations of the systematic screening study	102
6.4	Results of revision of metal-on-metal hips	102
6.4.1	Limitations of the revision result study.....	105
7	Conclusions and future prospects	107
8	Errata.....	109
9	Acknowledgements.....	110
10	References	112
11	Original publications.....	136

List of Original Communications

The thesis is based on the following original publications referred to in the text by their Roman numerals I to V.

I. Lainiala O, Moilanen T, Hart A, Huhtala H, Sabah S, Eskelinen A. Higher blood cobalt and chromium levels in patients with unilateral metal-on-metal total hip arthroplasties compared to hip resurfacings. *Journal of Arthroplasty*. In press. *Reproduced with kind permission from Elsevier.*

II. Lainiala O, Elo P, Reito A, Pajamäki J, Puolakka T, Eskelinen A. Comparison of extracapsular pseudotumors seen in magnetic resonance imaging and in revision surgery of 167 failed metal-on-metal hip replacements. *Acta Orthop*. 2014; 85 (5): 474-9. *Reproduced with kind permission from Acta Orthopaedica.*

III. Lainiala O, Elo P, Reito A, Pajamäki J, Puolakka T, Eskelinen A. Good sensitivity and specificity of ultrasound for detecting pseudotumors in 83 failed metal-on-metal hip replacements. *Acta Orthop*. 2015; 86 (3): 339-44. *Reproduced with kind permission from Acta Orthopaedica.*

IV. Lainiala O, Eskelinen A, Elo P, Puolakka T, Korhonen J, Moilanen T. Adverse reaction to metal debris is more common in patients following MoM total hip replacement with a 36 mm femoral head than previously thought: results from a modern MoM follow-up programme. *Bone Joint J*. 2014; 96-B (12): 1610-7. *Unedited, pre-publication version of the manuscript published in The Bone Joint Journal. Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery.*

V. Lainiala O, Reito A, Elo P, Pajamäki J, Puolakka T, Eskelinen A. Revision of Metal-on-Metal Hip Prosthesis Results in Marked Reduction of Blood Cobalt and Chromium Ion Concentration. *Clin Orthop Relat Res*. 2015; 473 (7): 2305-13. *Reproduced with kind permission from Springer Science and Business Media.*

Abbreviations

95% CI = 95% Confidence Interval

AAOS = American Academy of Orthopaedic Surgeons

ALVAL = Aseptic lymphocyte-dominated vasculitis-associated lesion

AOANJRR = Australian Orthopaedic Association National Joint Replacement Registry

ARMD = Adverse Reaction to Metal Debris

ASR = Articular Surface Replacement, Depuy Orthopaedics, Warsaw, IN, USA

BHR = Birmingham Hip Resurfacing, Smith & Nephew, Memphis, TN, USA

BMI = Body Mass Index

Co = Cobalt

CoC = Ceramic-on-Ceramic

CoCr = Cobalt-Chromium (alloy)

CoP = Ceramic-on-Polyethylene

Cr = Chromium

CT = Computed Tomography

FDA = Food and Drug Administration, United States

MHRA = Medicines and Healthcare products Regulatory Agency, UK

MoM = Metal-on-Metal

MoP = Metal-on-Polyethylene

MRI = Magnetic Resonance Imaging

NICE = National Institute for health and Care Excellence, UK

NJR = National Joint Registry, England and Wales

OA = Osteoarthritis

OHS = Oxford Hip Score

OR = Odds ratio

ppb = parts per billion

ROM = Range of Motion

SD = Standard Deviation

TGA = Therapeutic Goods Administration, Australia

THA = Total Hip Arthroplasty

Abstract

High hopes were placed on the third generation metal-on-metal (MoM) hip replacements, as they were considered to be an excellent option for young and physically active patients for whom the conventional metal-on-polyethylene (MoP) hip replacement was not durable enough. The problem with MoP replacements was the high rates of polyethylene wear and the osteolysis associated with wear debris. Over one million MoM hips were implanted in the 2000s. Unfortunately, higher than anticipated revision rates were reported for hip resurfacings in the Australian Orthopaedic Association National Joint Registry Annual Report 2007, in addition to several individual centers writing case reports about periprosthetic soft tissue abnormalities related to pain and implant failure. The term Adverse Reaction to Metal Debris (ARMD) was created to describe these soft tissue lesions related to the increased wear of metallic bearing surfaces and the inflammatory reaction to metal debris. Around the world, orthopaedic hospitals launched screening programs in order to detect these new types of abnormalities with the help of clinical examination, plain radiographs, whole blood cobalt (Co) and chromium (Cr) measurements and cross-sectional imaging.

The aim of this thesis is to evaluate the usefulness of diagnostic tools used to detect ARMD, and to investigate the effects of the systematic screening program and operative treatment policy at our institution. The aim of study I was to identify the MoM implant brands with a high percentage of elevated whole blood Co and Cr levels, along with the patient and implant-specific risk factors for elevated ion levels. In studies II and III, we sought to determine the sensitivity and specificity of magnetic resonance imaging (MRI) and ultrasound for detecting extracapsular pseudotumors, which are common ARMD-related findings. In study IV, we evaluated the effect of our systematic MoM screening program on the revision rate and number of ARMD cases detected in a cohort of Pinnacle (Depuy Orthopaedics, Warsaw, IN) MoM total hip arthroplasties (THA). Systematic screening of the Pinnacle cohort was launched in January 2012, and our aim was to evaluate the effect of screening by comparing pre- and post-screening statistics. In study V, we determined the effect of the revision surgery on the whole blood Co and Cr levels and hip function.

In study I, we found that elevated whole blood metal ion levels (>7 parts per billion, ppb) are more common in large head size MoM THA than in patients with resurfacing (17.4% vs 5.9%, $p<0.001$). In resurfacings, small femoral head size, high inclination and young age increased the risk for elevated ions, and in THAs the corresponding risk factors were female gender, large femoral head size and long time between surgery and ion measurement. In study II, we found sensitivity of 71% and specificity of 87% for MRI in detecting extracapsular pseudotumors. The sensitivity was significantly lower if more than one year had elapsed since imaging, which would implicate that over one-year-old MRI/ultrasound imaging should not be used to guide clinical decisions. In study III, ultrasound had a sensitivity of 83% and specificity of 92% in the trochanteric region, and 79% and 94% in the iliopsoas region, respectively. In study IV, the launch of the screening program revealed 29 new cases of ARMD decreasing the implant survival rate from 96% (95% confidence interval [95% CI], 95 to 98) to 86% (95% CI, 82 to 90) with only three cases found before the screening. In study V, we noticed a clear decreasing trend towards normal levels in blood Co and Cr levels after the revision of MoM resurfacings and THAs, although Cr remained elevated for several years in a few patients. The median Oxford Hip Score (OHS) improved from the preoperative value to the 1-year postoperative value in the unilateral resurfacing and THA groups.

Elevated whole blood metal ion levels are common among MoM hip resurfacings and THAs, and the risk factors for elevated metal ion levels are similar to those for revision surgery. Both MRI and ultrasound provide good accuracy for imaging extracapsular pseudotumors and, based on our results, neither is superior over the other. On the other hand, over one year old cross-sectional imaging should not be used in surgical planning. We observed that systematic screening of MoM hips with blood Co and Cr measurements and cross-sectional imaging reveals a vast number of hips with ARMD. However, it is hard to estimate the true significance of this finding, as the natural history of ARMD is unclear, and it is not certain which patients would benefit most from the surgical intervention and revision of a MoM hip replacement and which patients would benefit from a conservative approach. After all, even though the revision of a MoM implant was an effective procedure to diminish systemic metal ion burden virtually in all patients, many patients were left symptomatic and in some cases the postoperative situation was actually worse than the preoperative one. In future, it is important that the best possible treatments for various grades of ARMD lesions are determined and that stratified guidelines for treatment are created in order to ensure the best possible outcome.

Tiivistelmä

Kolmannen polven metalli-metalli-tekonivelille (metal-on-metal, MoM) asetettiin suuria odotuksia, ja niitä pidettiin erinomaisena vaihtoehtona etenkin nuorille ja aktiivisille potilaille, joille perinteiset metalli-polyetyyleeni-liukuparin omaavat lonkkatekonivelet eivät olleet riittävän pitkäikäinen vaihtoehto. Polyetyleenista valmistettu liukupinta kului usein liian nopeasti, ja sen pinnasta irronneet polyetyleenipartikkelit aiheuttivat osteolyysia lonkan luihin. 2000-luvun alusta lähtien lonkan nivelrikosta kärsiville potilaille on asennettu yli miljoonaa MoM-tekoniveltä. Nämä tekonivelet näyttivät aluksi lunastavan niihin kohdistuneet suuret odotukset, kunnes vuoden 2007 raportissaan Australian ortopediyhdistys ilmoitti yllättäen MoM-tekoniveliin liittyvän odottamattoman paljon uusintaleikkauksia, ja useat sairaalat alkoivat tehdä ilmoituksia lonkkaan ilmaantuvista pehmytkudosmassoista, joihin liittyy kipua ja mekaanista oireilua. Termiä metallireaktio (engl. ARMD, Adverse Reaction to Metal Debris) alettiin käyttää MoM-liukuparin kiihtyneeseen kulumiseen liittyvistä tulehduksellisista reaktioista lonkan ympäriskudoksissa. Kun yksi käytetyimmistä MoM-tekonivelmalleista vedettiin pois markkinoilta runsaiden ongelmien vuoksi, herättiin tilanteeseen ympäri maailmaa. Potilaita ryhdyttiin kutsumaan ylimääräisille tarkastuskäynneille, joissa heidän oireensa kartoitettiin, ja tarkemmat tutkimukset veren koboltti- (Co) ja kromi-mittauksin (Cr), sekä kuvantamisin röntgenillä, magneetilla ja ultraäänellä aloitettiin metallireaktioiden löytämiseksi.

Tämän väitöskirjatyön tavoitteena oli arvioida metallireaktion diagnostiikassa käytettävien menetelmien ja seuranta-protokollan luotettavuutta ja käyttökelpoisuutta sekä tutkia metallireaktion hoitona käytettävien uusintaleikkausten tuloksia Tekonivelsairaala Coxassa. Ensimmäisessä osatyössä tutkittiin kohonneille veren Co- ja Cr-pitoisuuksille altistavia implantteihin, leikkaustekniikkaan ja potilaskohtaisiin ominaisuuksiin liittyviä riskitekijöitä. Toisessa ja kolmannessa osatyössä tavoitteena oli määrittää magneetti- ja ultraäänikuvantamisen herkkyyks ja tarkkuus metallireaktioon liittyvien pehmytkudospseudotuumorien kuvantamisessa. Neljännen osatyön tavoitteena oli arvioida systemaattisen seurantaohjelman vaikutuksia havaittujen metallireaktioiden sekä uusintaleikkausten määrään Pinnacle-mallin (Depuy Orthopaedics) MoM-lonkan saaneita potilaita sisältävässä kohortissa.

Tämän kohortin systemaattinen seuranta aloitettiin vasta 2012, joten seurantaa edeltävää ja sen jälkeistä tilannetta vertaamalla arvioitiin seurannan merkitystä. Viidennessä osatyössä arvioitiin metallireaktion vuoksi tehtyjen lonkan uusintatekonivelleikkausten tuloksia, erityisesti MoM-tekonivelen uusintaleikkauksen vaikutusta veren metalli-ionipitoisuuksiin ja potilaan oireisiin.

Ensimmäisessä osatyössä havaittiin, että varrellisen suurinuppisen MoM-tekonivelen saaneilla potilailla on merkittävästi useammin kohonneita (>7 ppb) veren Co- ja Cr-pitoisuuksia kuin pinnoitetekonivelen saaneilla (17.4% vs 5.9%, $p<0.001$). Pinnotteen saaneilla potilailla riskiä kohonneille ioneille lisäsivät pieni komponentin koko, korkea kuppikomponentin kallistuskulma sekä potilaan nuori ikä, ja varrellisen kokotekonivelen saaneilla potilailla puolestaan naissukupuoli, suuri komponentin koko ja leikkauksesta kulunut aika. Toisessa osatyössä todettiin että magneettikuvantamisen herkkyys pseudotuumorien tunnistamisessa oli 71% ja tarkkuus 87%. Herkkyys oli merkittävästi huonompi, jos kuvantaminen oli tehty yli vuosi ennen uusintaleikkausta, minkä perusteella yli vuoden vanhoja kuvantamistutkimuksia ei tulisi käyttää kliinisen päätöksenteon tukena. Kolmannessa osatyössä todettiin että ultraäänien herkkyys pseudotuumorien löytämiseksi lonkan posterioriselta puolelta oli 83% ja tarkkuus 92%, ja anterioriselta puolelta vastaavasti 79% ja 94%. Neljännessä osatyössä havaittiin seurannan lisäävän uusintaleikkausten määrää, ja tekonivelen 9 vuoden kiinnipysyvyys (engl. survival) laski 23 kuukauden seurannan aikana arvosta 96% (95% luottamusväli, 95-98) arvoon 86% (95% luottamusväli 82-90). Tänä aikana havaittiin 29 uutta metallireaktiota, kun ennen seurantaa metallireaktioita oli havaittu ainoastaan kolmella potilaalla. Viidennessä osatyössä todettiin, että MoM-tekonivelen uusintaleikkauksen jälkeen kaikkien potilaiden veren Co- ja Cr-arvot laskivat, ja vain muutamilla Cr jäi koholle pidemmässä seurannassa. Vuoden seurannassa oirekyselypisteet (Oxford Hip Score) paranivat tilastollisesti merkitsevästi leikkausta edeltäneistä arvoista niillä, joilla uusintaleikkaus tehtiin vain toiseen lonkkaan.

Kohonneiden veren metalli-ionipitoisuuksien havaittiin olevan yleisiä erityisesti varrellisen suurinuppisen MoM-tekonivelen saaneilla potilailla, ja riskitekijät kohonneille pitoisuuksille ovat samoja kuin uusintaleikkauksen tunnetut riskitekijät. Kuvantamista käsittelevissä osatyöissä sekä magneetti- että ultraäänikuvantaminen olivat varsin luotettavia, eikä nykykirjallisuuden perusteella kumpaakaan voi nostaa yksiselitteisesti toisen yläpuolelle. Tuoreet kuvantamistutkimukset ovat tärkeitä pehmytkudosmuutosten arvioimiseksi, eikä päätösten tulisi perustua vuotta vanhempiin MRI- ja ultraäänikuviiin. Systemaattinen seuranta auttaa löytämään metallireaktioita, mutta koska oireettomien löydösten merkityksestä ja kehittymisestä

pitkän ajan seurannassa ei ole riittävästi tietoa, ei seurannan hyötyyn ja kustannustehokkuuteen voi vielä luotettavasti ottaa kantaa. Vaikka uusintaleikkaus poistikin tehokkaasti metalli-ionien lähteen, oli moni potilas uusintaleikkauksen jälkeenkin oireinen ja muutamat jopa oireisempia kuin ennen leikkausta. Nämä löydökset herättävät uusia tärkeitä jatkokysymyksiä: ketkä potilaat hyötyvät uusintaleikkauksesta, keiden kohdalla seuranta olisi parempi vaihtoehto, ja mitkä ovat ne vaikeaa kudostuhoa ennustavat tutkimuslöydökset, joiden perusteella oireettomalle potilaallekin kannattaa tehdä uusintaleikkaus? Tulevaisuudessa on tärkeää keskittyä arvioimaan eri hoitovaihtoehtojen hyötyjä ja haittoja, ja luomaan nykyistä yksilöllisemmin räätälöityjä hoito- ja seurantasuosituksia parhaan lopputuloksen saavuttamiseksi.

1 Introduction

Even though conventional metal-on-polyethylene (MoP) hips have performed well in elderly patients with osteoarthritis (OA) (Charnley 1972), traditional hip arthroplasty has not provided a long-term solution for young and active patients (Mäkela et al. 2011). After the development of two generations of hip replacements using metal-on-metal (MoM) bearing surfaces since the 1950s (McKee and Watson-Farrar 1966, Weber 1996), it was believed that the third generation hip replacement would be third time lucky. After promising initial results for third generation MoM hip resurfacings (McMinn et al. 1996, Daniel et al. 2004), both MoM hip resurfacings and stemmed total hip arthroplasties (THA) gained popularity around the world (Bozic et al. 2009, National Joint Registry [NJR] 2010).

Unfortunately, higher than anticipated failure rates were reported for certain MoM hip resurfacing and THA designs (Australian Orthopaedic Association National Joint Replacement Registry [AOANJRR] 2007, Depuy Orthopaedics 2010), and some manufacturers recalled some of their MoM implants (American Academy of Orthopaedic Surgeons [AAOS] 2012). At the same time, more and more papers were published about adverse cystic- and mass-like soft tissue reactions termed “pseudotumor” in the immediate vicinity of the hip with MoM articulation (Boardman et al. 2006, Gruber et al. 2007, Pandit et al. 2008). The term Adverse Reaction to Metal Debris (ARMD) (Langton et al. 2010) was established to describe these sterile and non-malignant lesions that include extracapsular soft tissue pseudotumors, macroscopic necrosis and metallosis. At the microscopic level, these lesions were described as aseptic lymphocytic vasculitis-associated lesion (ALVAL) and immunologic reaction towards the cobalt (Co) and chromium (Cr) particles from bearing surface wear (Willert et al. 2005).

Following the reports of unacceptably high failure rates and ARMD in MoM hips, several authorities published their guidelines for the screening of MoM hip resurfacings and THAs to help orthopaedic surgeons to identify those patients at risk of suffering a failure of their hip replacement (UK Medicines and Healthcare products Regulatory Agency [MHRA] 2012, US Food and Drug Administration [FDA] 2012, Health Canada 2012, Australian Therapeutic Goods Administration [TGA] 2012, Hannemann et al. 2013). All screening protocols include clinical

assessment of hip function, plain radiographs to detect potential implant loosening and osteolysis, blood or serum Co and Cr measurements to evaluate the rate of implant wear, and cross-sectional imaging with magnetic resonance imaging or ultrasound to detect possible periprosthetic soft tissue lesions.

There is, however, no clear consensus on how patients suffering from ARMD should be treated. A study that reported poor results for revisions of MoM hip resurfacings due to pseudotumors raised major concerns (Grammatopolous et al. 2009), and it was suggested that early revision of MoM implants would provide a better outcome (Sandiford et al. 2010, Skinner and Kay 2011). However, several longitudinal studies have shown only small changes in pseudotumors between two cross-sectional imagings (Almoussa et al. 2013, Ebreo et al. 2013, van der Weegen et al. 2013a, Reito et al. 2014b), which raise questions about the need for revision surgery in asymptomatic patients with ARMD. Diagnostic risk stratification and treatment algorithms have been published (Lombardi et al. 2012, Kwon et al. 2014) for MoM hips, but no study has investigated the outcome and cost-effectiveness of these algorithms.

2 Review of the literature

2.1 Concept of hip replacement

In conventional stemmed THA, the femoral head and proximal neck of the femoral bone are surgically removed. An artificial canal is created for the proximal medullary space and a femoral prosthesis comprising stem and head components is inserted into the canal. The acetabulum is enlarged with an instrument called a reamer, and a cup component is inserted. (Siopack and Jergesen 1995). Hip resurfacing differs from stemmed THA by the conservation of the femoral neck and head. In hip resurfacing, a cylindrical head cutter is used to shape the femoral head in order to fit the head surfacing component. The technique for inserting the acetabular component is similar to that used in stemmed THA. (McMinn et al. 1996, Figure 1). The acetabular component can be either modular, in which a separate liner with a bearing surface is inserted into a larger metal cup, or monoblock comprising a one piece shell with ultra-high molecular weight polyethylene (UHMWPE), ceramic or metal articulating surfaces (Young et al. 2002).

Two methods are used for the fixation of the hip replacement components: cemented and cementless. In cemented fixation, polymethyl methacrylate bone cement is used to attach the components to bone. In cementless fixation, the components are partially or completely coated with a porous surface, onto which the bone grows in order to provide fixation (so-called osseointegration). (Siopack and Jergesen 1995).

Because of the variety of bearing surface-couples and their different wear properties; advantages and disadvantages exist for joint replacements. Soft bearing couples include UHMWPE or the more wear resistant cross-linked polyethylene (XLPE) acetabular component, and a femoral component made of metal or ceramic. “Hard-on-hard” bearings include metal-on-metal (MoM), ceramic-on-ceramic (CoC) and ceramic-on-metal couples. Decreased wear is an advantage among hard bearing couples, but unfortunately fractures of ceramic components are seen and MoM bearings may be affected by ARMD. (Rajpura A et al. 2014).

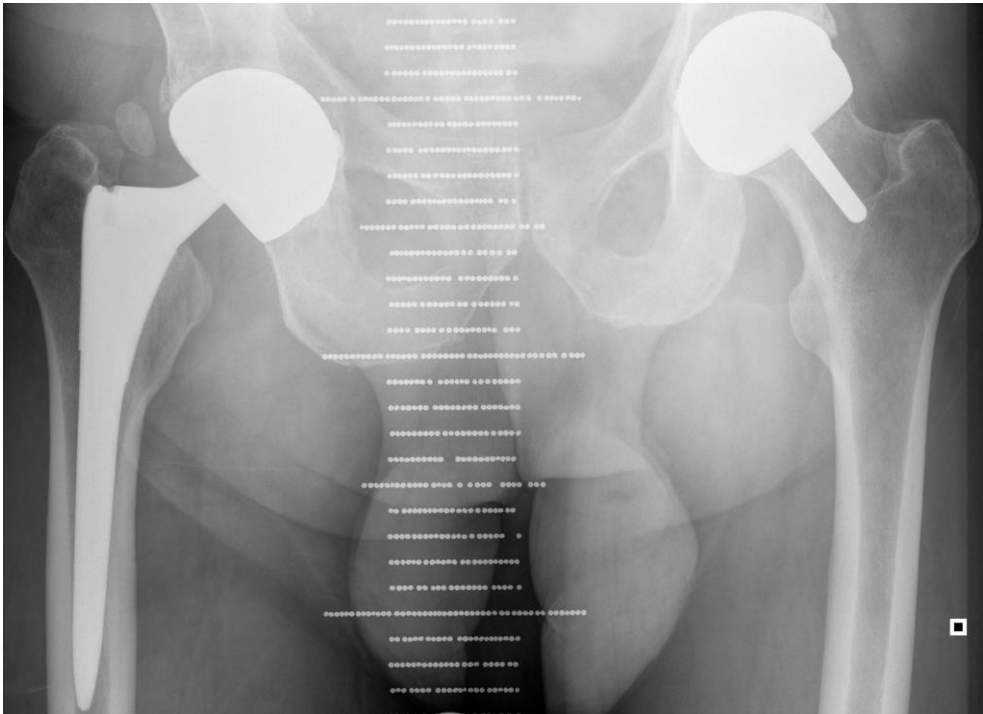


Figure 1. Radiograph of hip arthroplasty. The right hip (on the left of the image) demonstrates the concept of stemmed large head size total hip arthroplasty. The cup component is attached to the pelvic acetabulum, the femoral neck is cut, and the stem component is fitted in the medullary canal of the femur (thigh bone). The head component is attached to the stem. The left hip (on the right in the image) demonstrates hip resurfacing, in which the acetabulum is prepared accordingly, but the femoral neck is left uncut and the head is shaped to fit the resurfacing component.

2.2 History

2.2.1 Total hip arthroplasty and metal-on-metal bearings

The earliest attempts to treat osteoarthritis (OA) of the hip were excision arthroplasties in the late 1700s and interpositional arthroplasties in the early 1900s (Gomez and Morcuende 2005). In the 1920s and 1930s, Smith-Petersen experimented with mould arthroplasty, a concept in which a glass mould was placed over the femoral head to allow the cartilage surface to regenerate (Smith-Petersen 1948). The first hemiarthroplasties using rubber, ivory or acrylic heads were invented

between 1910 and 1920 (as cited in Judet and Judet 1950, Gomez and Morcuende 2005). The use of an acetabular component, which resulted in the invention of total hip arthroplasty, was introduced in 1938 (Wiles 2003). The first metallic hemiarthroplasty prosthesis with an intramedullary stem was first described in 1942 (Moore and Bohlman 2006). The first arthroplasties to be distributed around the world were developed by Thompson in 1950 (Thompson 1952), and by Moore and Bohlman in 1952 (Moore 1952, Gomez and Morcuende 2005).

MoM THA was introduced by McKee and Watson-Farrar in the early 1950s (McKee and Watson-Farrar 1966) and followed by Ring in the 1960s (Ring 1968). However, John Charnley had managed to develop a stainless steel-on-polyethylene THA design with superior clinical results (Charnley 1972). As the Charnley low friction MoP implant gained popularity, and component loosening was commonly seen in first generation MoM hips (Dandy and Theodorou 1975), the use of MoM implants decreased (Triclot 2011).

The higher need for component durability in young and active patients (Callaghan et al. 1998), as well as the particle disease seen in MoP hips resulting in osteolysis and component loosening (Harris 1994) increased interest in alternative bearing surfaces (Singh et al. 2013). A second generation MoM THA using a high carbon cobalt-chromium-alloy was developed in the early 1980s (Weber 1996) and promising early results were reported (Dorr et al. 1996). After the short-term success of MoM hip resurfacing, interest in large-diameter MoM THAs increased due to the advantages of lower wear (Dowson et al. 2004), lower risk for dislocation (Cuckler et al. 2004) and impingement (Crowninshield et al. 2004) compared with smaller head sizes (Lombardi Jr et al. 2011, Singh et al. 2013).

2.2.2 Hip resurfacing

The principles of hip resurfacings are based on the mould arthroplasty presented by Smith-Petersen in the 1920s, in which a glass mould was placed over the femoral head to facilitate the regeneration of cartilage (Smith-Petersen 1948). John Charnley developed the first actual hip resurfacings using Teflon bearing surfaces, but quickly abandoned the concept due to high wear, loosening and tissue reactions (Charnley 1961, Charnley 1966, Amstutz et al. 1998). In the 1960s and 1970s, several surgeons experimented with MoM and MoP resurfacing systems. Müller and Boltzy as well as Gerard used MoM resurfacing systems, but these were abandoned due to aseptic loosening (as cited in Amstutz et al. 1998). In the 1970s, Paltrinieri and Trentani used

a metal head and polyethylene cup, a development followed by several other surgeons. (as cited in Amstutz et al. 1998).

In the 1980s, Wagner among others used a hip resurfacing design with a metal head and plastic socket (Wagner and Wagner 1996). Although the early results of these designs were promising (Lapp and Schatzker 1981, Howie et al. 1990), high revision rates were seen in longer follow-up (Head 1982, Howie et al. 1990), which led largely to the abandonment of these hip resurfacing designs (Amstutz et al. 1998). Despite the problems, hip resurfacing was seen as an attractive concept especially for younger patients for whom the durability of conventional hip arthroplasty was not sufficient (Amstutz et al. 1998, McMinn 2003). Eventually, Derrick McMinn developed what were to be the first third generation MoM hip resurfacing designs, “McMinn Resurfacing” manufactured by Corin (Cirencester, UK) and Birmingham Hip Resurfacing (BHR), manufactured by Midlands Medical Technology (McMinn et al. 1996, McMinn 2003). Promising early results were presented by McMinn’s center (McMinn 2003, Daniel et al. 2004, Treacy et al. 2005). The results from their center were, however, criticized due to the exclusion of the subgroup of patients with unsatisfactory results (Cutts and Carter 2006). Promising results for the BHR were also published a few years later by an independent center (Steffen et al. 2008).

The upsides of resurfacing with a MoM bearing surface were argued to be greatly reduced bearing surface wear, conservation of the femoral neck, lower risk of dislocation due to a large head size and easier revision surgery (Amstutz et al. 1998, McMinn 2003).

2.2.3 Emerging problems with metal-on-metal hips

The MoM bearing quickly gained popularity. For example, in 2009, MoM bearings accounted for approximately 35% of the THAs in the United States of America (Bozic et al. 2009). In England and Wales, MoM THAs accounted for 11% in 2008 (Smith et al. 2012b), and hip resurfacings accounted for 6% in 2009 (NJR 2010). In 2012, it was estimated that more than one million hip implants using MoM bearing couples had been implanted worldwide (AAOS 2012).

Abnormal soft tissue reactions had already been described in the first generation MoM hips (Evans et al. 1974, Jones et al. 1975), and as the new generations of MoM hips became widely used, reports about macroscopic soft tissue abnormalities (Boardman et al. 2006, Gruber et al. 2007, Pandit et al. 2008, Toms et al. 2008) and histologic reactions (Willert et al. 2005, Davies et al. 2005) due to metal debris

became more frequent. In addition to the concerns raised by individual surgeons, Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) expressed their concern in their 2007 Annual Report that stated that Articular Surface Replacement (ASR) (Depuy Orthopaedics) and Durom (Zimmer, Warsaw, IN, USA) resurfacings had higher than anticipated revision rates (AOANJRR 2007). It was not until 2010, however, that the actual controversy about MoM hip replacements began. In April 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) UK published a medical device alert concerning wear related soft tissue reactions in MoM hips (MHRA 2010). In August 2010, Depuy Orthopaedics voluntarily recalled their ASR hip implants after they had received unpublished information from the National Joint Registry (NJR) of England and Wales that showed a 5-year revision rate of 12% for ASR hip resurfacing and 13% for ASR XL THA (Depuy Orthopaedics 2010). The company was accused of hiding information on the poor performance of their product (Cohen 2011), and along with a large amount of publicity came also the lawsuits (Dyer 2010). In addition, two other MoM designs were recalled: Durom by Zimmer in 2008 and R3 by Smith & Nephew (Memphis, TN, USA) in 2012 (FDA 2014).

2.3 Reasons and risk factors for failure

Many of the reasons for failure in MoM hip resurfacings and THAs are similar to those seen in hip replacements with other bearing surfaces. However, the majority of the cases of ARMD are seen in MoM hips. In MoM resurfacings, early periprosthetic femoral neck fractures are occasionally seen, as the femoral neck is conserved. (AOANJRR 2014, NJR 2014).

2.3.1.1 Resurfacings

The most common reasons for revisions are listed in the Table 1. MoM hip resurfacings were significantly more frequently revised for ARMD, aseptic loosening, lysis, pain, periprosthetic fracture, implant wear, malalignment, implant fracture and head-socket size mismatch compared with a cohort of all hip replacements in the NJR registry. Dislocation and infection were less common in hip resurfacings. (NJR 2014).

Table 1. The reasons for failure of hip resurfacings and metal-on-metal total hip arthroplasties in the National Joint Registry (NJR) of England and Wales and the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR).

Hip Resurfacings		Total Hip Arthroplasty	
NJR	AOANJRR	NJR	AOANJRR
Pain 26%	Loosening 33%	ARMD 28%	ARMD 40%
ARMD 20%	ARMD 24%	Pain 22%	Loosening 28%
Loosening 15%	Fracture 21%	Loosening 14%	Infection 11%
Fracture 7%	Infection 6%	Infection 6%	Dislocation 6%
Lysis 5%	Pain 6%	Dislocation 4%	Fracture 6%

In NJR data, the number of revisions is expressed as revisions/1000 patient years at risk. To allow for comparison, these values were converted into percentages by dividing the number of revisions by reason by the number of revisions for all reasons combined. Loosening refers to aseptic loosening and fracture to periprosthetic fracture. The NJR started registering ARMD as a mode of failure in 2008 and the Australian registry in 2009.

Large studies that included the multivariable analysis of registry data reported a higher risk for revision in female patients with resurfacing compared with men (Smith et al. 2012a, Canadian Arthroplasty Society 2013). In the AOANJRR 2014 data, females with hip resurfacing due to OA had a higher revision rate than men, and worse results were achieved from revisions due to indications other than OA (AOANJRR 2014). Also, a recent meta-analysis showed a 2.5 times higher risk for revision of hip resurfacing in women compared with men without stratification for implant size (Haughom et al. 2015). Female gender has been described as an independent risk factor in several other studies (Coulter et al. 2012, Murray et al. 2012, Matharu et al. 2013). In hip resurfacings, more revisions are performed on patients with small component size (AOANJRR 2014), and an increased revision risk has been observed for small component head size in multivariable analysis as well (Holland et al. 2012, Murray et al. 2012, Smith et al. 2012a, Canadian Arthroplasty Society 2013, Matharu et al. 2013). Although gender and implant size are clearly related variables, as women usually need smaller implants, there is no clear consensus as to which is the more significant one (Amstutz et al. 2011, Holland et al. 2012, Murray et al. 2012, Van Der Straeten et al. 2013, Matharu et al. 2013). Other factors in addition to small component size that have been presented as possible reasons for the inferior results of resurfacings in women are a higher incidence of metal allergy, ligamentous laxity, differences in hip anatomy and a higher prevalence of developmental dysplasia (Haughom et al. 2015).

Contradicting results on the effects of age have been published. In NJR data, age did not predict revision in hip resurfacings (Smith et al. 2012a), whereas in Australian

data older age was a risk factor in men, but not among women (AOANJRR 2014). In the Canadian data, age was not associated with risk for revision (Canadian Arthroplasty Society 2013). The Canadian Arthroplasty Society stated that diagnosis of childhood hip problems is associated with a higher risk for revision in resurfacings (Canadian Arthroplasty Society 2013) and also Australian data showed a worse outcome for hip resurfacings performed with indications other than OA (AOANJRR 2014).

Clear brand-specific differences are seen in revision rates. In the AOANJRR 2014 Annual Report, the 5-year revision rate ranges from 3% to 17%; ASR having almost twice as high a 7-year revision rate compared with the second worst performing implant (AOANJRR 2014). Also, in the NJR 2014 Annual Report the ASR has clearly higher revision rates (7-year revision rate 23%) compared with all MoM resurfacings pooled (7-year revision rate 9%). In two large studies based on NJR and Canadian arthroplasty registry data, several MoM resurfacing designs including ASR, Conserve plus (Wright Medical, Memphis, TN, USA), Cormet (Corin Group, Cirencester, UK), Durom and ReCap (Biomet, Warsaw, IN, USA) were associated with a higher risk for revision compared with Birmingham Hip Resurfacing (Jameson et al. 2012, Canadian Arthroplasty Society 2013). Design features attributed to a higher risk of failure in MoM hip resurfacings are sub-hemispherical design resulting in a reduced arc of cover as well as small radial clearance (Fisher 2011). A possible factor that could have increased the brand-specific differences in terms of revision rate is the psychological effect of implant recalls. The recalls may have lowered the revision threshold in certain MoM brands and for the whole MoM hip replacement class. Only one study so far has addressed this issue. In that study, pre-recall and post-recall Oxford Hip Scores (OHS) and cup inclinations were similar. However, the percentage of the revisions of the recalled ASR replacement system from all the revised MoM replacements increased from 28% to 36%. (Tibrewal 2014).

2.3.1.2 Total Hip Arthroplasties

The most common reasons for revision are presented in Table 1. The rates for revisions due to ARMD, pain, infection, malalignment, lysis, implant wear and head-socket size mismatch were higher compared with the whole NJR hip arthroplasty cohort. There was no difference in the revision rate for aseptic loosening, dislocation and for periprosthetic or implant fracture. (NJR 2014). In AOANJRR data, a significantly higher number of revisions due to loosening, ARMD and infection were seen compared to MoP bearing surfaces. However, the infection diagnosis in

AOANJRR is not confirmed by linking with microbiological data. As a result, ARMD misdiagnosed as infection may cause bias in this figure (Mikhael et al. 2009). (AOANJRR 2014).

In MoM THAs, AOANJRR reported a higher revision rate for females, which was also seen in multivariable analyses based on NJR data (Smith et al. 2012c) and data on 1440 MoM THAs from a single center (Lombardi Jr et al. 2015). Conversely to hip resurfacings, the large component size used in MoM THAs increases the risk of revision (Smith et al. 2012c, AOANJRR 2014). In NJR data, young age was a risk factor for women, but not for men (Smith et al. 2012c). However, in Australian data, young age was a risk factor for failure in both genders (AOANJRR 2014). Young age has also been described as an independent risk factor in a multivariable analysis from a single center study (Lombardi Jr et al. 2015).

Clear brand-specific differences are also seen in MoM THAs. In the AOANJRR 2014 Annual Report, the 5-year revision rate ranges from 4% to 24% in MoM THAs with ASR having almost twice as high a 7-year revision rate compared with the second worst performing implant (AOANJRR 2014). Furthermore, in the NJR 2014 Annual Report, the ASR has clearly a higher revision rate (7-year revision rate 37% for ASR XL THA) compared with the pooled data of all MoM THAs (7-year revision rate 13%) (NJR 2014). As was the case with hip resurfacings, implant recalls may have affected the revision rates of certain MoM THA brands.

2.4 Adverse Reactions to Metal Debris

As was the case with the first MoM hip arthroplasty designs, the problems associated with wear debris were described decades ago. Macroscopic intracapsular metallosis, necrosis, and large periprosthetic fluid collections (Jones et al. 1975) along with the histology including macrophages, lymphocytes, giant cells, vasculitis, fibrin and necrosis (Evans et al. 1974) were all described in the 1970s. A few case reports about periprosthetic fluid-collections or masses were published in the beginning of this century (Madan et al. 2000, Boardman et al. 2006). The term aseptic lymphocyte-dominated vasculitis associated lesion (ALVAL) was established to describe the histological findings seen in a study performed on second-generation MoM hips (Willert et al. 2005). However, large-scale problems with MoM hips were not acknowledged until 2006-2008, when an increasing number of reports about soft tissue abnormalities were published (Boardman et al. 2006, Gruber et al. 2007, Pandit

et al. 2008). An umbrella term Adverse Reaction to Metal Debris (ARMD) was established to describe failures associated with pain, large sterile periprosthetic effusions and/or macroscopic necrosis, metallosis and osteolysis (Langton et al. 2010). In addition, the acronym adverse local tissue reaction (ALTR) is sometimes used to describe these reactions, although ALTR also encompasses other reactions than those related to metal debris (Engh et al. 2010, Lohmann et al. 2014).

The term pseudotumor is used to describe the cystic or solid periprosthetic masses associated with MoM hips that are neither infective nor malignant (Pandit et al. 2008). Various minimum size definitions such as ≥ 5 cm (Mokka J et al. 2013), ≥ 2 cm (Bosker et al. 2012) or ≥ 1 cm (Williams et al. 2011) have all been suggested for pseudotumor-like abnormalities. There is no consensus on the exact definition of a pseudotumor. Pain, swelling, sensation of pressure and clicking are the most commonly described symptoms associated with pseudotumors. However, pseudotumors are often asymptomatic (Bosker et al. 2015). Pseudotumors are usually less than 10 cm in diameter with a median of approximately 4 cm to 6 cm (Chang et al. 2013, Bosker et al. 2015) and less than 120 cm³ in volume with a median of approximately 30 cm³ to 60 cm³ (Williams et al. 2011, Bayley et al. 2015). However, extremely large pseudotumors that violate adjacent structures have been described as well (Fu et al. 2015).

The prevalence of ARMD has been widely studied. However, as there is no unambiguous definition for ARMD, several imaging studies have considered a pseudotumor as being equal to ARMD; whereas revision-based prevalence studies require histological and/or macroscopic evidence of ARMD. If only studies from primary centers (unselected patient material) that have implemented systematic imaging are taken into account, the prevalence of pseudotumors is 4% to 28% in hip resurfacings (Kwon et al. 2011, Bisschop et al. 2013, Scaglione et al. 2015) and 9% to 59% in MoM THAs (Hasegawa et al. 2013, Mokka et al. 2013, Hwang et al. 2014, Bosker et al. 2015, Bayley et al. 2015). However, these studies included variable definitions of pseudotumors and not all of them are directly comparable with each other. In those studies that did not apply imaging and therefore only classify revision confirmed cases as ARMD, the figures are naturally much lower, ranging from 0.1% to 5.0% (Engh et al. 2010, Canadian Hip Resurfacing Study 2011, Sugano et al. 2014, AOANJRR. 2014).

Pseudotumors have been attributed to high acetabular inclination (Chang et al. 2013), increased wear of the MoM hip (Kwon et al. 2010) and elevated blood Co and Cr concentrations (Chang et al. 2013, Bosker et al. 2015), although pseudotumors are also seen in low-wearing, well-positioned hips (Matthies et al. 2012). It has been

suggested that pain, subluxation and swelling predict the presence of a pseudotumor (Mokka et al. 2013, Bosker et al. 2015), but there are also several reports that show a similar prevalence of pseudotumors both in symptomatic and asymptomatic patients (Hart et al. 2012, Fehring et al. 2014). Some authors have suggested that the pseudotumors associated with painful MoM hips are larger (Hart et al. 2012, Bisschop et al. 2013), but contradicting results have been presented as well (Fehring et al. 2014). Larger pseudotumor size has also been associated with high blood metal ion levels (Chang et al. 2013).

There are several pseudotumor grading systems that take into account the contents of the pseudotumors (fluid-filled/cystic, mixed or solid) and/or size (Anderson et al. 2011, Hart et al. 2012, Hauptfleisch et al. 2012). The clinical significance of the type of pseudotumor is still an unanswered question. Many of the pseudotumors in recent studies have been either cystic or mixed, whereas solid pseudotumors are less common (Hart et al. 2012, Hasegawa et al. 2013, Nishii et al. 2014, Muraoka et al. 2014, Bayley et al. 2015). Based on a large number of cystic pseudotumors among asymptomatic patients, it has been suggested that cystic pseudotumors may just be the consequence of the weakness of the joint capsule due to capsulotomy (Sabah et al. 2011, Madanat et al. 2015), and less clinical importance should be placed on cystic pseudotumors (Hart et al. 2012).

Other common abnormal findings in MoM hips include osteolysis (Randelli et al. 2013), cheese-like necrotic tissue (Natu et al. 2012), synovitis (Liddle et al. 2013), metallosis (Daniel et al. 2012) and the staining of the synovial fluid by Co and Cr debris (Daniel et al. 2012, Halim et al. 2014).

Few studies have described the prevalence of osteolysis. In small head size MoM THAs imaged with plain radiographs, femoral osteolysis was seen in 10% and acetabular osteolysis in 0% of hips, which is similar to figures in ceramic-on-polyethylene (CoP) hips (Lubbeke et al. 2014). In a mixed cohort of symptomatic patients with resurfacings and MoM THAs, computed tomography (CT) showed osteolysis in 30% of hips (Robinson et al. 2014). Another cohort of symptomatic patients imaged with magnetic resonance imaging (MRI) demonstrated osteolysis in 10% of resurfacings and in 24% of large diameter THAs (Hayter et al. 2012a). In cohorts of large diameter head MoM THAs imaged with MRI, prevalences of 7% and 23% were reported (Chang et al. 2013, Fehring et al. 2014). Meta-analysis including high quality randomized controlled studies stated that the incidence of osteolysis is 4% in CoC and 18% in MoP hips (Hu et al. 2015). However, based on the scarcity of studies designed to specifically report the prevalence of osteolysis in

unselected cohorts of MoM hips, it is hard to reliably compare these rates to those of MoM hips.

Muscle atrophy has been described in 23% to 90% of MoM hips with typically gluteal muscles involved (Toms et al. 2008, Sabah et al. 2011, Hayter et al. 2012a, Fox et al. 2014, Berber et al. 2015). Muscle atrophy is described as being associated with female gender and elevated blood metal ion levels (Berber et al. 2015). It has been suggested that the muscle damage may be related to surgical approach, and not directly to ARMD (Fox et al. 2014).

Typical symptoms of ARMD include pain in the groin or buttocks, swelling around the hip, reduced exercise tolerance, limping, limited range of motion (ROM), local nerve palsy and noise from the hip (squeaking, clanking) (Skinner and Kay 2011, FDA 2012, Health Canada 2012). In a single center study involving stemmed large-diameter head MoM THAs, 3% of patients had experienced swelling, 25% groin pain and 23% clicking sensations (Bosker et al. 2015). It is not clear if MoM hips are more often related to postoperative persistent pain compared to MoP THAs (Bartelt et al. 2010, Lavigne et al. 2011b). The prevalence of persistent groin pain has been reported to be 15% to 18% among MoM hip resurfacings at 1-2 years after surgery (Bin Nasser et al. 2010, Bartelt et al. 2010, Lavigne et al. 2011b), with pain being more common in younger patients (Bartelt et al. 2010) and female patients (Bin Nasser et al. 2010). The prevalence of persistent groin pain in MoM THAs has been reported to be 10% to 35% (Lavigne et al. 2011b, Lardanchet et al. 2012, Saragaglia et al. 2015). The majority of patients in previously mentioned studies reported only mild pain (Bartelt et al. 2010, Lavigne et al. 2011b, Lardanchet et al. 2012). A prevalence of 35% for pain in other areas of the hip region (Smeekes et al. 2015) and prevalences of 49% for pain and 11% for mechanical symptoms (grinding, clicking, etc) in patients with MoM THAs have been reported (Chang et al. 2012). Whole blood metal ion levels have been reported to be higher in patients experiencing pain both in resurfacings and MoM THAs (Hart et al. 2009a, Lardanchet et al. 2012, Smeekes et al. 2015).

2.4.1 Histopathology

Mild foreign-body reactions were described among classic first generation McKee-Farrar, Huggler and Muller type MoM hips. In modern MoM hips, the term ALVAL was established to describe typical lymphocyte dominated histological reaction. (Willert et al. 2005). Several other authors have further described histological changes

(Davies et al. 2005, Pandit et al. 2008, Campbell et al. 2010, Natu et al. 2012). Although perivascular lymphocytic infiltration is typically seen in MoM hips, it is not a pathognomonic phenomenon, as infiltrates are also seen in non-MoM hips and knee replacements (Ng et al. 2011, Fujishiro et al. 2011).

Initially, ARMD was described to be hypersensitivity reactions (Willert et al. 2005), but further studies have suggested that lymphocytic hypersensitivity reaction is not the only mechanism for ARMD. T-cell-mediated type IV delayed hypersensitivity reaction (adaptive immunity, lymphocyte-dominated) and foreign body reaction (non-specific immunity, macrophage- and giant cell-dominated granulomatous reaction) have been suggested as the two main types of histological reactions seen to be associated with ARMD (Grammatopoulos et al. 2013, Bauer et al. 2014), with some of the tissues retrieved from MoM hips expressing both characteristics and sometimes referred to as “mixed type” (Berstock et al. 2014). Several classifications for histologic findings have been presented (Davies et al. 2005, Campbell et al. 2010, Natu et al. 2012, Grammatopoulos et al. 2013). The most used scoring system, the ALVAL score (Campbell et al. 2010), is used to describe three histological findings seen in MoM hips: degree of abnormality in synovial lining (scored 0-3), number of lymphocytes and macrophages (0-4), and degree of tissue organization (0-3). The maximum total score is 10, indicating severe ALVAL, whereas a total score of 0 to 4 represents a mild reaction. Figure 2. describes two histopathological images, one with high ALVAL score and one with low ALVAL score. Other features commonly described are tissue necrosis (Davies et al. 2005), thickness of lymphocytic cuff, type of lymphocytic infiltrate, histiocytes and the metal particle load (Natu et al. 2012).

In a hypersensitivity-type reaction, typical findings are diffuse perivascular T- and B- lymphocytic infiltration, plasma cells, disruption of periprosthetic tissue, necrosis, high endothelial venules, fibrin accumulation, few macrophages and sometimes eosinophiles (Willert et al. 2005, Bauer et al. 2014). Metal ions accumulating in the hip joint form complexes with proteins and activate Cd4+ and Cd8+ T-lymphocytes (Hallab and Jacobs 2009), leading to macrophage recruitment (Grammatopoulos et al. 2013). Lymphoid aggregates are sometimes present (Mittal et al. 2013). Diffuse chronic inflammation is typically T-lymphocyte-dominated, whereas lymphoid aggregates usually include both B- and T-cells (Mahendra et al. 2009, Natu et al. 2012, Mittal et al. 2013). Large numbers of macrophages are seldom seen along with large lymphocytic aggregations (Campbell et al. 2010).

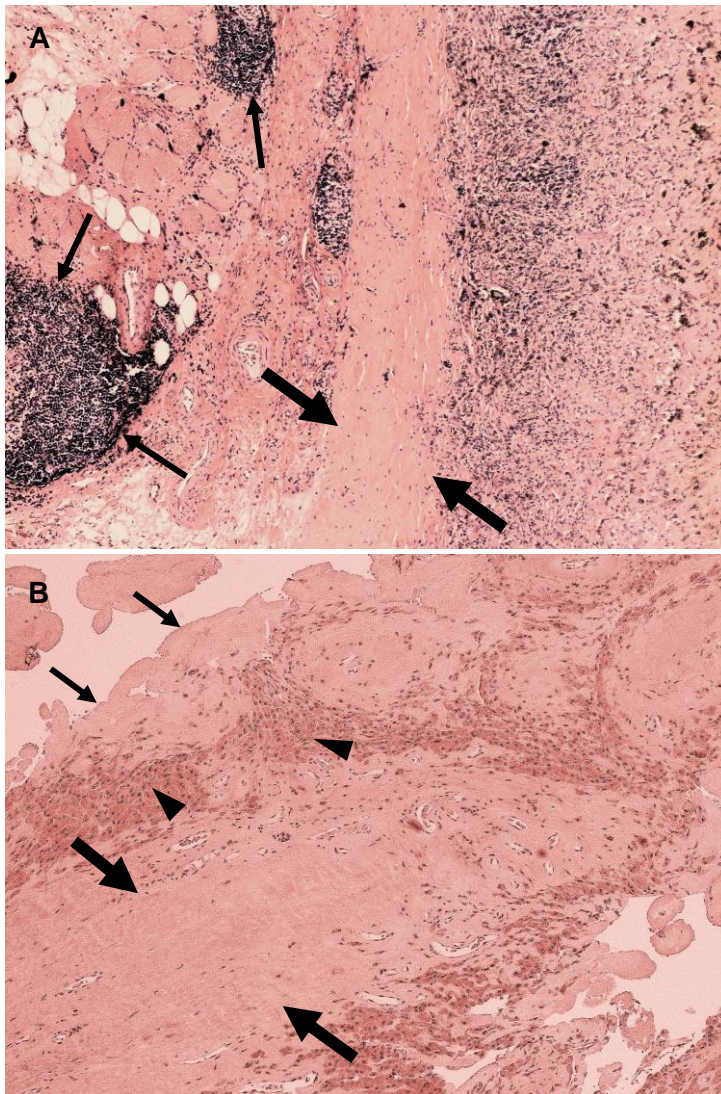


Figure 2. A) The upper image shows a synovial tissue sample with a high aseptic lymphocytic vasculitis-associated lesion (ALVAL) score. The inflammatory cells seen are predominantly lymphocytes, many of them in perivascular aggregates (thin arrows). Thick acellular areas can be seen (thick arrows). This sample received an ALVAL score of 9 (2 for synovial lining, 4 for inflammatory infiltrate and 3 for tissue organization).

B) The lower image shows a synovial tissue sample with a low ALVAL score. Disrupted synovial lining can be seen (thin arrows). Inflammatory cells are predominantly macrophages (arrow heads). Marked loss of normal arrangement can be seen, with thick acellular areas (thick arrows). This sample received an ALVAL score of 5 (2 for synovial lining, 1 for inflammatory infiltrate and 2 for tissue organization). Hematoxylin and eosin staining, magnification of 200x.

After the acknowledgement of ARMD with MoM hips, it was suggested that hypersensitivity reactions are a response to Co, Cr or nickel ions (Pandit et al. 2008). In older studies, sensitization towards Co and Cr has been reported in CoCr THAs (Granchi et al. 2000, Hallab et al. 2005). However, in a more recent study, enhanced lymphocytic response towards nickel was more common in patients with MoM hip resurfacing compared with controls, whereas lymphocytic reaction towards Co or Cr was not seen. The authors observed no difference in sensitization between patients with or without pseudotumors, which they suggested supports the idea that hypersensitivity is not the dominant (or at least not the only) mechanism for the formation of a pseudotumor. (Kwon et al. 2010).

Macrophage-dominated granulomatous reactions are characterized by macrophages with visible phagocytosed particles, foreign-body giant cell, fibroblasts, small blood vessels and typically only a small number of lymphocytes (Goodman 2007, Lohmann et al. 2013). Macrophages phagocytose metal debris and activate T-lymphocytes through antigen presentation (Hallab and Jacobs 2009). Both soluble (metal ions) and particulate metal debris may activate macrophage reaction (Hallab and Jacobs 2009). Phagocytized wear particles are transported to lysosomes where the acidic environment corrodes metal, leading to high local metal ion concentrations (Grammatopoulos et al. 2013). Co and Cr have been described to induce apoptosis (low concentrations) and necrosis (high concentrations) in macrophages (Huk et al. 2004). The Co and Cr concentrations in blood and synovial fluid, however, are considered insufficient to cause direct tissue damage. Instead, the damage may be caused by Co and Cr accumulating in phagosomes, where they reach toxic concentrations and result in the death of macrophages and the release of lysosomal enzymes. Lysosomal enzymes and the “metal ion wave” released after cell death cause damage to the surrounding tissues. (Xia et al. 2011, Grammatopoulos et al. 2013).

The lymphocyte-dominated reaction may progress and cause symptoms more rapidly than a macrophage-dominated reaction. The most extensive tissue damage has been reported in patients with a lymphocyte-dominated hypersensitivity type reaction and in the absence of high wear (Campbell et al. 2010). Additionally, a significantly shorter time from primary surgery to revision has been reported for hips with lymphocyte-dominated reaction compared with macrophage-dominated reaction. (Berstock et al. 2014). High implant wear appears to be a necessity for the development of a macrophage-dominated reaction, as most studies only report macrophage-dominated reactions in high wearing MoM hips (Campbell et al. 2010, Grammatopoulos et al. 2013, Berstock et al. 2014). For lymphocyte-dominated

reactions, only moderate (Grammatopoulos et al. 2013) to non-existent (Ebrahimzadeh et al. 2015) correlations between wear and ALVAL score have been reported, and typical ALVAL reactions have been reported both in low and high wearing hips (Campbell et al. 2010, Grammatopoulos et al. 2013, Berstock et al. 2014). Therefore, it seems that high implant wear may be associated with either macrophage- or lymphocyte-dominated reaction, whereas low implant wear would typically be associated only with lymphocyte-dominated reaction. However, contradicting results compared to previous studies have been presented, as the total metal content of periprosthetic tissue, but not the serum level, has been described to be significantly higher in tissues with lymphocytic reaction compared with macrophage-dominated reaction. In that study, serum metal ion levels were elevated in all 28 patients, but only one of the six macrophage-dominated tissue samples had high metal content and the contents in the other five were among the lowest in that study. (Lohmann et al. 2013). Further, it has been presented that lymphocyte-dominated reaction is associated with a smaller median size of wear debris particle and a larger total number of particles (Singh et al. 2015).

2.4.2 Risk factors for Adverse Reaction to Metal Debris

Risk factors for revision due to ARMD are similar to those for revisions overall. Female gender in both resurfacings and MoM THAs, and small head size in resurfacing and large head size in MoM THAs are reported to be associated with increased risk for revision due to ARMD. Results for other factors are variable.

In univariate analyses, female gender (Ollivere et al. 2009, Glyn-Jones et al. 2009, Murray et al. 2012), small femoral head size (Ollivere et al. 2009, Langton et al. 2011b, Murray et al. 2012, Reito et al. 2013), young age (Ollivere et al. 2009), high cup inclination (Ollivere et al. 2009) and body mass index (BMI) (Ollivere et al. 2009) have been described as risk factors for revision of hip resurfacing due to ARMD. An almost 6-times higher risk for revision of MoM hip resurfacing due to ARMD was reported for women in a recent meta-analysis, which was, however, not assessed for other variables (Haughom et al. 2015).

In a multivariable analysis including 1419 MoM resurfacings, of which 26 were revised for pseudotumor, female gender and young age were risk factors (Glyn-Jones et al. 2009). No difference was seen in that study between implant brand, primary diagnosis and implant size, although when implant size was analyzed as a continuous variable, the effect was almost significant. In an independent series of 646 hip

resurfacings, multivariable analysis showed female gender as the only significant risk factor for revision due to pseudotumor, whereas there was no difference in age, implant size or preoperative diagnoses (Murray et al. 2012). In a cohort of 168 ASR hip resurfacings with head size of less than 50 mm, low cup coverage (resulting from high inclination and small sector angle of the cup), was the only independent risk factor for revision due to ARMD, whereas there was no relation to age, implant size, gender, preoperative diagnosis or ROM (Reito et al. 2013). Brand-related risk factors for ARMD were seen in a Cox regression analysis of 4226 resurfacings with adjustment for surgeon and implant size (Langton et al. 2011b)

Among stemmed ASR THAs, both small (< 45 mm) and large (≥ 55 mm) head size have been reported to be associated with failure due to ARMD (Langton et al. 2011a). Only two studies including multivariable analysis have described risk factors for revision due to ARMD in MoM THAs. In 312 ASR MoM THAs with head size < 50 mm, female gender, low cup coverage, high preoperative ROM and Corail stem were independent risk factors for revision due to ARMD, whereas implant size, age and preoperative diagnosis were not associated with risk (Reito et al. 2013). Another study by the same authors with ASR THAs using headsize > 50 mm also showed an increased risk for Corail stems, and also for increasing head size (Reito et al. 2015).

2.4.3 Risk factors for pseudotumors

Whereas female gender and femoral head size are often reported as risk factors for revision, the risk factors for the mass or cystic pseudotumor seen in cross-sectional imaging are not uniformly acknowledged.

In resurfacings, the multivariable analysis of 143 BHRs showed an increased risk for PT only in patients with elevated Co and Cr levels, whereas no significance was seen in age, sex, inclination, head size and BMI (Bisschop et al. 2013). A large head-neck ratio (ratio of the femoral component diameter and the width of the femoral neck) often seen in women is described to promote impingement and edge wear, and thus increases the risk for pseudotumor (Grammatopoulos et al. 2010)

Elevated blood metal ion levels and hip symptoms have been presented as a risk factor for pseudotumor in MoM THAs (Mokka et al. 2013, Bosker et al. 2015), although contradicting results exist as well (Bayley et al. 2015). Several recent studies including multivariable analysis have failed to show patient and implant position-related risk factors for pseudotumors detected in cross-sectional imaging in large diameter MoM THAs. No difference has been seen between genders, large and small

femoral head size, cup inclination, age and BMI (Mokka et al. 2013, Muraoka et al. 2014, Bosker et al. 2015, Bayley et al. 2015)

In a study with a mixed cohort of hip resurfacings and MoM THAs, no association was seen between pseudotumor formation and cup coverage, age, gender, BMI, type of implant or blood metal ion levels (Williams et al. 2011).

2.4.4 Differential diagnosis

The underlying factors for symptoms, such as pain, are frequently identical in MoM when compared with conventional MoP hips. Common causes of symptoms such as component loosening, instability, periprosthetic fracture, osteolysis, trochanter bursitis as well as iliopsoas and rectus femoris tendinitis can often be diagnosed with clinical examination and imaging. (Kwon et al. 2014). It is imperative to always rule out other intrinsic (from the hip) as well as extrinsic (originating from elsewhere, eg. spine) reasons for hip symptoms before considering ARMD as the primary source of the symptoms (Lombardi et al. 2012). ARMD is a new diagnostic challenge in the case of a painful MoM hip. Case reports with ARMD mimicking infection with elevated C-reactive protein (CRP), erythrocyte sedimentation rate and elevated white blood cell count as well as infection-like purulent fluid in revision surgery with negative bacterial cultures have been published (Mikhael et al. 2009, Galbraith et al. 2011). Because not all patients with MoM hip and elevated CRP and erythrocyte sedimentation rate have periprosthetic joint infection, synovial fluid white blood cell count should be determined, preferably with a manual count, to achieve the best possible accuracy for diagnosis (Yi et al. 2015).

2.5 Systemic effects of implant metals

In vitro and animal studies have shown a large number of potential adverse effects for implant metals. Erythropoiesis and bone marrow impairment, a decreased number of immune system cells, toxicity towards the liver, kidneys, lungs, heart and nervous system, a decrease in male and female fertility as well as carcinogenic effects have been described (Polyzois et al. 2012). Although cobalt, chromium and nickel are important trace elements in human physiology (Masse et al. 2003), concerns about systemic effects of high concentrations *in vivo* have been presented.

The effects of heavy metal poisoning are a much-studied subject in occupational medicine (Keegan et al. 2007), but the documentation of the systemic effects in patients with hip replacements relies much on case reports. As a result of a systematic review, it has been suggested that Co concentration of less than 300 ppb is unlikely to cause adverse hematopoietic, cardiovascular, neurological or reproductive system effects (Finley et al. 2012). Cr is considered to have a less significant systemic effect compared to Co, as the most carcinogenic and toxic form of Cr is hexavalent that is only acquired through inhalation, whereas the ions released from implant wear and corrosion are not as potent (Brent and Devlin 2013). Both Co and Cr are excreted through the kidneys. Co is excreted to urine in larger amounts, whereas Cr has a tendency to be bound on proteins, which impairs excretion (Newton et al. 2012).

Many of the case reports about systemic metal toxicity are not about patients with MoM hips, but actually about patients with a poorly functioning or broken MoP, CoC or CoP hip. Several authors have reported cases where a fractured ceramic component was replaced with a metallic component. The remaining ceramic debris has resulted in high wear of the metallic component and ultra-high blood Co (398 to 6521 ppb) concentrations causing systemic symptoms (Steens et al. 2006, Oldenburg et al. 2009, Ikeda et al. 2010, Pelclova et al. 2012, Zywił et al. 2013, Apel et al. 2013). The most important symptoms and findings are described in Table 2. The symptoms and findings reported have included loss of vision and hearing with peripheral numbness (serum Co 398 ppb, Cr 56 ppb) (Steens et al. 2006), poor concentration, fatigue, hearing loss, eczema, hypothyroidism and cardiomyopathy (Co 625 ppb, Cr 81 ppb) (Oldenburg et al. 2009), malaise, muscle weakness and sensorineural auditory impairment (Co >400 ppb, Cr 221 ppb) (Ikeda et al. 2010), polyneuropathy, deafness, cardiomyopathy and hypothyroidism (Co 506 ppb, Cr 14 ppb) (Pelclova et al. 2012) and decline in vision, malaise, cardiomyopathy, hypothyroidism, diabetes and neuropathy (Co 446 ppb, Cr 46 ppb) (Apel et al. 2013). In all these studies, a complete or partial resolution of the symptoms was seen after the revision of the metallic component in revision surgery. Two centers reported cobalt-induced cardiomyopathy resulting in the death of a patient (Co 1085- 6521 ppb) (Gilbert et al. 2013, Zywił et al. 2013). Systemic effects have also been reported with a poorly functioning MoP hip. Blindness, severe deafness and lower limb hyposthenia (Co 549 ppb, Cr 54 ppb) were described in a patient with such a hip replacement (Rizzetti et al. 2009). One center described five patients with MoM resurfacing, all of whom had depression and anxiety as prodromal symptoms, which in four of the cases was followed by tinnitus and hearing loss, and vertigo in one patient. In two of these five patients, neurological function improved after the revision. Also, cardiomyopathy

was diagnosed in three patients, and cardiovascular function improved in two of them after the revision. (Tower 2012).

Table 2. The symptoms and findings that have been linked to systemic cobalt and chromium exposure.

Neurological symptoms and findings	Cardiovascular symptoms and findings	Other symptoms and findings
Loss of vision	Cardiomyopathy	Fatigue
Loss of hearing	Shortness of breath	Hypothyroidism
Peripheral numbness	Lowered ejection fraction	Malaise
Poor concentration	Pericardial effusion	Eczema
Tinnitus		Diabetes
Vertigo		Depression

For neurological symptoms, the blood or serum cobalt values of 15 ppb to 625 ppb and for Cr 14 ppb to 221 ppb have been reported, and for cardiovascular symptoms and findings the values have been Co 14 ppb to 6521 ppb and Cr 4 ppb to 81 ppb.

Although in the cases mentioned above the Co levels were ultra-high, systemic symptoms have been also described in patients with an order of magnitude smaller elevation of blood metal ion levels. A new cardiomyopathy causing dyspnea was diagnosed in a patient with MoM THA (plasma Co 13.6 ppb, Cr 4.1 ppb), with improvement in cardiovascular function after the revision (Machado et al. 2012). Fatigue and the taste of metal in their mouths in patients with ASR MoM THA (serum Co 24 ppb, Cr 12 ppb), and muscle fatigue, cramps and dyspnea in other patients with ASR MoM THA (serum Co 15 ppb) were reported, with resolution of the symptoms after the revision of the implant (Mao et al. 2011). Blurred vision, the taste of metal in the mouth and morning nausea were reported by a patient with ASR MoM hip resurfacing (Co 44.7 ppb, Cr 30.9 ppb) with no progression of symptoms, so follow-up was chosen as the line of treatment (Ng et al. 2013).

In an age and gender matched case-control study that included 35 patients with MoM hips and 35 patients with conventional THAs, lower cardiac ejection fraction and larger end-diastolic left ventricular diameter, suggestive of reduced cardiac function, was reported for patients with the MoM hip. In that study, no difference in neuropsychological, renal, hepatic or endocrinologic function was observed. However, MRI confirmed metal deposition in the liver and spleen. (Prentice et al. 2013). In another study with the same matched population, lower gray matter attenuation in the occipital cortex and basal ganglia, as well as smaller size of the optic chiasm was seen in patients with systemic Co and Cr exposure due to MoM

replacement, suggesting that metal exposure may result in cell loss of the visual system (Clark et al. 2014). In a study of 516 patients with MoM THAs, no association was seen between self-reported neurological symptoms and blood Co and Cr levels (van Lingen et al. 2014). However, it is possible that the Co and Cr levels in that study were too low to cause neurological symptoms (Max Co 153 ppb). Concerns about nephrotoxicity have been presented. However, a study including 31 MoM resurfacings with 10-year follow-up did not observe any difference in renal markers compared with controls without implants (Corradi et al. 2011).

Local pseudotumors may lead to other abnormalities in the limb. Deep vein thrombosis (DVT) extending from calf to iliac vessel resulting from a large pseudotumor mass in a hip treated with MoM hip resurfacing (Memon et al. 2013), and DVT from the popliteal to the femoral vein also caused by a pseudotumor in a hip treated with MoM THA have been described (Parfitt et al. 2012). Also, swelling of the leg due to a pseudotumor that mimicks DVT has been reported in a patient with a MoM hip replacement (Maurer-Ertl et al. 2011).

Concerns about the effects on fertility and birth defects have been raised because Co and Cr from a hip replacement has been shown to be transported to the amniotic fluid and bloodstream of the fetus through the umbilical cord (Ziaee et al. 2007, Novak et al. 2014). However, no known cases of teratogenicity or other adverse effects due to maternal hip replacement have been reported (Oppermann et al. 2015). In two case reports, a pregnant mother with a MoM hip and a newborn baby were followed-up with blood metal ion measurement. In the first study, the blood Co of the mother was 51 ppb and Cr 25 ppb. Transportation of ions through the placenta and amniotic fluid was observed and nine weeks after delivery the blood Co of the healthy male child was 10 ppb and Cr 6.7 ppb (Oppermann et al. 2015). In the other study, the mothers blood Co was 138 ppb and Cr 39 ppb, and eight weeks after the delivery the Co of the healthy newborn male baby was 13 ppb and Cr 2.5 ppb (Fritzsche et al. 2012). Based on these studies, it would seem that the wear of the MoM hip implant in the mother does not necessary cause damage to the baby, but it has to be noted that the follow-up after labour was short in both reports, and therefore careful evaluation is required when a female with a MoM hip wishes to get pregnant. Occupational studies have raised concerns about the poor quality of sperm due to Co and Cr exposure (Keegan et al. 2007). Two studies have reported an increased metal ion concentration in sperm (Nikolaou et al. 2013, Chen et al. 2015). Of these, the prospective study reported a decreased percentage of morphologically normal sperm in 25 males with MoM hips compared with 25 males with MoP hips (Chen et al. 2015), whereas the retrospective study showed no difference in quality

of sperm between 11 males treated with MoM hips compared with 5 healthy volunteers (Nikolaou et al. 2013).

2.5.1 Risk for cancer

In occupational medicine, the association between metal exposure and cancer has been described (Keegan et al. 2007), and *in vitro* studies have shown that wear debris cause chromosomal damage (Daley et al. 2004). Therefore, concerns about the potential carcinogenic effects of hip replacements, especially with a MoM bearing surface, have been presented.

Recent studies have reported a similar rate of cancer in conventional hip replacements compared to the general population, with a reduced risk for smoking-related cancers and a variably increased risk for prostate cancer, skin cancer and hematopoietic cancers. In a meta-analysis published in 2006, the overall risk for malignancies was similar in conventional hip replacements compared to the general population, with a lower risk for lung, esophageal, laryngeal and gastrointestinal tract cancer, whereas the risk for prostate cancer and melanoma was elevated (Onega et al. 2006). In a Finnish population-based study, the overall incidence of cancer in patients with conventional hip arthroplasties was similar to that in the general population, accompanied by a reduced risk for nodal non-Hodgkin's lymphoma, stomach cancer and lung cancer, and an elevated risk for prostate cancer and a slight increase in late hematopoietic cancers (multiple myelomas and Hodgkin lymphomas) (Visuri et al. 2010). In a Scottish population-based study, the overall risk for cancer and the risk for prostate cancer and multiple myeloma was increased (Brewster et al. 2013).

There are only a few reports about the risk of cancer in patients with MoM hips. In NJR data, the overall risk for cancer was lower with resurfacings and slightly lower in MoM THAs compared with other bearing surface THAs. In resurfacings, the risk for hematological cancer and prostate cancer was reduced and the risk for skin cancer and renal cancer was similar. The risk for specific cancer types was similar in MoM THAs compared with other bearing surfaces. (Smith et al. 2012b). In a Finnish population-based study, the overall risk for cancer in patients with a MoM hip was similar to those with a conventional hip replacement, but a higher risk for soft-tissue sarcoma and basalioma was seen. However, the increased risk may be by change, as there were only seven cases of sarcomas in that study, and the increased risk of basalioma may be due to confounding factors, as for example, young and healthy

patients eligible for MoM hip replacement are more likely to have increased exposure to the sun (Mäkela et al. 2014).

In conclusion, the recent studies on patients with MoM hips have not reported an increased risk for cancer, but it should be noted that follow-up times of MoM hip replacements are rather short and the follow-up may be too short to detect long latency malignancies.

2.6 Screening protocols

After the acknowledgement of the problems with MoM hips, several authorities provided guidance for the follow-up of MoM hips: Medicines and Healthcare Products Regulatory Agency of the United Kingdom (MHRA 2012), the United States Food and Drugs Administration (FDA 2012), European guidelines (Hannemann et al. 2013), Therapeutic Goods Administration of Australia (TGA 2012) and Health Canada (Health Canada 2012).

In all follow-up protocols, the follow-up intensity is stratified by symptoms, as symptomatic patients with MoM hips are more closely followed. There is a slight variation as to which implants are considered to be “high risk designs”. Large head (≥ 36 mm) THAs (TGA 2012, MHRA 2012, Hannemann et al. 2013) and small head size (≤ 45 mm) resurfacings (TGA 2012) are considered to be risk designs in some guidelines and closer follow-up is recommended. MHRA also names both ASR resurfacing and ASR XL THA as high risk designs demanding closer follow-up (MHRA 2012). The basic tools of MoM follow-up are clinical examination, plain radiographs, whole blood metal ion measurements and cross-sectional imaging with magnetic resonance imaging or ultrasound. For symptomatic patients, all five guidelines suggest blood metal ion measurements and cross-sectional imaging, but the screening of asymptomatic patients ranges from clinical examination only (Health Canada 2012, FDA 2012) to a combination of ion measurement and cross-sectional imaging of the asymptomatic risk design (TGA 2012).

Criticism has been aimed at the current guidelines. Stratification of follow-up by implant type (resurfacing/THA) and size is insufficient in some guidelines, and suboptimal cut-off values are being used. There is wide variability in the cost of the follow-up between guidelines, and more research should be placed on the cost effectiveness of the screening. (Matharu et al. 2015b).

2.7 Blood and serum metal ion concentrations

2.7.1 Rationale for blood Co and Cr measurements

Blood Co and Cr levels are widely used as a screening method for poorly functioning and high wearing MoM implants, as the ion levels have been shown to correlate with the wear of metallic bearing surfaces (De Smet et al. 2008, Hart et al. 2013). Blood metal ion levels also correlate with metal ion concentration in the synovial fluid, and therefore while reflecting the systemic exposure, blood and serum concentrations depict the local exposure as well (De Smet et al. 2008, Davda et al. 2011, Lass et al. 2014).

2.7.2 Methods of measurement

Typically, blood samples are acquired with a needle connected to a tube containing ethylenediaminetetraacetic acid (EDTA) for anticoagulation. If serum measurements are done, a tube containing blood is centrifuged. (Daniel et al. 2007). Inductively coupled mass spectrometry equipped with collision cell or dynamic reaction cell technology or sector field inductively coupled plasma mass spectrometry and accurate measurement for concentrations as low as 1 ppb should be used (FDA 2013). Confounding factors such as high physical activity (Khan et al. 2006), other metallic implants, occupational exposure, renal insufficiency and dietary supplements should be noted when interpreting the results (FDA 2013). Whole blood concentrations reflect the systemic exposure better than serum concentrations, and therefore should be preferred (Daniel et al. 2007). Blood and serum levels should not be used interchangeably (Daniel et al. 2007, Smolders et al. 2011, Sidaginamale et al. 2013). Newton presented that Co is equally divided between plasma and red blood cells, but that Cr is more abundant in plasma (Newton et al. 2012), and similar figures were presented by Smolders (Smolders et al. 2011). Although some authors have suggested that blood and serum concentrations are also not interconvertible (Daniel et al. 2007), a formula for converting whole blood values to serum values has been published (Smolders et al. 2011).

2.7.3 Units of measurement

The units used to describe concentrations of serum or blood are micrograms per liter ($\mu\text{g/L}$), nanograms per milliliter (ng/mL), parts per billion (ppb, 10^{-9}) and nanomoles per milliliter (nmol/mL). Because

$$\mu\text{g/L} = 1000 \text{ ng}/1000 \text{ mL} = \text{ng/mL},$$

$\mu\text{g/L}$ and ng/mL are interchangeable. Parts per billion describes mass fraction, and because one liter of blood/serum weighs approximately 1000 grams,

$$1 \mu\text{g/L} = 10^{-6} \text{ g} / 1000 \text{ g} = 10^{-9} = 1 \text{ ppb},$$

$\mu\text{g/L}$ and ppb can be used interchangeably as well. Values measured in moles per volume can be converted to mass per volume by multiplying moles per volume value by molar mass of Co (58.93 g/mol) or Cr (52.00 g/mol).

2.7.4 Normal versus elevated wear and metal ion levels

In the normal population, blood Co concentrations are <1 ppb in 93% of patients and Cr <2 ppb in 97% of patients (Sidaginamale et al. 2013). Immediately after implantation, a MoM bearing surface has a low wearing rate. Subsequently, the implant will enter a “running in” phase during which the wear rate of a bearing surface will increase significantly. Finally, a “steady state” with a lower, constant rate of wear will be achieved. (Heisel et al. 2008). In studies with blood or serum Co and Cr measurements, a steady state is usually achieved between six months and two years after implantation (Heisel et al. 2008, Bisseling et al. 2015). After reaching the steady state, the Co and Cr levels remain relatively constant both in small head MoM THAs (Lazennec et al. 2009, Bernstein et al. 2012) and resurfacings (Amstutz et al. 2013, Van Der Straeten et al. 2013). A slight decrease in serum Co and Cr levels after 10 years of implantation of MoM resurfacings has been reported (Van Der Straeten et al. 2013). Currently, there is no long-term follow-up data for large head MoM THAs.

The increased wear of the component (Kwon et al. 2010) as well as higher blood/serum metal ion levels (De Smet et al. 2008, Langton et al. 2010) are often seen in patients with ARMD in their hips. Blood Co or Cr concentration of 7 ppb has been proposed as a cut-off-value for poorly functioning MoM hips by the UK

Medicines and Healthcare products Regulatory Agency (MHRA 2012), but this value was reported to have rather low sensitivity for detecting failed MoM hips (Hart et al. 2011) and MoM hips with abnormal MRI findings (Malek et al. 2012). As a result, alternative cut-off values have been proposed. Hart suggested that the optimal whole blood Co and Cr cut-off value for the unexplained failure of a MoM hip would be 5 ppb (Hart et al. 2011). Sidaginamale reported blood Co 5.0 ppb and Cr 8.4 ppb as being sensitive cut-off values to detect increased wear (Sidaginamale et al. 2013). Van der Straeten suggested that cut-off values of 4.0 ppb for Co and 4.6 ppb for Cr should be used for unilateral resurfacings and 5.0 ppb and 7.4 ppb for bilateral resurfacings, respectively (Van Der Straeten et al. 2013). De Smet suggested that above Co 19 ppb and Cr 17 ppb levels metallosis is very likely to be present (De Smet et al. 2008). There is no consensus on which cut-off value should be used, and the use of mildly elevated blood or serum Co and Cr measurements as a sole indication for revision surgery is discouraged (Hart et al. 2014). However, values less than 2 ppb are considered to be related to low risk for ARMD. It should also be noted that all these cut-off values are defined for local reactions, and no data is available for cut-off value for adverse effects related to high systemic Co and Cr burden. (Hannemann et al. 2013).

2.7.5 Effect of implant type on blood cobalt and chromium levels

MoM hips can be divided into three separate categories: hip resurfacings, small head (<36 mm) THAs and large head (≥ 36 mm) THAs (NJR 2014). There is a variety of bearing surfaces on the market. The most commonly used are MoP, CoP, CoC and MoM. MoM bearings are associated with significantly higher blood/serum Co and Cr levels compared with THAs with MoP (Antonioni et al. 2008), CoC (Savarino et al. 2008, Hart et al. 2009b) and CoP bearing surfaces (Rasquinha et al. 2006).

Higher Co levels have been described for large head THAs compared with resurfacings, whereas results on Cr have been incongruent. Two randomized controlled trials reported higher serum Co levels in patients that had large head THAs compared with resurfacings with identical bearing surfaces, whereas only the other reported higher serum Cr as well (Garbuz et al. 2010, Beaulé et al. 2011). Higher blood Co and similar Cr in MoM large head THAs compared with resurfacings were also seen in a prospective cohort study (Vendittoli et al. 2011).

There is incongruity in the direct comparisons between small and large head MoM THAs. The only randomized controlled trial that included a direct comparison

of large and small head THAs revealed no difference in blood Co and Cr levels between 36 mm and 28 mm MoM THAs (Engh Jr et al. 2009). Higher serum Co and Cr were reported for a 28 mm MoM THA compared with a 36 mm MoM THA (Antoniou et al. 2008). In another study, higher Cr was reported for small head (≤ 32 mm) THAs compared with large head (≥ 38 mm) sizes, whereas no difference in Co was seen (Hallows et al. 2011).

Higher or similar Co and Cr levels have been reported for MoM hip resurfacings compared with small head (< 36 mm) MoM THAs. One randomized controlled trial described significantly higher whole blood Co and Cr concentrations for resurfacings compared with 28 mm MoM THAs (Bisseling et al. 2015), whereas other randomized controlled trial observed no difference in whole blood Co or Cr levels between 28 mm THAs and resurfacings (Vendittoli et al. 2013). Significantly higher serum Cr levels but no difference in Co was described for hip resurfacings compared with 28 mm THAs in a retrospective study (Savarino et al. 2013).

The studies with a direct comparison between large and small head THAs, large head THAs and resurfacings, as well as small head THAs and resurfacings are scarce. However, in a systematic review about blood/serum ions in MoM hips, indirect comparison between the studies showed that median concentrations of Co and Cr concentrations in patients with large head THAs and resurfacings were higher when compared with small diameter MoM THAs (Hartmann et al. 2013), which is in accordance to published implant survival figures (AOANJRR 2014).

2.7.6 Taper wear

In MoM THAs, the head component is attached to the stem by a taper-trunnion junction. The word “trunnion” refers to the junction area of the stem (“male component of the junction”) and “taper” to the junction area of the head component (“female component of the junction”) (Langton et al. 2012). As there is no difference in the rate of bearing surface wear between resurfacings and large head MoM THAs (Matthies et al. 2011), taper wear is considered to be one of the main reasons for poor survival and higher blood metal ion levels in MoM THAs compared with resurfacings with an identical bearing surface (Garbuz et al. 2010, Smith et al. 2012c, NJR 2014).

Most of the volumetric wear in the trunnion-taper-interface originates from the female component (Bishop et al. 2013). The volume of material loss from the taper is of a similar magnitude as that from the bearing surface, but the taper is a

predominant source of debris only in a minority of cases with bearing surface being the main source in others (Matthies et al. 2013). Two wear patterns have been described for taper wear: asymmetric, wear associated with toggling and friction, and axisymmetric, attributed to galvanic corrosion (Bishop et al. 2013). These two mechanisms are probably connected, as damage by micromotion and friction is likely to remove the passive oxidative layer protecting the implant, and expose the implant to corrosion (Panagiotidou et al. 2015). Both mechanical fretting (Langton et al. 2012) and corrosive (Matthies et al. 2013) mechanisms have been proposed as the primary mechanisms of taper wear. The presence of corrosion is virtually a universal finding in tapers, which is suggested to support the corrosive theory (Matthies et al. 2013).

Large head size as well as the long neck of the femoral component increasing the horizontal lever arm has been reported to increase taper wear (Langton et al. 2012, Panagiotidou et al. 2015, Brock et al. 2015). One study reported no association between corrosion score, femoral head size and femoral offset (Nassif et al. 2014). Tapers exist with various lengths and diameters, and differences in surface topography (grooves) between the tapers in various stem models have been described (Munir et al. 2015). Short trunnion length is suspected to increase the risk for edge loading of the taper and increases contact at the trunnion base, while also increasing susceptibility to flexing of the trunnion. In addition, rough grooved trunnion surfaces are suggested to increase taper wear in cases with micromotion by imprinting the grooves in the taper (Brock et al. 2015). In disagreement with other literature, one study suggested that thick tapers with long contact length increase the risk for corrosion (Nassif et al. 2014). The orientation of the acetabular component does not affect the amount of taper wear (Langton et al. 2012, Elkins et al. 2014).

The rate of corrosion appears to be dependent on the combination of the materials in the head-neck junction. One study found that ceramic-CoCr couples are less susceptible to corrosion compared with CoCr/CoCr and CoCr/Titanium (Ti) couples (Panagiotidou et al. 2015). Another paper stated that a Ti-Ti interface is less related to corrosion than Ti-CoCr or CoCr-CoCr interphases (Nassif et al. 2014).

2.7.7 Implant orientation

Normal wear of the bearing surfaces has been reported to result in elliptical wear patterns. Stripe/scratch damage possibly caused by third body wear has also been described in MoM bearing surfaces (Clarke et al. 2014). An association between high

acetabular inclination and bearing surface wear (De Haan et al. 2008b, Hart et al. 2013) and between high inclination and blood metal ion concentrations (De Haan et al. 2008b, Langton et al. 2011) has been reported in several studies. Both excessive and insufficient acetabular anteversion are also associated with increased bearing surface wear (Hart et al. 2011a) and elevated blood metal ion levels (Langton et al. 2011, Hart et al. 2011b). As single parameters, inclination and anteversion explain only 16% to 28% of component wear and blood metal ion levels (Matthies et al. 2014). Edge loading (wear area crossing over the edge of acetabular component) is a risk factor for increased wear (Kwon et al. 2010, Glyn-Jones et al. 2011, Underwood et al. 2012, Hart et al. 2013). The combined effect of inclination, acetabular sector angle and size of component can be estimated by calculating arc of cover, which is also more suitable for estimating edge loading compared to inclination (De Haan et al. 2008b). Furthermore, the acetabular version can be included in the model by calculating the smallest distance between the center of the wear patch and the edge of acetabular component, which is called contact patch to rim distance (Langton et al. 2009, Underwood et al. 2012). Contact patch to rim distance explains up to 68% of the bearing surface wear and 48% of blood cobalt levels (Matthies et al. 2014) and has high sensitivity and specificity for predicting serum metal ion levels exceeding 7 ppb (Yoon et al. 2013).

2.7.8 Other implant-related factors affecting blood cobalt and chromium

Low clearance (difference in radius between the head and cup components) has been described as a factor resulting in edge loading, and thus increasing wear and blood metal ion levels (Underwood et al. 2012). The recalled ASR and Durom implants are both low clearance designs (Heisel et al. 2009). Neither small nor large femoral head sizes are clear risk factors for elevated blood or serum metal ion levels in MoM hip resurfacings or THAs. In cohorts of resurfacings, both small head size (Desy et al. 2011, Emmanuel et al. 2014) and large head size (Langton et al. 2011a) have been reported to have an association to high blood Co and Cr, with some studies reporting the lack of a statistically significant difference (Hart et al. 2011b). Also, among large diameter THAs, both negative (Emmanuel et al. 2014, Bayley et al. 2015) and positive (Vendittoli et al. 2011) relationships between head diameter and blood metal ion levels have been observed, along with studies reporting no statistical significance (Langton et al. 2011a, Hasegawa et al. 2012, Chang et al. 2013, Matharu et al. 2015a).

No association between implant wear and head size was seen in a mixed cohort of resurfacings and THAs (Hart et al. 2013).

Significant differences in blood Co and Cr levels between large diameter THA brands have been reported (Lavigne et al. 2011a, Lardanchet et al. 2012). Differences between brands were also seen after multivariable adjustment for age, gender, component head size and inclination (Matharu et al. 2015a). Metallurgy, manufacturing process, type of coating, use of adapter sleeve and variance in modular junctions are possible factors causing brand-specific differences (Lavigne et al. 2011a, Lardanchet et al. 2012, Matharu et al. 2015a). Higher metal ion levels have been reported for an open femoral head component design used in larger head size THAs, which is suggested to be due to a larger contact surface for passive corrosion (Vendittoli et al. 2011). Hip replacements with a modular stem have twice as high a risk for revision at 10-year follow-up compared to stems with only a modular interface between the stem and head component. Elevated serum Co and Cr levels were reported for all patients with modular stems in a recent study (Molloy et al. 2014).

2.7.9 Patient-related factors affecting blood cobalt and chromium

Generally, it is considered that female patients have an increased risk for elevated blood metal ion levels and the development of ARMD, but there is some incongruity in study results. Higher whole blood Co and Cr levels have been described in females with MoM resurfacings compared with males (De Haan et al. 2008b, Hart et al. 2011b). In some studies, association was significant only in relation to Co (Bayley et al. 2015) and in some only to Cr (Desy et al. 2011), and some studies did not find any association (Vendittoli et al. 2011). Association with gender is sometimes proposed to be due to the relationship between gender and femoral head size, but female gender has also been reported as an independent risk factor after adjustment for femoral head size (Hart et al. 2011b). Association between female gender and blood Co has also been reported in MoM THAs (Bayley et al. 2015), but several studies have also reported no relationship between gender and blood metal ion levels (Hasegawa et al. 2012, Matharu et al. 2015a). No association between implant bearing surface wear and sex has been seen in multivariable analyses (Glyn-Jones et al. 2011, Hart et al. 2013).

In most studies, the BMI is reported to have no association with whole blood metal ion levels (Hart et al. 2011b, Hasegawa et al. 2012), although minor positive

(Emmanuel et al. 2014) and negative (Hart et al. 2011b, Hasegawa et al. 2012) correlations have been reported as well. The age of the patient is not a risk factor for elevated metal ion levels (Vendittoli et al. 2011, Beaulé et al. 2011, Hart et al. 2011b, Hasegawa et al. 2012). No association was reported with hip ROM and metal ion levels (Liu and Gross 2013). However, exercise has been shown to increase blood Co levels which may result in higher blood metal ion concentrations in some physically active patients (Khan et al. 2006). Renal function is a potential factor affecting blood and serum levels as Co is almost completely eliminated by the kidneys and has a very short half-life. Excretion of Cr to urine is more time consuming and Cr has a higher tendency to bind to proteins in the blood and to be stored in tissues such as the liver and spleen (Urban et al. 2004, Newton et al. 2012). Healthy kidneys can increase the Co excretion in cases with increased wear (Daniel et al. 2010).

2.8 Imaging of Adverse Reactions to Metal Debris

The main imaging modalities for abnormalities related to ARMD are MRI and ultrasound because of their superior ability to detect intra- and extra-articular soft tissue lesions (Bestic and Berquist 2013). Surgeons use three-dimensional MR-images for preoperative planning to facilitate optimal resection (Liddle et al. 2013). CT is preferable for imaging bony structures (Cahir et al. 2007), but its ability to detect ARMD-related soft tissue lesions is inferior when compared to MRI or ultrasound. Thus, it is rather rarely used. (Roth et al. 2012, Robinson et al. 2014). Plain radiographs are used for defining component orientation and detecting ARMD related osteolysis and are also helpful in differential diagnostics of painful MoM hips (Chen et al. 2011, Bestic and Berquist 2013). However, plain radiographs cannot reliably detect soft tissue lesions (Toms et al. 2008).

2.8.1 Imaging findings

Typical soft tissue abnormalities associated with ARMD are extracapsular pseudotumors containing a variable proportion of solid and cystic elements (Pandit et al. 2008). Pseudotumors are seen in the iliopsoas and/or posterolateral region, and may communicate to joint space and involve adjacent muscles (Fang et al. 2008). In relatively small studies, cystic pseudotumors have been described more typical in the

posterolateral region, whereas solid pseudotumors may be more often anteriorly located (Pandit et al. 2008, Fang et al. 2008, Hauptfleisch et al. 2012). It has been suggested that the location of abnormalities follows the path of least resistance and that cystic pseudotumors are typically connected to the joint mimicking local bursae (Fang et al. 2008, Madanat et al. 2015). ARMD may also be intra-articularly limited. These cases may present effusion, thickening and protrusion of the joint capsule without separate pseudotumor formation (Nishii et al. 2012, Hayter et al. 2012a). Wear debris induced osteolysis may also be found in the acetabular or femoral region (Hayter et al. 2012a). Muscle atrophy is a common finding in MRI of a MoM hip (Sabah et al. 2011, Berber et al. 2015) and is suggested to be a combination of muscle disuse and postoperative changes (Campe and Palmer 2013). The specificity of muscle atrophy to MoM hip replacements and ARMD has been questioned (Fox et al. 2014).

2.8.2 Plain radiographs

Even the extensive soft tissue changes easily detected by MRI are not seen in plain radiographs (Toms et al. 2008). Therefore, radiographs have no true role in the imaging of soft tissue ARMD, although it has been suggested that metallosis could be seen as cloud-like opacification in radiographs (Bestic and Berquist 2013). Component loosening, fractures and heterotopic ossification, the typical causes of pain and failure in conventional hip replacements, can also be present in MoM hips. In symptomatic patients, such causes should be ruled out with plain radiographs (Ostlere 2011, Chen et al. 2011). Femoral neck narrowing, which is mostly described as a benign finding, is quite commonly seen in cases with hip resurfacing (Hing et al. 2007). The clinical significance of neck narrowing is still unclear (Gerhardt et al. 2015).

Orientation of the acetabular component, i.e., inclination (or abduction) and version, is a significant factor affecting component wear (Matthies et al. 2014). Inclination is easily measured from anteroposterior plain radiographs using the plane of ischial tuberosities as reference (Figure 3). True lateral anteversion can be determined from lateral radiographs (Pulos et al. 2011, Figure 3). Version can also be determined from plain radiographs using software such as Ein Bild Roentgen Analysis (EBRA) (Krismer et al. 1995), or with mathematical methods (Reito et al. 2012).

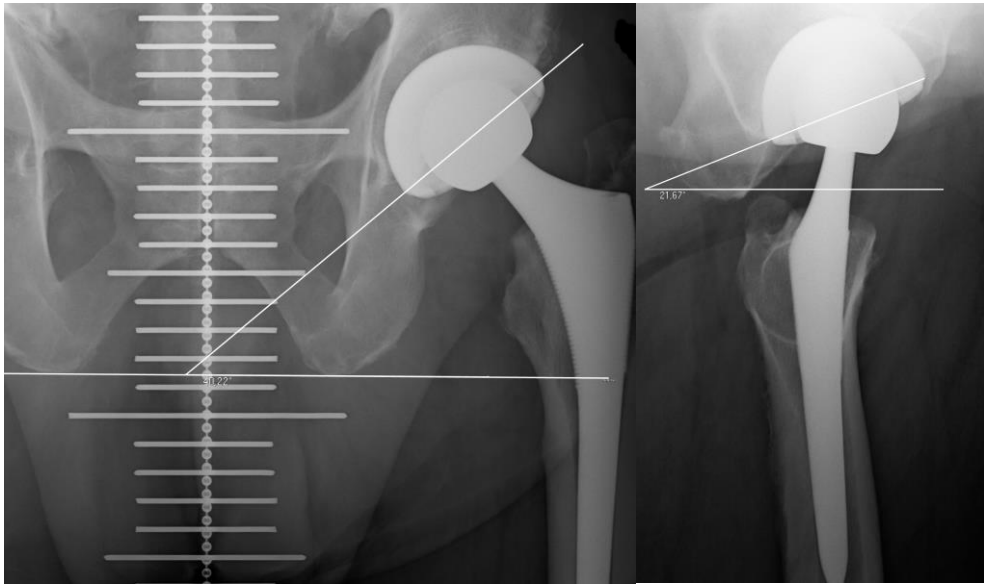


Figure 3. The measurement of inclination from anteroposterior pelvic radiograph using the plane of ischial tuberosities as reference is demonstrated on the left. The measurement of true lateral anteversion from lateral hip radiograph is demonstrated on the right. The horizontal plane is used as reference.

2.8.3 Magnetic resonance imaging

MRI is a popular option for MoM hips due to good tissue differentiation (Cahir et al. 2007). The disadvantages of MRI include high cost (385-709 €, depending on the MRI sequences used [Marjut Keskivinkka, Imaging Centre of Tampere University Hospital, personal communication, 18.8.2015]), long examination time and sometimes limited availability (Nam et al. 2014). Magnetic resonance imaging is contraindicated in patients with, for example, certain pacemakers and cerebral aneurysm clips (Kwon 2014). Magnetization of metallic implants produces artifacts in the form of signal void and geometric distortion that obscure the adjacent soft-tissue and bone abnormalities (Cahir et al. 2007, Campe and Palmer 2013). The use of higher magnetic field strengths in new scanners increases the volume of artifacts (White et al. 2000). There are various ways to reduce artifacts, and specific sequences have been developed for the imaging of MoM hips (Olsen et al. 2000, Campe and Palmer 2013). In cases where fat suppression is required, fast (turbo) spin echo sequences and short tau inversion recovery can be used to reduce metal artifacts. Decreasing voxel size, increasing frequency encoding gradient strength, broader

bandwidth and lower magnetic field strength may also help to reduce artifacts. (Ostlere 2011, Duggan et al. 2013, Campe and Palmer 2013). Specific sequences for metal artifact reduction such as Slice Encoding for Metal Artifact Correction (SEMAC) (Lu et al. 2009) and Multiple Acquisition Variable Resonance Image Combination (MAVRIC) (Koch et al. 2009) enhance the image quality, but also increase the scan time and reduce resolution (Garbuz et al. 2014). The use of gadolinium contrast agent is reported to not reveal any additional ARMD lesions, but is stated to make the abnormalities more conspicuous (Muller et al. 2014).

MRI appearance of ARMD lesions is variable. Fluid-filled pseudotumors are typically isointense to muscle in T1-weighted and hyperintense in T2-weighted images. The signal characteristics of the capsule are isointense in T1-weighted and low intensity in T2-weighted images. (Yanny et al. 2012). Signal intensity may, however, vary according to the degree of metallosis, protein contents or blood products inside the lesion or in the capsule. The solid components usually show a low signal in T2-weighted images. (Ostlere 2011).

Several pseudotumor grading systems have been published (Anderson et al. 2011, Hart et al. 2012, Hauptfleisch et al. 2012). In the system published by Anderson, the findings are divided into normal (A), infection (B) and mild to severe MoM disease (C1-C3). The grading takes into account the presence of periprosthetic soft tissue mass/fluid cavity, size of abnormality and the involvement of adjacent structures (Anderson et al. 2011). The pseudotumor grading system published by Hart is based on MRI signal appearance and the findings are labeled as normal, flat fluid-filled and thin-walled (1), non-flat fluid-filled with thick or irregular walls (2a), atypical contents with thick or irregular walls (2b) and solid pseudotumors (3) with no cut-off limits for pseudotumor size (Hart et al. 2012, Figure 4). Grading by Hauptfleisch includes the contents of pseudotumor and the wall thickness of cystic pseudotumors: Grade I is a thin-walled (<3 mm) cystic mass, grade II is a thick-walled (>3 mm) cystic mass and grade III is predominantly solid mass (Hauptfleisch et al. 2012). In a study comparing these classifications, the highest reliability was reported for Anderson classifications (Anderson et al. 2011), whereas the classification by Hart/Matthies (Matthies et al. 2012, Hart et al. 2012) received the lowest reliability figures (van der Weegen et al. 2013b). However, it should be noted that the Anderson classification is based on the size of pseudotumor, which is more or less an objective value, whereas grading by Hart is based on signal appearance of the pseudotumor, which leaves much more room for the subjective opinion of the radiologist.

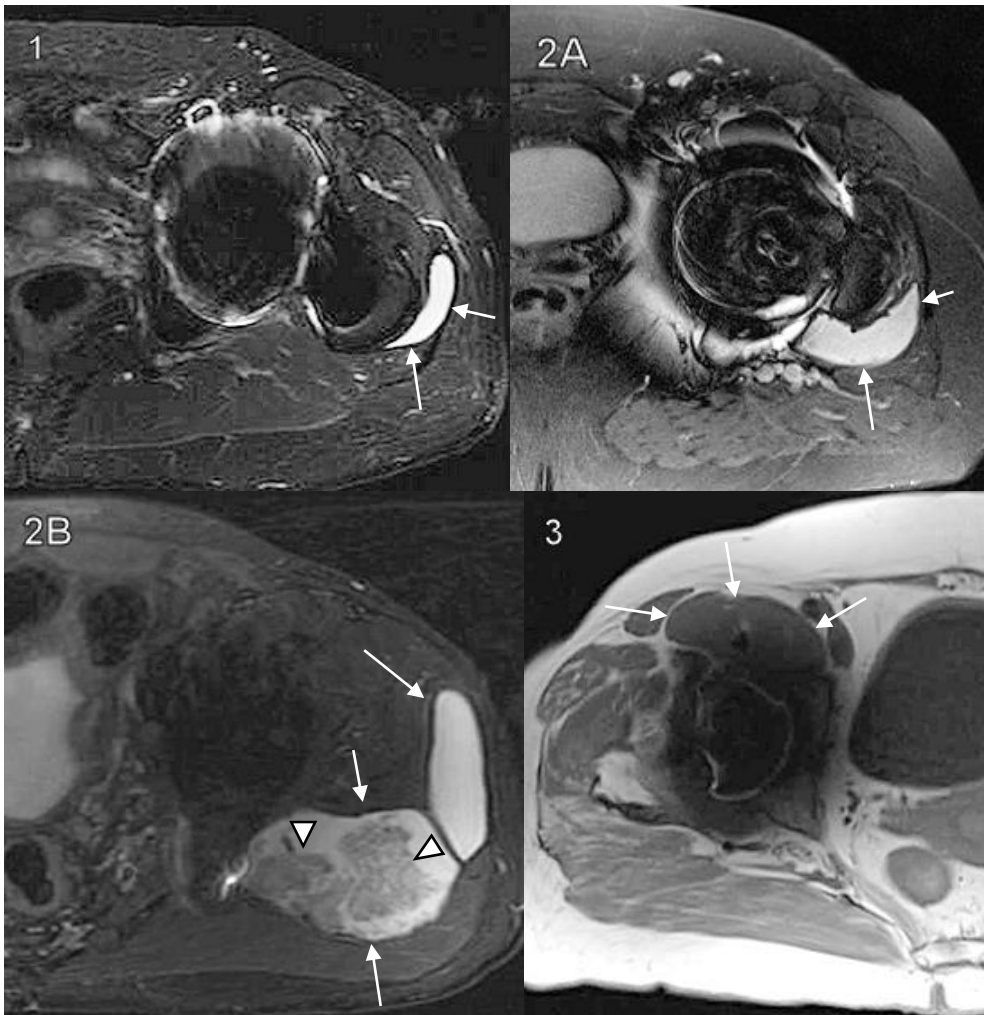


Figure 4. The axial short tau inversion recovery (STIR) magnetic resonance image (MRI) on the top left shows small thin-walled fluid-filled pseudotumor (Hart grade 1) at trochanteric region of the left hip. The axial STIR image on the top right shows a thick walled, fluid-filled pseudotumor in trochanteric region, representing Hart grade 2a. The axial STIR image on the bottom left shows trochanteric pseudotumor with thick walls and atypical low signal intensity contents (arrow heads) representing Hart grade 2b. The axial T1-weighted image on the bottom right shows predominantly solid anterior pseudotumor, Hart grade 3, with signal intensity almost identical to that of surrounding muscle. In all images, the outer borders of pseudotumor wall are marked with arrows. (Hart et al. 2012).

In MRI, osteolysis appears as well-marginated intraosseous and low signal intensity (T1) lesions that contrast with intramedullary fat (Hayter et al. 2012b). In clinical studies, the ability of MRI to detect osteolysis has been worse than that of CT due

to metal artifacts (Robinson et al. 2014, Waldstein et al. 2014). Muscle atrophy is seen as the decrease in volume and fatty replacement of muscle tissue (Sabah et al. 2011). Wear-induced synovitis and synovial thickening is seen as intermediate or mixed intensity debris in MRI with a possible expansion of the pseudocapsule to adjacent bursae seen (Hayter et al. 2012b).

2.8.4 Ultrasound

Some institutions consider ultrasound as the first-line investigation tool as it has good soft-tissue differentiation, it is cheaper (73 € [Marjut Keskvinkka, Imaging Centre of Tampere University Hospital, personal communication, 18.8.2015]), and more accessible when compared to MRI, and it is not compromised by metal artifacts (Fang et al. 2008, Williams et al. 2011, Nishii et al. 2012). Ultrasound also has the advantage of being able to acquire guided biopsies and fluid aspirations, and is not contraindicated for patients with pacemakers or other ferromagnetic hardware (Kwon 2014). Ultrasound is somewhat dependent on the experience of radiologist and offers limited possibilities for retrospective re-grading (Kwon 2014, Nam et al. 2014).

Imaging should include the anterior, lateral and posterior aspect of the pelvis and proximal femoral region to achieve thorough imaging of the hip region (Fang et al. 2008, Siddiqui et al. 2013). Pseudotumor grading for ultrasound, similar to previously described for MRI grading (Hart et al. 2012), has been introduced: Type 1 finding is a thin-walled cystic pseudotumor with fluid contents seen as a hypoechoic collection with thin, clear margins, type 2 is a thick walled (>2 mm) cystic pseudotumor with atypical contents seen as a lesion with irregular, thick walls and echogenic material inside the lesion and type 3 is solid with complex and often variable echo-texture (Siddiqui et al. 2013, Figure 5). Further, Siddiqui and colleagues used grading for muscle atrophy based on a previously published system in which atrophy was graded from 0 (no change) to 3 (70% size reduction with fatty replacement) (Bal and Lowe 2008, Siddiqui et al. 2013). Capsular thickening and joint effusion can be also diagnosed in an ultrasound examination (Nishii et al. 2012).

Osteolysis cannot be diagnosed by ultrasound (Ostlere 2011). Despite the high-resolution images obtained by ultrasound, the use of ultrasound pictures is of limited value in preoperative planning due to limited 3D visualization (Liddle et al. 2013), and preoperative planning will be, to a large extent, based on the radiologist description of the extent of the lesions.

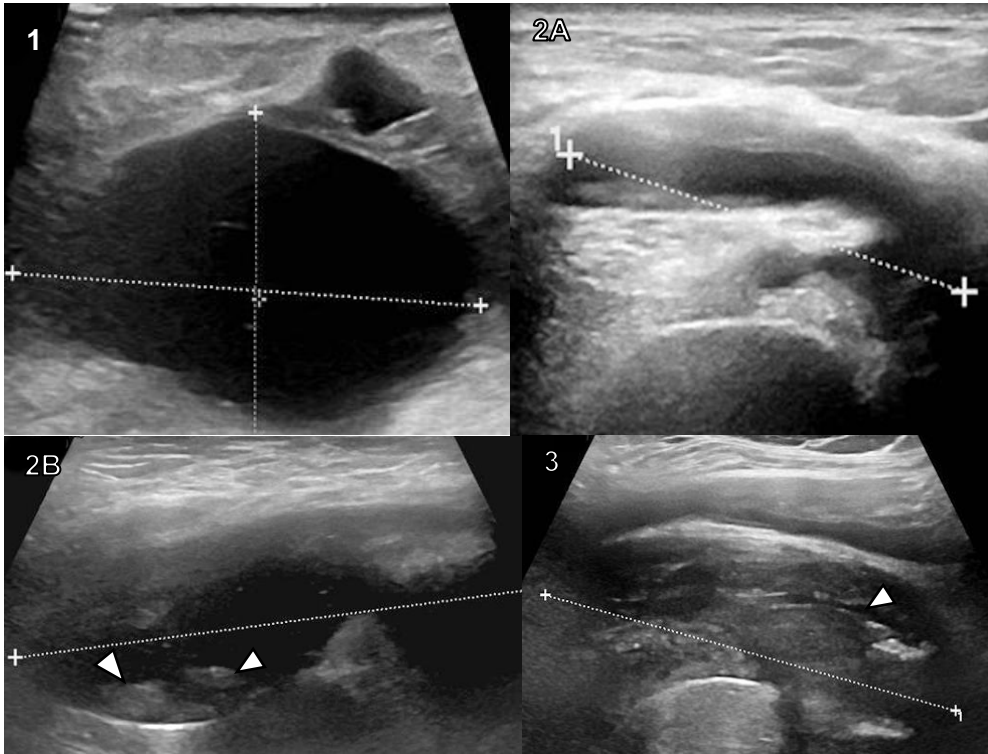


Figure 5. Top left ultrasound image shows thin-walled fluid-filled pseudotumor representing Hart grade 1. Fluid appears hypoechoic (black). Top right image shows thick-walled fluid-filled pseudotumor (Hart grade 2a). Thickened walls are seen hyperechoic as compared to fluid. Bottom left image shows thick-walled pseudotumor with hyperechoic contents (arrow heads) representing Hart grade 2b. The bottom right image shows predominantly solid pseudotumor (Grade 3) with only small amount of fluid in the middle (arrow head). (Hart et al. 2012, Siddiqui et al. 2013).

2.8.5 Computed Tomography

In the same way as MRI, CT is also susceptible to artifacts related to metallic prostheses. Artifacts can be reduced by decreasing the detector collimation and pitch, increasing the kilovolt peak and milliampere-seconds, and by using appropriate imaging algorithms and section thickness. CT is especially useful in the determination of component orientation and fixation, as well as in detecting osteolysis, component loosening and periprosthetic fractures. (Roth et al. 2012, Kwon 2014). The ability of CT to detect pseudotumours is inferior to that of MRI

due to inferior soft tissue contrast, and as previously stated MRI and ultrasound are more valuable tools for the imaging of soft tissues (Robinson et al. 2014). However, the study by Robinson was criticized for using out of date CT techniques, and some consider CT as a viable option for imaging soft tissues (Wellenberg et al. 2015). A high dose of ionizing radiation is associated with the use of CT (Brenner and Hall 2007).

2.8.6 Accuracy of cross-sectional imaging

Two of the earlier studies have compared imaging findings to revision findings (Nawabi et al. 2013, Liddle et al. 2013), whereas others have used other cross-sectional imaging modalities as the gold standard (Garbuz et al. 2014, Muraoka et al. 2014, Nishii et al. 2014, Siddiqui et al. 2014, Robinson et al. 2014). Nawabi studied fluid, solid and mixed synovial patterns seen in MRI and described a sensitivity of 94% and specificity of 87% for MRI when an ALVAL score >5 was used as the gold standard for synovitis. They also performed analyses with intraoperative severe tissue damage (fluid collection with moderate to severe synovial reaction with or without metallosis) as the gold standard, and observed sensitivity of 90% and specificity of 86% for MRI. (Nawabi et al. 2013). Liddle reported that MRI provided a sensitivity of 85% and specificity of 59% for detecting pseudotumours with revision surgery finding as the gold standard. They did not consider small fluid-filled pseudotumours seen in MRI as significant findings, which may explain the relatively low specificity reported in that study. (Liddle et al. 2013). Four prospective studies (Garbuz et al 2014, Nishii et al. 2014, Robinson et al. 2014, Siddiqui et al. 2014) and one retrospective study (Muraoka et al. 2014) have evaluated the sensitivity and specificity of imaging modalities by using other imaging modalities as “the gold standard”. These studies are listed in Table 3. It should be noted that, due to various definitions of pseudotumors, the results are not directly comparable. Three of these studies suggested that ultrasound should be used as a primary cross-sectional imaging modality due to lower cost, higher availability and sufficient accuracy, and that MRI should be considered in cases where abnormality is seen in ultrasound (Garbuz et al. 2014, Muraoka et al. 2014, Nishii et al. 2014). One study suggested that MRI should be the primary imaging modality due to better 3D visualization and muscle atrophy discrimination. In that study, ultrasound was considered better for detecting joint effusion and tendinous pathologies. (Siddiqui et al. 2014). The sensitivity of CT for detecting pseudotumors compared to MRI is reported to be insufficient (Robinson

et al. 2014). In recent clinical studies by Robinson et al. and Waldstein et al., CT was better than MRI for detecting osteolysis (Waldstein et al. 2014, Robinson et al. 2014), whereas MRI was better for detecting osteolysis in a cadaver study including implants with Ti shell and plastic liner (Walde et al. 2005).

Table 3. Sensitivity and specificity of imaging modalities in recent studies.

Author	Modality studied	Gold standard	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Garbuz 2014	MRI	Agreement of MRI and US	92 (71-100)	100 (91-100*)
	US	Agreement of MRI and US	100 (76-100)	96 (88-100)
Muraoka 2014	US	MRI	72 (53-85)	88 (82-92)
Nishii 2014	US	MRI	74 (55-87*)	92 (79-98*)
Robinson 2014	CT	MRI	44 (25-65)	100 (87-100)
Siddiqui 2014	US	MRI	69 (39-91)	83 (36-97)

MRI, magnetic resonance imaging; US, ultrasound; CT, computed tomography. * Confidence intervals were not presented in the original publication, so they were calculated if sufficient raw data was presented (Herbert 2013).

2.8.7 When to image and to re-image?

The United Kingdom MHRA recommends imaging with MRI or ultrasound for all symptomatic patients with MoM hips. For asymptomatic patients, imaging is recommended for all patients with Depuy ASR THAs or resurfacings, and for patients with large diameter (≥ 36 mm) head MoM THAs who have elevated blood metal ion levels (MHRA 2012). Further, the Hip Society has recommended the imaging of all patients who have MoM hip replacements with a poor track record (Lombardi et al. 2012). Cross-sectional imaging for symptomatic patients with MoM hips is recommended by the FDA in the United States (FDA 2012).

Guidelines by the authorities do not take a stance on when cross-sectional imaging should be repeated. Several authors, however, have published on the repeated imaging of MoM hips, all presenting that the development of pseudotumors is a slow and relatively rare process, and that there is seldom a need for repeated imaging more frequently than at one year intervals. Almousa et al. studied the natural history of pseudotumors in a cohort of 15 non-revised hips that went through repeated ultrasound imaging at a mean of 25.8 months (range, 21 to 31) after the initial ultrasound. Ten patients had pseudotumors at initial ultrasound. Of these, the

size of the pseudotumor increased significantly in six, two of which had evidence of damage to adjacent muscle. One transformed from cystic to solid. Three pseudotumors (one solid, 31 cm³, and two cystic, 10 cm³ and 12 cm³) completely disappeared. Further, five patients had isolated fluid collections, of which four disappeared completely, and the fifth increased from 25 cm³ to 136 cm³. (Almoussa et al. 2013). Ebreo et al. reported results of serial (two to four scans per patient) MR imaging of 103 hips. They found a correlation between the severity of pseudotumor grade and the time from the index surgery to MRI. At first MRI, a grade C1 pseudotumor was seen in 16 hips, grade C2 in 15 and C3 in 5. Of the 16 grade C1 pseudotumors, 3 regressed to normal (A), one advanced to grade C2 and one to C3. Of the 15 grade C2 pseudotumors, three advanced to C3. Of the 63 hips with normal initial scan, six developed changes consistent with ARMD. The authors did not recommend imaging more often than annually. (Ebreo et al. 2013). Van der Weegen et al. described the development of pseudotumors at 8 months (range 6 to 12) follow-up in a cohort of 37 hips including 14 pseudotumors at first MRI. At second imaging, five pseudotumors had become smaller and four enlarged. The grade (Anderson et al. 2011) of one pseudotumor regressed from C2 to C1, and one new grade C2 pseudotumor had developed. They concluded that the imaging interval up to one year is safe. (Van der Weegen et al. 2013a). Reito et al. studied retrospectively 154 hips that had gone through repeated imaging with MRI at a median interval of 19 months (range, 5 to 32). They observed a new pseudotumor in 10 hips (7 thin- and 3 thick-walled cystic), the progression of a thin-walled cystic pseudotumor to a thick-walled cystic pseudotumor in three hips, and the disappearance of a thin-walled cystic pseudotumor in 4 hips. (Reito et al. 2014b). Hasegawa et al. studied 24 hips with pseudotumors at index MRI, with follow-up MRI performed after a mean 20 months (range, 8 to 34) interval. They saw increase of pseudotumor size in eight and decrease in six hips, with a decrease of median size. Hasegawa further described that pseudotumors increasing size had a significantly larger initial size compared to those remaining or decreasing in size. (Hasegawa et al. 2014).

2.9 Revision surgery of metal-on-metal hip

2.9.1 Indications

The cumulative incidence of revisions performed on MoM resurfacing and THA hips is significantly higher than that on other bearing surfaces (NJR. 2014, AOANJRR. 2014). In the NJR Annual Report 2014, MoM resurfacings had higher revision rates for aseptic loosening, pain, fracture, malalignment, lysis, implant wear and for other reasons, and MoM THAs for pain, infection, malalignment, lysis, implant wear and for other indications compared to all bearing types (NJR. 2014). Although ARMD is not specific to MoM hips (Carli et al. 2011), most revisions for ARMD are reported in the MoM population, with 3.9 (95% CI 3.4 to 4.4) revisions per 1000 patient-years in MoM hip resurfacings and 5.5 (95% CI 3.1 to 9.7) in MoM THAs, compared to 0.75 (95% CI 0.7 to 0.8) in all hips (NJR 2014). In the Australian registry data, metal-related pathology accounts for 24.3% of MoM resurfacing and 39.9% of MoM THA revisions (AOANJRR 2014).

Guidelines for considering revision surgery because of ARMD are available, although the threshold for actually performing the revision varies greatly between different institutions. The advice given by the UK MHRA is to consider revision of large-diameter (≥ 36 mm) MoM THAs or ASR resurfacings even in asymptomatic patients if cross-sectional imaging is abnormal and/or rising blood metal ion levels are seen. For small head size (< 36 mm) THAs and resurfacings, revision considerations are recommended only if abnormal imaging and/or elevated metal ion levels are accompanied by symptoms. (MHRA 2012). The Hip Society has presented two algorithms for the treatment of patients with MoM hips: one for asymptomatic and one for symptomatic patients. In the algorithm for asymptomatic patients, all patients go through radiographs and blood/serum metal ion measurements. The results are evaluated together with the implant's track record, and may lead to cross-sectional imaging. Based on these findings, either routine follow-up is continued, the patient is invited for a new follow up visit in three to six months, or revision is considered. In the Hip Society algorithm for symptomatic patients, other reasons for symptoms (infection, loosening, tendonitis, extrinsic pathologies) are ruled out with inflammatory parameters and radiographs, followed by blood/serum metal ion measurement and the cross-sectional imaging of all patients. The data is combined with the implant's track record and based on all these, the patient will either return for a new follow-up visit in three to six months, or

revision is considered. Monitoring with a lower threshold for examinations is suggested for patients with a recalled implant. (Lombardi et al. 2012). European consensus statement advises that for patients with findings indicative of ARMD, revision may be considered for symptomatic patients and/or patients with progressive osteolysis and/or large or expanding pseudotumor, and/or progressive neck thinning, and/or Co-ions above cut-off level. Revision should also be considered in cases with excessive high Co (>20 ppb). (Gunther et al. 2013).

2.9.2 Revision procedure

At the moment, there is no consensus on what type of surgical technique or implant will give the best outcome in the revision of MoM resurfacings or THAs. It was previously suggested that when a patient with resurfacing experiences femoral fracture or femoral loosening, it is possible to revise only the femoral component by cutting the femoral head and seating a femoral stem (femoral only revision) and this “revisability” was considered as a theoretical upside for resurfacing (Ball et al. 2007). More often, if the acetabular component has to be changed, a total revision comprising the exchange of the acetabular component, neck osteotomy and the seating of the stem component (combined femoral and acetabular revision) is applied (Liddle et al. 2013, Su and Su. 2013). It has also been suggested that in some cases the resurfacing head can be retained with the replacement of the acetabular component (acetabular only revision) with a polyethylene or metal bearing (Pritchett 2014). In Australian data, the combined revision of the femoral and acetabular component is the most popular option (61%), followed by femoral only (35%) and acetabular only (4%) revisions, neither of which was shown to be superior compared with the other in terms of re-revision rate (Wong et al. 2015). However, a decline in the number of single component revisions performed can be seen in registry data with combined acetabular and femoral revisions gaining popularity (AOANJRR 2014). A previous study from Australian registry data reported inferior results for acetabular only revision (de Steiger et al. 2010), and the poor results for primary MoM THAs (as femoral only revision of resurfacing results in MoM THA) (AOANJRR 2014) may have guided surgeons to consider combined acetabular and femoral revision as a primary option. A dual-mobility femoral prosthesis has been suggested as a one-component-revision option in cases of failed femoral prosthesis with the desire to convert a MoM bearing surface to MoP (Verhelst et al. 2012,

Pritchett 2014, Snir et al. 2015). However, the results of this method have been reported only in small studies with short follow-up.

In revisions of MoM THAs, the well-fixed femoral stem can be retained with an exchange of the modular head (Liddle et al. 2013). In cases with well-fixed, properly orientated modular acetabular component without major osteolysis in the acetabulum, an isolated head and liner change to CoC, CoP or MoP is possible. However, in cases with a monoblock acetabular component, the component has to be removed (Griffin et al. 2012). In cases with a loose stem, the stem component has, of course, to be replaced (Stryker et al. 2014).

There is no definitive data on which bearing surface should be used for the revision of MoM hips with ARMD. CoC, CoP or MoP components are considered favorable, as they further reduce the Co and Cr burden compared to MoM (De Haan et al. 2008a, Liddle et al. 2013). A study using Australian registry data found no difference between the bearing surfaces used in the revisions of MoM hip resurfacings (Wong et al. 2015). Still, some authors consider MoM components as a viable option for revision (Gross and Liu 2014).

No consensus is available on how much debridement should be done when performing a revision for ARMD. Resection of all necrotic and metallic tissue is often recommended (Griffin et al. 2012), although extensive tissue resections have been reported to be associated with instability (Grammatopolous et al. 2009) and possible nerve injury (Munro et al. 2013). Therefore, some authors have considered limited debridement as an option (Gross and Liu 2014). A constrained liner has been suggested for patients treated with vast tissue resections (Griffin et al. 2012). However, high failure rates seen with the constrained liners used for revision raises concerns (Noble et al. 2012).

2.9.3 Post-revision follow-up

No official guidelines on postoperative follow-up after revision for ARMD have been made. The European consensus statement has advised against the routine postoperative Co and Cr monitoring because there are no effective interventions available after revision (Gunther et al. 2013). In the institution of Liddle et al., patients were followed-up at 6, 12, 26 and 52 weeks postoperative with clinical assessment, blood metal ions, radiographs and hip scores. Cross-sectional imaging was performed on patients with postoperative pain. (Liddle et al. 2013). Pritchett followed his patients radiographically at 2 weeks, 6 weeks, 6 months and thereafter

annually. Harris Hip Score was recorded at final follow-up. No metal ion measurements or cross-sectional imaging was used for postoperative follow-up. (Pritchett 2014).

2.9.4 Results of revision surgery

2.9.4.1 Post-operative complications and re-revisions

In the Australian registry, the 10-year cumulative percentage for re-revisions of hip resurfacings is 27.1% (95% CI, 22 to 33) (AOANJRR 2014). Table 4 encompasses the studies that have reported the complications and re-revisions after the revisions of MoM hip resurfacings or MoM THAs. The specific complications and reasons for re-revision are listed in Table 5. Several studies have reported that revisions due to metal debris-related pathologies have a high complication rate (Grammatopolous et al. 2009, Munro et al. 2013, Stryker et al. 2014). It has, however, also been stated that acceptable results can be achieved from these revisions (Gross and Liu 2014).

2.9.4.2 Functional outcome

In the study by Grammatopolous et al. resurfacings revised for pseudotumors provided a significantly worse clinical outcome compared to other indications (Grammatopolous et al. 2009). Su and Su reported that resurfacings revised for unexplained pain resulted in significantly worse functional scores compared to cases where the etiology of symptoms was clear (Su and Su 2013). Revisions of MoM resurfacings for other reasons than ARMD generally provide good results in terms of functional scores. Ball et al. and Eswaramoorthy et al. observed no difference in functional scores or pain between patients with resurfacing revised to THA compared to primary THA (Ball et al. 2007, Eswaramoorthy et al. 2009). De Haan et al. reported an increase of mean Harris Hip Score from 73 to 90 (De Haan et al. 2008a), and De Smet et al. from 70.4 to 93.1 after revision of hip resurfacings (De Smet et al. 2011). Liddle et al. reported an increase in OHS from a preoperative median 15 to 37 (Liddle et al. 2013). In 90 resurfacing hips treated with one-component revision due to ARMD, Pritchett saw an increase of mean Harris Hip Score from 72 to 93 (Pritchett 2014). Studies with MoM THAs did not include functional scores.

Table 4. Complications and reasons for re-revisions after a revision of MoM hip resurfacings and stemmed MoM THAs

Author (year)	Implants (HR/THA)	Two most common revision indications	Follow-up time, years (mean, range)	Complications without re-operation	Re-operations	Other
Ball (2007)	21/0	16 Femoral loosening, 5 neck fracture	3.8 (1.0-9.4)	3 (14%)	0 (0%)	No difference compared to primary THA
De Haan (2008a)	42/0	34 component malposition, 6 loosening	2.7 (1.0 – 7.3)	3 (7%)	4 (10%)	-
De Smet (2011)	113/0	68 cup malpositioning, 57 osteolysis	2.6 (0-8.4)	5 (4%)	6 (5%)	Less complications in later revised
Eswaramoorthy (2009)	29/0	12 loosening, 11 pain	5.0 (1.7-11.7)	0 (0%)	1 (3%)	No difference compared to primary THA
Gilbert (2010)	76/0	31 femoral fracture, 26 osteonecrosis	3.8 (NA)	0 (0%)	4 (5%)	Revisions for loosening had worse outcome
Grammatopolous (2009)	53/0	21 fracture, 16 pseudotumor	3.0 (0.8-7.2)	3 (6%)	10 (4%)	More complications in patients with pseudotumors
Gross (2014)	58/0	58 ARMD	5.2 (2.0-11.4)	2 (3%)	2 (3%)	No complications in patients with ARMD
Liddle (2013)	32/7	31 ARMD/unexplained, 8 “conventional”	2.5 (1.0-4.5)	0 (0%)	2 (5%)	Revisions in hips with solid pseudotumor
Matharu (2014)	46/18	64 ARMD	4.5 (1.0-14.6)	5 (8%)	8 (13%)	Hips revised to MoM had higher risk for re-revision
Munro (2013)	0/32	19 ARMD, 10 acetabular loosening	2.1 (0.8-4.0)	12 (38%)	6 (20%)	Less loosening in porous cups
Pritchett (2014)	90/0	90 ARMD	5.1 (3.0-9.8)	0 (0%)	3 (3%)	All failures in patients revised to MoM
Stryker (2014)	0/114	58 metallosis, 31 aseptic loosening	1.2 (0-10.2)	10 (9%)	18 (16%)	Patients with complication were older than those without
Su (2013)	55/0	23 mechanical reason, 13 metallosis	2.3 (0.7-6.7)	0 (0%)	2 (4%)	Those revised for unexplained pain had worse clinical result
Wyles (2014)	0/37	19 loosening, 8 ARMD	2.8 (2.0-6.8)	0 (0%)	3 (8%)	Higher infection rate than expected

HR, hip resurfacings; THA, total hip arthroplasty; ARMD, Adverse Reaction to Metal Debris; MoM, metal-on-metal. “Loosening” refers to aseptic loosening.

Table 5. Complications and reasons for re-revisions after a revision of MoM hip resurfacings and stemmed MoM THAs.

Author (year)	Complications without revision	Complications that required revision
Ball (2007)	1 nerve palsy, 1 intraoperative fracture, 1 intraoperative	None
De Haan (2008a)	3 dislocations	1 dislocation, 1 acetabular loosening, 1 femoral loosening, 1 acetabular protrusion
De Smet (2011)	4 dislocations, 1 infection	2 component loosening, 2 infections, 1 dislocation, 1 metal sensitivity
Eswaramoorthy (2009)	None	1 persistent pain
Gilbert (2010)	None	3 infections, 1 loosening
Grammatopolous (2009)	3 nerve palsies	4 infections, 3 dislocations, 2 loosening, 1 fracture
Gross (2014)	1 recurrent dislocation, 1 superficial infection	2 loosening
Liddle (2013)	None	1 instability, 1 incomplete pseudotumor resection
Matharu (2014)	1 infection, 1 DVT, 1 nerve palsy, 1 dislocation, 1 hematoma	2 dislocations, 2 recurrent ARMD, 1 infection, 1 component mismatch, 1 loosening, 1 unexplained pain
Munro (2013)	9 dislocations, 2 nerve injuries, 1 loosening	3 dislocations, 3 loosening
Pritchett (2014)	None	1 loosening, 1 ARMD, 1 infection
Stryker (2014)	7 aseptic loosening, 7 deep infections, 5 dislocations, 3 acetabular fractures, 2 superficial infections, 2 infected hematoma, 1 hematoma, 1 delayed wound healing	18 hips went through re-revision, it was not specified which ones had complications
Su (2013)	None	2 infections
Wyles (2014)	None	3 infections

“Infection” without further definition refers to deep infection. “Loosening” refers to aseptic loosening. DVT, deep venous thrombosis. ARMD, Adverse Reaction to Metal Debris.

2.9.4.3 Blood metal ion levels

Ebreo et al. were the first to report a decrease in blood Co and Cr levels after the revision of MoM hips with a mean follow-up of two years (Ebreo et al. 2011). Ball et al. also reported a decline in serum Co and Cr levels at 1-year follow-up. They saw a less predictable decline with ultra-high Cr levels (>20 ppb) compared to Co or low Cr. In some of their patients, serum Cr remained elevated for over a year after the revision of a MoM bearing. (Ball et al. 2013). Durrani et al. further described elevated blood Cr levels 12 months after the revision of a MoM implant (Durrani et al. 2014), which they believed to be due to the accumulation of Cr in the liver and spleen (Urban et al. 2004), mobilization of Cr stored in the adjacent tissues (Hart et al. 2010) or reduced renal clearance.

2.9.4.4 Recurrence of pseudotumors/ARMD

Grammatopolous et al. reported recurrent pseudotumors in three of five hips requiring further revision surgery in their cohort of 53 revised resurfacings (6%) (Grammatopolous et al. 2009). After 113 MoM resurfacing revisions, De Smet et al. performed six re-revisions, with one of them being for “metal sensitivity” (De Smet et al. 2011). Munro et al. reported pseudotumor recurrence in three (9%) of 32 MoM THA revisions (Munro et al. 2013). Among 39 MoM revisions in a study by Liddle et al., one incompletely resected pseudotumor required a re-revision (Liddle et al. 2013). Pritchett observed one (2%) recurrent ARMD among 43 patients treated with new MoM components in revision (Pritchett 2014). Other studies described in previous paragraphs did not include cases with residual/recurrent ARMD. None of the studies systematically implemented postoperative cross-sectional imaging.

2.9.4.5 Radiographs

Ball et al. reported no component loosening in 21 revised resurfacings with a minimum follow-up time of one year (Ball et al. 2007). Eswaramoorthy et al. reported three non-progressive radiolucent lines at the femoral side with no

suspicion of any component loosening in a cohort of 29 resurfacings converted to THAs (Eswaramoorthy et al. 2009). Munro et al., on the contrary, reported radiographic evidence of acetabular loosening in four out of 17 (24%) fiber metal acetabular components in their study (Munro et al. 2013).

2.9.4.6 What predicts a poor result of revision for ARMD?

There are only few studies that have analyzed factors predicting the result of revision surgery. Matharu included a wide range of pre- and intraoperative factors and studied whether they predicted the risk for complications or re-revisions. The only risk factor identified was revision to MoM bearing, which increased the risk of re-revision (Matharu et al. 2014). Also, another study suggested that revision to MoM bearings yields a worse outcome, as well as the revision of a hip with a solid pseudotumor (Liddle et al. 2013). In a cohort with 51% of revisions performed for metallosis, those patients that suffered a postoperative complication were significantly older (mean 66 years versus 58 years) than those who did not suffer a complication (Stryker et al. 2014). Fiber metal acetabular components have a higher risk for component loosening compared to porous tantalum cups (Munro et al. 2013).

2.10 The current role of metal-on-metal hip replacements

2.10.1 Guidelines by authorities

Despite the wear-related problems in MoM hips, the majority of the national and international authorities have not recommended discontinued use of MoM hip resurfacings or stemmed THAs so far, but instead emphasize careful patient selection and follow-up (MHRA 2012, TGA 2012, Health Canada 2012, FDA 2012, Hannemann et al. 2013). Some of the national orthopaedic associations have advised against the use of all MoM hip replacements, or specifically large diameter THAs. The British Hip Society has advised against the use of large diameter (≥ 36 mm) MoM THAs, but not against small head MoM THAs or resurfacings (British Hip Society 2012). The Finnish Arthroplasty Association has advised against the use of all MoM hip

replacements (Finnish Arthroplasty Association 2015), and the Dutch Orthopaedic Association has advised against the use of all large diameter (≥ 36 mm) MoM replacements until further information about safety is available (Verheyen and Verhaar 2012).

2.10.2 MoM hip resurfacings

A minimum of 10-year clinical results have been reported for only two resurfacing designs: namely the BHR and Conserve plus. There are several studies reporting survivorship of BHR, both from the designing (Matharu et al. 2013, Daniel et al. 2014) and independent centers (Murray et al. 2012, Holland et al. 2012, Van Der Straeten et al. 2013, Reito et al. 2014b, Mehra et al. 2015). For Conserve plus, only the designing center has reported results with follow-up of more than 10 years (Amstutz et al. 2010). All the studies on BHR have reported worse implant survival figures for females (74% to 92% at 10 to 15 years) compared with males (93% to 100%) (Murray et al. 2012, Holland et al. 2012, Van Der Straeten et al. 2013, Matharu et al. 2013, Daniel et al. 2014, Reito et al. 2014b, Mehra et al. 2015). Three out of six studies including multivariable analysis identified small femoral head size as a risk factor for failure (Holland et al. 2012, Murray et al. 2012, Matharu et al. 2013). In registry data of NJR and AOANJRR, the overall revision rates are 13% at 10 years (NJR. 2014) and 11.2% at 13 years (AOANJRR 2014), with point estimates of individual resurfacing brands varying from 9% to 31% (10-year) and 4% to 24% (7-year), respectively.

Based on the higher revision rates compared to conventional THAs in registry data, the risk for ARMD and the lack of studies showing significantly improved functional outcome compared to conventional THAs, the discontinued use of MoM resurfacings has been suggested (Dunbar et al. 2014). However, that article has been criticized for only accounting for registry data, and omitting analysis of the excellent results of some resurfacing brands in specific subgroups (Matharu et al. 2015c). Some have suggested that the use of MoM resurfacings can be continued, but that the indications should be refined to include mainly male patients with OA, and that only head sizes of 46 mm and above should be used (Cadossi et al. 2015, Matharu et al. 2015c). Also, the importance of thorough patient counselling about unique failure types of resurfacings (neck fracture, etc.), risk for ARMD and unknown long-

term effects is emphasized (Matharu et al. 2015c). The use of MoM resurfacings in women has been questioned (Murray et al. 2012).

2.10.3 MoM total hip arthroplasties

NJR data has described overall revision rates of 22% at 10 years (NJR 2014) for MoM THAs. In Australian registry data, the results of small head sizes are better (10-year revision rate 5.7% for ≤ 28 mm and 6.5% for 30-32 mm) compared to large sizes (10-year revision rate 12.9% for 36-40 mm and 25.5% for > 40 mm), with 7-year revision rates of individual component brands ranging between 4.3% and 37.2% in large head size MoM THAs (AOANJRR 2014). A study based on analyses from the NJR registry advised against using stemmed large diameter stemmed MoM hip replacements (Smith et al. 2012c). However, this advice has been criticized for lumping together all the stemmed MoM devices and patient groups, as there are differences in implant designs and results for certain patient groups (Amstutz and Le Duff 2012).

Only one center has reported clinical results with follow-up exceeding 10 years for large diameter MoM THAs. In that study, 12-year implant survival of 87% (95% CI, 84% to 90%) was reported, with female gender, young age and high acetabular inclination as risk factors for failure (Lombardi Jr et al. 2015). Early and mid-term results have varied from catastrophic (51% survival at 6 years (Langton et al. 2011a) and 38% seven years (Reito et al. 2013)) to excellent between large diameter head size THA brands (Engh et al. 2010, Barrett et al. 2012). Even though a high prevalence (20%) of pseudotumors has been reported in small head size MoM THAs as well (Hwang et al. 2014), excellent 11 to 19-year survival figures (Grubl et al. 2007, Nikolaou et al. 2011, Randelli et al. 2012, Hwang et al. 2013) have been presented accompanied by registry data showing a low revision rate in small head size MoM THAs (AOANJRR 2014).

Of the most recent studies, several authors have reported that they have discontinued the use of large diameter MoM THAs (Levy and Ezzet 2013, Lombardi Jr et al. 2015), and some have stated that clearly longer-term results are needed (Saragaglia et al. 2015). The small head size MoM THA is considered to be a viable option by some institutions, although the potential risk of ARMD has raised some concerns (Hwang et al. 2013).

2.10.4 Comparison to National Institute for Health and Care Excellence criteria

According to United Kingdom National Institute for Health and Care Excellence (NICE) criteria, primary hip replacements should have a revision rate of 10% or less at 10-year follow-up (NICE 2000). In the NJR Annual Report 2014, 10-year revision rates of both hip resurfacings (13%) and stemmed MoM THAs (22%) exceeds the NICE benchmark. For MoM THAs, this is true both in males and females in all age groups. Unfortunately, NJR does not separate small and large diameter MoM THAs. However, among hip resurfacings, the revision rate is acceptably below the NICE criterion for males in all age groups, whereas females have a revision rate approximately double the NICE standard in all age groups. Of specific resurfacing brands, BHR and Durom (recalled) have revision rates within 10% at 10 years, whereas ASR, Cormet and Conserve plus clearly have a higher percentage. (NJR. 2014). In the Australian registry Annual Report 2014, revision rates of hip resurfacings performed for primary OA as well as small head MoM THAs operated on for any reason are within the NICE criteria, whereas the revision rate of large diameter THAs is clearly higher. Also, AOANJRR data shows acceptable revision rates for males in all age groups, whereas revision rates of females in all age groups are unacceptably high. Males with head size >50 mm have an acceptable revision rate, whereas males with small components and females with any size components do not. BHR is the only one of the four resurfacing brands with 10-year follow up that fulfils the criterion. Among THAs, large head sizes (≥ 36 mm) have a higher revision rate than the NICE standard both in females and males, and in all age groups. The Pinnacle MoM acetabular system is the only large head MoM THA with a 10-year revision rate below the NICE benchmark. (AOANJRR 2014).

Based on registry data, the use of resurfacings in certain patients and small head diameter THAs in all patients can be rationalized, but the use of large diameter components is more problematic. It has been stated that “the era of one device fits all has long gone” (Amstutz and Le Duff 2012), and some centers have chosen to continue the use of some hip resurfacing and small diameter THA brands at least in certain patient groups, even though the risk for ARMD remains and the long-term systemic effects of accumulating metal debris is unknown (Migaud et al. 2012, Cadossi et al. 2015, Matharu et al. 2015c).

3 Aims of the Study

The purpose of this thesis was to investigate diagnostic methods for detecting ARMD associated with MoM hips, and to investigate the results of the systematic screening and operative treatment established at our institution.

The specific aims of the studies were to investigate:

- Study I: Implant and patient-specific risk factors for elevated whole blood cobalt and chromium ion levels and the percentage of elevated ions among patients operated on with various MoM implant brands
- Study II: Sensitivity and specificity of MRI for detecting extracapsular pseudotumors
- Study III: Sensitivity and specificity of ultrasound for detecting extracapsular pseudotumors
- Study IV: Effect of systematic screening protocol including blood metal ion measurements and targeted cross-sectional imaging on the revision rate in MoM hips
- Study V: Clinical results, blood metal ion levels and imaging after the revision of a metal-on-metal hip due to Adverse Reaction to Metal Debris

4 Patients and methods

4.1 Patients

At our institution, 2868 large-diameter head size (≥ 36 mm) MoM resurfacings or MoM THA hips (2398 patients) were implanted between November 2000 and February 2012. For study I, we identified all patients with a unilateral MoM hip and at least one previous whole blood metal ion measurement. Patients with bilateral MoM hip replacements (470 patients, 940 hips) were excluded, as the individual effect of each hip could not be determined. A total of 1928 patients with unilateral MoM hip resurfacing or THA were identified. The implants used are described in Table 6.

Table 6. Implant brands included in study I.

Brand (manufacturer)	Hip Resurfacings	Total Hip Arthroplasties
ASR (Depuy Orthopaedics, Warsaw, IN, USA)	303	375
BHR (Smith & Nephew, Memphis, TN, USA)	257	96
Conserve+ (Wright Medical, Memphis, TN, USA)	10	2
Continuum (Zimmer, Warsaw, IN, USA)	-	4
Durom (Zimmer, Warsaw, IN, USA)	113	41
M2A (Biomet, Warsaw, IN, USA)	-	67
Mitch (Finsbury Orthopedics, Leatherhead, UK)	4	13
MMC (Zimmer, Warsaw, IN, USA)	16	9
Pinnacle (Depuy Orthopaedics, Warsaw, IN, USA)	-	294
R3 (Smith & Nephew, Memphis, TN, USA)	-	76
ReCap (Biomet, Warsaw, IN, USA)	48	200

The mean age at primary surgery was 58.9 years (standard deviation, SD 10.0), 1133 (58.8%) of the patients were males and indication for surgery was OA in 1481 cases (77%). Twelve hips had already been revised before the start of the screening, 25 patients died before the ion levels were measured and measurements were not available due to other unspecified reasons for 143 patients. A population of 1748 patients with large-diameter headsize MoM

hips and at least one blood metal ion measurement was identified. In 304 patients, a contralateral hip implant with bearing surface other than MoM was identified, but none of these were excluded from the study group, as median Co and Cr levels were similar to those without contralateral hip implants (median Co 1.2 vs 1.2 ppb, $p=0.506$ in resurfacings and 2.2 vs 2.4 ppb, $p=0.939$ in THA, and median Cr 1.4 vs 1.4 ppb, $p=0.555$ in resurfacings and 1.6 vs 1.6 ppb, $p=0.460$ in THA). There was a significantly higher percentage of males among patients with resurfacings compared to patients with THAs (67.8% vs 53.5%, $p<0.001$). The patients with resurfacing were younger (mean age 54.7 years [SD 9.2] vs 61.3 years [SD 9.3], $p<0.001$), had lower BMI (27.7 [SD 4.3] vs 28.6 [SD 5.4], $p<0.001$), higher ROM (231 degrees [SD 47] vs 207 degrees [SD 57], $p<0.001$), and a longer follow-up time (5.3 years [SD 2.4] vs 4.7 years [SD 2.0], $p<0.001$), as compared to patients with MoM THAs. The mean acetabular inclination was similar in both groups (46.0 degrees [SD 6.9] vs 46.2 [SD 7.5], $p=0.560$).

For study II, we identified all patients operated on with ASR hip resurfacing or ASR XL THA between March 2004 and December 2009. ASR hip resurfacing had been used for 498 hips and ASR XL THA for 538 hips. Of these, we identified the ones that had been imaged with MRI in our systematic screening protocol to identify hips with ARMD and whose implant was later removed in a revision surgery. At the time of study II, 232 ASR hips in 218 patients had been revised. Pre-revision MRI had been performed on 158 patients (170 hips) and 155 of them had given their informed consent for MoM studies and were included (167 hips). There were 39 ASR resurfacings and 128 ASR XL THAs. Eight patients had bilateral XL THA, three had bilateral resurfacing and one had an XL THA on one side and a resurfacing on the other. The analyses in this study were also repeated with the exclusion of the 12 patients with bilateral MoM hip replacements to control clustered observations bias (Ranstam et al. 2011). Mean age at the time of revision was 53.0 years (SD 9.5) in the hip resurfacing group and 64.1 years (SD 8.8) in the THA group. Twelve (34%) patients were men in the hip resurfacing group and 43 (36%) in the XL THA group. Mean time between primary surgery and revision was 5.4 years (SD 1.5) in resurfacings and 4.6 years (SD 1.3) in THAs, and median time between pre-revision imaging and revision surgery was 6.7 months (range, 0.9 to 19.7) and 8.8 months (range, 0.8 to 27.2), respectively. Indication for primary surgery was OA in 125 (75%) patients.

Study III included the patients with any MoM hip replacement that had been imaged with ultrasound before revision. At the time of the data collection in May 2013, 433 MoM hips in 397 patients had been revised. Pre-revision ultrasound was available for 125 hips (117 patients). A patient was excluded if the interval between imaging and revision surgery was longer than one year, as we had previously observed significantly worse sensitivity for cross-sectional imaging performed over one year before the revision (Lainiala et al. 2014) which left us with 116 hips in 109 patients. Also, if MRI had been performed less than one year before imaging with ultrasound, the hip was excluded from the analyses, as the previous imaging could cause bias in the results. After these exclusions, 86 hips in 82 patients remained. Of four patients with bilateral revision, only the right hip was analyzed to avoid clustered observations bias (Ranstam et al. 2011). Therefore, 82 patients (82 hips) met the inclusion criteria. Of these, revision surgery was performed for 78 patients due to ARMD, two for infection, one for loosening of the acetabular component, and one for the malpositioning of the acetabular component associated with pain and a sensation of subluxation. Reasons other than ARMD were included in this study, contrary to study II, as a reviewer from the publishing journal considered it more clinically relevant to describe sensitivity and specificity in a cohort of painful hips, not just in a cohort of hips with ARMD. The study included 64 MoM THAs: 35 ASR, two M2A, three Mitch, nine Pinnacle, six R3, three ReCap, four BHR, one Durom and one Conserve plus THA. There were 18 resurfacings including nine ASR and nine BHR resurfacings. Mean age at the time of revision was 53.5 years (SD 12.9) in the hip resurfacing group and 65.7 years (SD 8.4) in the MoM THA group. Thirty-two (39%) patients were males. Mean time between primary and revision surgery was 5.4 years (SD 1.8) and median time between ultrasound and revision was 4.1 months (range, 0.3 to 11). Indication for primary surgery was OA in 61 hips (74%).

For study IV, we identified all patients with Pinnacle 36 mm head size MoM hip implants operated on at our institution. Between December 2002 and September 2010 a total of 371 patients (430 hips) had received such a Pinnacle hip. All 371 patients were included in implant survival analysis. However, results of blood Co and Cr measurements, OHS and cross-sectional imaging were reported only for those 326 patients (378 hips) who gave their informed consent for screening. The mean age was 62.7 years (SD 7.1) and mean follow-up 7.5 years (SD 2.0). There were 172 males (202 hips) and 199

females (228 hips). Indication for primary surgery was OA in 343 (80%) of cases. The stem components used were Summit in 398 hips (93%), Corail in 17 (4%), S-ROM in 14 (3%) and Prodigy in one.

For study V, 240 patients (263 hips) with ASR hip resurfacings or ASR XL THAs who had gone through a revision surgery between December 2005 and April 2013 were identified. A minimum one-year postoperative follow-up was mandatory for inclusion. Of the total 240 patients, we excluded 33 patients (36 hips) with revision for indications other than ARMD, leaving us with 207 patients (227 hips) who had gone through revision for ARMD. To increase the homogeneity of our study cohort, we further excluded the patients revised before the ASR recall in 2010, as preoperative examinations and postoperative follow-up was different in those patients (12 patients, 12 hips, three with remaining contralateral ASR hips). Our final study cohort included 198 patients (215 hips), of which 154 patients (166 hips) had ASR XL THAs and 44 patients (49 hips) had ASR hip resurfacings revised. The stems that had been used in the index THAs were Summit in 119, Corail in 36, S-ROM in nine, Prodigy in one and Proxima in one. In two cases the stem had to be revised, and the Summit stem was used. In revisions of resurfacings, the Summit stem was used in 38 hips, Zimmer M/L Taper in four, S-ROM in four, and Corail in three. The Deltamotion (Depuy) cementless monoblock CoC cup was used in 64 revisions, cementless modular Pinnacle (Depuy) cup in 55 revisions (CoC in 39, CoP in nine and MoP in seven). The cementless porous-coated modular Continuum (Zimmer) cup was used in 61 revisions (CoC in 32, CoP in 15, MoP in 11 and constrained MoP in three), and the cementless Trabecular Metal (Zimmer) tantalum cup in 34 revisions (MoP in 25, CoP in one, constrained MoP in seven and constrained CoP in one). The Exceed (Biomet) CoC liner was used in one revision. Ti sleeve adapters were applied when ceramic head components were used. The study population included 77 males (85 hips) and 121 females (130 hips). The mean age was 62.1 years (SD 10.1 years), mean time from primary to revision surgery was 4.7 years (SD, 1.3 years, and mean postoperative follow-up was 2.3 years (SD 0.6 years). The primary diagnosis was OA in 156 hips (73%).

4.2 Methods

4.2.1 Primary surgeries and implants used

Resurfacings were mainly used in young (89% of patients aged ≤ 65 years) and active patients with good bone quality. Contraindications included avascular necrosis of the femoral head, severe developmental dysplasia of the hip, insufficient bone quality and renal dysfunction. Inflammatory arthritis was a relative contraindication. If a patient was considered to benefit from the large head size (for example risk for dislocation), but had contraindications for resurfacings, MoM THA was considered. Renal insufficiency was a contraindication for MoM THA as well.

Primary surgeries were performed by or under direct supervision of 22 orthopaedic surgeons (Ala-Mononen, Arnala, Eskelinen, Halonen, Honkanen, Kangas, Karila, Ketola, Kuusela, Lehtinen, Lehto, Lepistö, Moilanen, Niemeläinen, Niemi, Nieminen, Pajamäki J, Puolakka, Päivärinta, Raivio, Skyttä and Syrjä). The Harris Hip Score was used to evaluate the preoperative function of the hip (Harris 1969). Primary operations were performed using a posterior approach. In MoM THAs, the joint was exposed and femoral neck cut. The acetabulum was reamed and the cup component was fitted. Then, the medullary canal was prepared to allow for the seating of the femoral stem component. In MoM hip resurfacings, the femoral neck was left intact, and a cylindrical head cutter was used to allow seating of the resurfacing head component, followed by reaming of the acetabulum and inserting of the cup. The resurfacing head component was inserted after the cup component was fixed. The joint capsule, detached tendons and muscles, as well as fascia and subcutis were closed with absorbable sutures, and the skin with staples. Operations were performed in spinal anaesthesia. General anaesthesia was only used in rare exceptions. Cefuroxime antibiotic prophylaxis was used. If the patient was known to be allergic to penicillin or cephalosporines, clindamycin prophylaxis was administered. All patients were mobilized the day following surgery by a physiotherapist. Before the risk for ARMD was acknowledged, the patients were followed up with a follow-up program that included clinical assessment by a physiotherapist at one, three, five, and eight years after surgery, and plain radiographs at the same intervals.

4.2.2 Screening protocol

After the announcement of medical device alert concerning ASR MoM hip replacements by the UK MHRA in August 2010, Coxa Hospital for Joint Replacement launched a mass-screening program to identify those patients that had ARMD in their ASR hip. The program included the screening of all patients with ASR hip resurfacings or ASR XL THAs with blood Co and Cr measurements, MRI and OHS questionnaires. MRI was used as a primary imaging modality. If MRI was contraindicated, ultrasound was used for imaging. In the OHS questionnaire, each question was scored from 0 to 4, with a maximum score of 48 (Murray et al. 2007). In 2012, four extra questions were added to questionnaire. These extra questions asked the patients whether they had experienced one of the following: clanking or squeaking from the hip, sensation of subluxation, a sensation of pressure or numbness in the hip region.

In January 2012, the screening was expanded to patients with other MoM implant brands. However, systematic imaging was not performed on patients with other implant brands, but instead targeted imaging was performed on those patients with symptoms or elevated whole blood cobalt or chromium levels.

4.2.3 Blood metal ion concentration measurements

Blood samples were acquired from the antecubital vein with a twenty-one-gauge needle connected to a Vacutainer™ system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and trace element tubes containing sodium ethylenediaminetetraacetic acid (EDTA). The first 10 ml was disposed of to avoid metal contamination from the needle. Measurements were performed at the Finnish Institute for Occupational Health with dynamic reaction cell inductively coupled plasma (quadrupole) mass spectrometry (Agilent 7500 cx, Agilent Technologies, Santa Clara, CA, USA). Co and Cr concentrations were measured from whole blood.

4.2.4 Imaging

In studies including MRI (II, IV, V), imaging was performed with two 1.5T scanners (Siemens Magnetom Avanto, Siemens Healthcare, Erlangen, Germany and GE Signa HD, General Electric, Healthcare, Wisconsin, USA) using parameters designed to limit metal artifact (Table 7 and 8). The sequences used in the imaging were coronal and axial T1-weighted fast spin echo (FSE), and coronal, axial and sagittal short tau inversion recovery (STIR).

MR images were prospectively graded using Anderson classification (Anderson et al. 2011) and retrospectively regraded by a senior musculoskeletal radiologist with seven years' experience (Elo) using the classification by Hart et al. (2012). A pseudotumor was defined as any abnormal extracapsular cystic or solid mass, with or without connection to the joint capsule. Hips without extracapsular abnormalities were graded as 0. Thin-walled, fluid-filled pseudotumors were graded as grade 1. Grade 2a included fluid-filled pseudotumors with thick or irregular walls, and pseudotumors in grade 2b had thick or irregular walls and atypical contents. Grade 3 included solid pseudotumors. (Hart et al. 2012). The grading system used did not include location of the pseudotumor, so the analyses were not performed separately for the iliopsoas region and the trochanteric region.

Table 7. Parameters used with Siemens Magnetom Avanto 1.5 T (Siemens Healthcare, Erlangen, Germany).

Pulse sequence name	TR (ms)	TE (ms)	TI (ms)	FOV (mm)	Matrix size	ST (mm) / gap (mm)	BW (Hz/pixel)	ETL
Coronal T1 weighted Spin Echo	600	9		420	403x448	6.0/1.2	485	1
Coronal Turbo Inversion Recovery	3410	23	150	450	350x448	6.0/1.8	465	11
Transversal T1 weighted Spin Echo	440	9		420	302x448	6.5/1.2	485	1
Transversal Turbo Inversion Recovery	4871	24	150	420	392x512	6.0/1.8	465	11
Sagittal Turbo Inversion Recovery	3300	24	150	400	355x512	6.0/1.8	391	11

TR Time of Repetition (ms, millisecond), TE Time of Echo, TI Time of Inversion, FOV Field of View, ST Slice thickness, BW Band Width, ETL Echo Train Length, Radiofrequency coil used: combination of 6 channel body matrix coil and 24 channel spine matrix coil. Only 6 to 12 channels of the spine matrix coil were used.

Table 8. Parameters used with GE Signa HD 1.5 T (General Electric, Healthcare, Wisconsin, USA).

Pulse sequence name	TR (ms)	TE (ms)	TI (ms)	FOV (mm)	Matrix size	ST (mm) / gap (mm)	BW (Hz/pixel)	ETL
Coronal T1 weighted Spin Echo	620	18		430	256x512	6.0/1.0	122	2
Coronal Fast Inversion Recovery Transversal T1	3200	41	150	430	224x512	6.0/1.0	122	8
weighted Fast Spin Echo	610	19		440	224x512	6.0/1.5	122	2
Transversal Fast Inversion Recovery	4400	58	150	440	224x512	6.0/1.5	122	8
Sagittal Fast Inversion Recovery	6100	41	150	420	224x512	6.0/1.5	122	8

TR Time of Repetition (ms, millisecond), TE Time of Echo, TI Time of Inversion, FOV Field of View, ST Slice thickness, BW Band Width, ETL Echo Train Length. Radiofrequency coil used: 8- channel body coil.

Ultrasound examinations (Studies III, IV, V) were performed with Logiq e9 (GE Healthcare, Wisconsin, USA) by one of three musculoskeletal radiologists. In most cases, an ML 6-15-D linear transducer was used (4.5-15.0 MHz, 13x58 mm footprint, 50 mm field of view (FOV), and 8 cm depth of field (DOF)). In cases with poor visibility due to obesity, a 9L-D linear transducer (2.4-10.0 MHz, 14x53 mm footprint, FOV 45 mm, and DOF 12 cm) or a C1-5 convex transducer (1.6-6.0 MHz, 17x75 mm footprint, FOV 65 degrees and DOF 35 cm) was used. An anterior approach was used to evaluate the hip joint, the iliopsoas muscle and the tendon region. The greater trochanteric and deep fascia region were analyzed using a lateral approach. The trochanteric and gluteal region were analyzed from the posterior view. Pseudotumors were classified as fluid-filled, mixed type or solid based on the description consistency of the radiologists, contents and wall thickness. In fluid-filled pseudotumors, thin wall hypoechoic collection was mainly seen. Pseudotumors with significantly thickened wall and/or solid contents among the hypoechoic fluid were classified as mixed type. A soft tissue mass with a mainly solid echo structure was graded as a solid pseudotumor. Intracapsular findings were not systematically classified, and therefore they were not included in the analysis. Joint fluid aspirates were not routinely acquired.

Studies IV and V included an analysis of plain radiographs. A musculoskeletal radiologist (Elo) evaluated the radiolucencies and osteolysis. The presence or absence of abnormal findings was reported by using DeLee

zones (DeLee and Charnley 1976) at the acetabular side and Gruen zones (Gruen et al. 1979) at the femoral side. In study IV, all abnormalities seen in plain radiographs were reported. In study V, only abnormalities with significant progression between the immediate post-revision radiograph and the one-year postoperative radiograph were reported, as the intention in that study was to depict, if there was evidence, component loosening after the revision of a MoM hip. To achieve consensus regarding the significance of the findings, a team that included one radiologist (Elo) and three orthopaedic surgeons (Eskelinen, Puolakka, Pajamäki) discussed any images with abnormalities.

For studies I and IV, the orientation of the acetabular component was defined. Acetabular inclination (cup opening in the coronal plane) was measured from an anteroposterior pelvic radiograph by measuring the angle between two lines. The first represented the long axis of the acetabular component and the second line was drawn between the ischial tuberosities (horizontal reference plane, Figure 3). Acetabular anteversion was also determined from a plain anteroposterior pelvic radiograph using a previously described trigonometry-based mathematical method (Reito et al. 2012).

4.2.5 Revision surgery

Revision surgery of a MoM hip was considered if 1) a thick-walled pseudotumour with atypical contents (Hart grade 2b) or a solid pseudotumour (Hart grade 3) was seen in cross-sectional imaging regardless of symptoms and blood metal ion levels; or 2) the patient had both elevated metal ion levels (5 ppb) and hip symptoms despite a normal finding in cross-sectional imaging; or 3) increasingly and significantly symptomatic hip regardless of imaging findings or metal ion levels (Hart et al. 2012, Reito et al. 2013). In a few cases, an asymptomatic MoM hip replacement was revised due to ultra-high whole blood metal ion levels (typically ranging from 30 to 40 ppb to hundreds).

Revision surgeries were performed by or under the direct supervision of 15 orthopaedic surgeons (Ala-Mononen, Eskelinen, Halonen, Kangas, Ketola, Lehtinen, Lont, Niemeläinen, Niemi, Nieminen, Pajamäki, Puolakka, Päivärinta, Skyttä, Syrjä) using a posterior approach. In revision surgery of MoM THAs, the well-fixed stem was retained, and only the acetabular cup and head component were changed to metal-on-polyethylene, ceramic-on-

ceramic or ceramic-on-polyethylene. MoM resurfacings were converted to THAs by cutting the femoral neck and seating a new femoral stem component. Revision implants were chosen based on the surgeon's preference. However, certain principles were followed: 1) cementless components were used with only a few exceptions, 2) in hips with instability due to soft tissue resection, a constrained liner was used, 3) in hips with satisfactory stability, metal-on-polyethylene or ceramic-on-polyethylene components, or large head ceramic-on-ceramic components were used and 4) ceramic-on-ceramic components with 32 to 36 mm head size were used only in hips with excellent stability with trial components in situ. Extra-articular pseudotumors and inflamed and/or necrotic tissue with an overlying pseudocapsule were aggressively excised. Neurovascular structures were carefully preserved. Bone grafts were used in patients with marked osteolysis.

4.2.6 Definition of Adverse Reaction to Metal Debris

Failure was classified to be due to ARMD if the previously described criteria were met: 1) presence of metallosis or macroscopic synovitis in the joint; and/or 2) a pseudotumour was found during revision; and/or 3) a moderate to high number of perivascular lymphocytes along with tissue necrosis and/or fibrin deposition was seen in the histopathological specimen; and 4) perioperatively there was no evidence of component loosening or periprosthetic fracture. Infection was ruled out if all (at least 5) culture results from the samples obtained during revision surgery were negative, or bacterial growth in a single sample could be interpreted as contamination. (Reito et al. 2013).

Grading of the pseudotumors seen in revision for studies II and III was based on the consistency of the surgeon's description, wall thickness and content of pseudotumors. The grading was performed retrospectively. Descriptions were retrieved from surgical notes. Thin-walled cystic lesions were classified as fluid-filled pseudotumors, and lesions with only minor or no fluid-like component were classified as solid pseudotumors. If the pseudotumor was mainly fluid-filled, but consisted of a significant amount of solid debris, it was graded as mixed type. If several pseudotumors were present, the grading was based on the lesion containing the most solid components.

4.2.7 Post-revision follow-up

After the revision surgery for ARMD, decline of blood Co and Cr was confirmed with whole blood measurements at two, six and 12 months after the surgery, and thereafter at two year intervals. Additional annual follow-up visits were scheduled for patients with blood metal ion levels that remained elevated and for those who were still symptomatic. Clinical evaluation was performed, and OHS (Murray et al. 2007) registered at the same intervals. Anteroposterior and lateral radiographs of the hips and anteroposterior radiograph of the pelvis were obtained during two and 12 months follow-up visits. Cross-sectional imaging using MRI or ultrasound was used in patients with persisting high blood metal ion levels or unclear symptoms suggesting potential residual or recurrent ARMD.

4.3 Statistical methods

Mean values with range or standard deviation were reported for normally distributed variables and median with range for variables with skewed distribution. In all studies, differences between groups in variables Gaussian distribution were analyzed with student's T-test and differences in variables with non-Gaussian distribution with Mann-Whitney U –test. χ^2 -test was used to test associations between two categorical values. In all studies, two-sided p-value <0.05 was considered statistically significant. IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA) was used for statistical analyses in all studies.

In study I, risk factors for elevated whole blood Co and Cr levels were analyzed with binary logistic regression adjusted for implant brand, age, gender, time between index surgery and measurement, component head size and cup inclination angle. Hip ROM and BMI were not included in the final regression model due to the substantial number of missing values (ROM available for 90% of resurfacings and 84% of THAs, BMI available for 98% of resurfacings and 94% THAs). However, they were fitted in the regression model and were excluded from the final model after statistical insignificance was observed. ASR hip resurfacings and ASR XL THAs have been widely regarded as high-risk brands, and were recalled by their manufacturer (de Steiger et al. 2011, Langton et al. 2011b, MHRA. 2012, Matthies et al. 2014).

Therefore, we compared the other brands against ASR in terms of risk for elevated blood metal ion levels. Age, component head size, inclination and time between surgery and metal ion measurement were analyzed as continuous variables and for those odds ratios (OR) associated with one unit increase in exposure are presented. Implant brands with less than twenty patients were combined to group “other” for analysis.

In studies II and III, sensitivity, specificity as well as positive and negative predictive values were calculated for MRI and ultrasound for detecting extracapsular pseudotumors. The presence of any type of pseudotumors in MRI/ultrasound/revision was considered as a positive finding and the absence of extracapsular abnormalities as a negative finding. Cohen’s kappa-coefficient was used to evaluate the accuracy of the imaging gradings in relation to intraoperative grading. As the number of grades must be the same when using the kappa-coefficient, MRI findings 1 and 2a were combined to “fluid-filled” group, 2b was considered as mixed type and 3 as solid pseudotumor.

In study II, we assessed the effect of the time elapsed between MRI and revision surgery on the accuracy of MRI by dividing the hips into four groups based on the time between imaging and revision: less than three months, three to six months, six to 12 months, and more than 12 months. Sensitivity and specificity were calculated for each time cohort.

In study IV, Kaplan-Meier survivorship analysis with revision for any reason as an endpoint was used. Cumulative survival was reported until the number of hips at risk was lower than 20 at the end of the interval. Multivariable binary logistic regression was used to evaluate risk factors for elevated whole blood metal ion levels and revision. The Spearman correlation coefficient was used. For metal ion analyses, those patients with a contralateral implant other than Pinnacle MoM THA were excluded due to unknown effect of the contralateral implant. Patients with unilateral and bilateral Pinnacle MoM THA were analyzed separately in blood metal ion and OHS analyses. Logistic regression adjusted for age, gender, uni-/bilateral and model of the femoral component was used to analyze the risk factors for revision.

In study V, whole blood Co and Cr levels as well as OHS were reported separately for patients with unilateral and bilateral hip replacements as we considered it impossible to determine the confounding effect of the contralateral implant on the blood metal ion levels, and also the statistical testing was performed separately. A patient was considered to have a bilateral

hip replacement if they had any type (MoP, CoC, CoP or MoM) of hip implant on the contralateral side. Of 198 patients 130 (66%) did not have a contralateral hip replacement. In patients with bilateral revision, the differences between preoperative and postoperative OHS and blood metal ion values are presented only for the first revision to avoid clustered observation bias (Ranstam et al. 2011). Wilcoxon rank sum test was used to test significance in the change of blood metal ion levels and OHS. A change in percentage of poor/fair OHS and elevated blood metal ion levels were tested with related-sample McNemar test.

4.4 Ethical considerations

The studies were approved by the local ethics committee (April 27th 2011, R11006 and January 24th 2012 R11196). The procedures followed were in accordance with the Helsinki Declaration of 1975. Additional examinations or tests (eg. histological analysis of tissue removed in revision surgery) not included in the standard follow-up program were not performed unless informed consent was acquired.

5 Results

5.1 Blood cobalt and chromium concentrations (Study I)

Median blood Co and Cr levels and the proportion of elevated blood metal ion levels were higher in patients with THAs compared to those with resurfacings (Table 9, $p < 0.001$ for Co and $p = 0.001$ for Cr, for percentage 17.4% vs 5.9%, $p < 0.001$). Of the seven THA brands that included more than 20 hips, the percentage of elevated blood metal ions (> 7 ppb) was higher than 20% among five brands. The proportion was less than 10% in all hip resurfacing brands (Table 9). In comparison between THAs and resurfacing with identical bearing surfaces, patients with ASR, BHR and Durom THAs had a significantly higher percentage of elevated blood metal ion levels compared with patients with corresponding resurfacings (Table 9, for all analyses $p < 0.001$). A similar trend was not seen in patients with ReCap THAs and resurfacings (Table 9, $p = 0.336$).

In patients with resurfacings, a lower risk for elevated blood metal ion levels in the univariate model was seen with BHR and Durom resurfacings compared with ASR. Female gender, young age, high acetabular inclination and small femoral head size were associated with an increased risk for elevated levels in the univariate model. In multivariable analysis, the difference between Durom and ASR as well as that between females and males was no longer significant. (Table 10). High cup inclination, small head size and young age remained as independent risk factors for elevated blood metal ion levels. In univariate analysis, high postoperative ROM was related to a slightly increased risk for elevated blood metal ions (OR 1.01 per degree increase, 95% CI 1.00 to 1.02, $p = 0.024$), but not when included in the multivariable model (OR 1.01, 95% CI 1.00 to 1.02, $p = 0.109$). No increased risk was related to BMI in either univariate (OR 1.00, 95% CI 0.93 to 1.08, $p = 0.967$) or multivariable (OR 0.97, 95% CI 0.90 to 1.05, $p = 0.442$) analysis.

Table 9. Median whole blood cobalt (Co) and chromium (Cr) in various metal-on-metal hip resurfacing and total hip arthroplasty (THA) brands.

Resurfacing	n	Ions available	Surgery to ion measurement (years, range)	Median head size (mm, range)	Co (median,range)	Cr (Median,range)	Co or Cr > 7ppb (%; 95% CI)	OHS available	OHS (median, range)
ASR	303	293 (97%)	4.0 (1.0 – 6.8)	53 (43 – 63)	1.3 (0.5 – 224.7)	1.6 (0.5 – 93.9)	9.2 (6.4 – 13.1)	288 (95%)	44 (6 – 48)
BHR	257	228 (89%)	7.3 (0.5 – 10.6)	50 (42 – 58)	1.3 (0.4 – 201.2)	1.5 (0.5 – 93.5)	4.4 (2.4 – 7.9)	214 (83%)	46 (14 – 48)
Conserve+	10	8 (80%)	6.4 (6.0 – 6.9)	48 (46 – 56)	0.9 (0.6 – 1.3)	1.1 (0.8 – 2.0)	0.0 (0.0 – 32.4)	7	46 (36 – 48)
Durom	113	100 (88%)	5.5 (1.0 – 8.3)	54 (42 – 60)	0.9 (0.1 – 12.1)	1.0 (0.5 – 4.5)	2.0 (5.5 – 7.0)	93 (82%)	46 (20 – 48)
Mitch	4	4	4.9 (4.9 – 4.9)	48 (46 – 50)	1.1 (0.9 – 1.4)	1.3 (1.2 – 1.4)	0.0 (0.0 – 49.0)	4	48 (38 – 48)
MMC	16	16 (100%)	2.0 (0.8 – 3.1)	54 (48 – 60)	1.0 (0.5 – 5.8)	1.2 (0.6 – 4.4)	0.0 (0.0 – 19.4)	14 (88%)	47 (37 – 48)
ReCap	48	43 (90%)	3.2 (1.9 – 7.7)	50 (40 – 60)	1.2 (0.6 – 115.5)	1.3 (0.8 – 51.6)	4.7 (1.3 – 15.5)	41 (85%)	47 (22 – 48)
Total	751	692 (92%)	5.3 (0.5 – 12.8)	52 (40 – 63)	1.2 (0.1 – 224.7)	1.4 (0.4 – 93.9)	5.9 (4.4 – 7.9)	661 (88%)	45 (6 – 48)
THA	n	Ions available	Surgery to ion measurement (years, range)	Median head size (mm, range)	Co (median,range)	Cr (Median,range)	Co or Cr > 7ppb (%; 95% CI)	OHS available	OHS (median, range)
ASR	375	341 (91%)	3.4 (0.6 – 6.5)	49 (39 – 61)	3.3 (0.3 – 191.7)	1.9 (0.4 – 114.8)	25.2 (20.1 – 30.1)	329 (88%)	42 (1 – 48)
BHR	96	82 (85%)	5.5 (1.1 – 10.0)	50 (36 – 58)	3.8 (0.5 – 73.4)	2.2 (0.4 – 24.9)	23.2 (15.4 – 33.4)	64 (67%)	45 (8 – 48)
Conserve +	2	1	5.3	45 (42 – 48)	13.6	5.2	100.0 (20.7 – 100.0)	1	37
Continuum	4	4	2.6 (1.3 – 3.0)	40 (36 – 40)	1.7 (0.8 – 2.6)	1.5 (0.8 – 2.2)	0.0 (0.0 – 49.0)	4	44 (36 – 48)
Durom	41	36 (88%)	5.0 (2.9 – 7.5)	52 (42 – 58)	5.1 (0.6 – 14.4)	1.7 (0.4 – 5.4)	27.8 (15.7 – 41.9)	33 (80%)	44 (24 – 48)
M2A	67	51 (76%)	6.9 (2.9 – 10.1)	38 (38 – 38)	2.4 (0.3 – 97.3)	2.1 (0.3 – 47.8)	21.6 (12.5 – 34.6)	45 (67%)	45 (25 – 48)
Mitch	13	11 (85%)	4.9 (3.3 – 5.7)	48 (46 – 58)	2.8 (0.9 – 12.9)	1.5 (0.5 – 7.0)	27.3 (9.8 – 56.6)	10 (77%)	42 (28 – 48)
MMC	9	8	2.8 (1.8 – 3.2)	48 (44 – 50)	1.9 (0.8 – 5.3)	1.3 (0.8 – 3.1)	0.0 (0.0 – 32.4)	8	47 (40 – 48)
Pinnacle	294	278 (95%)	6.4 (1.7 – 10.1)	36 (36 – 36)	1.6 (0.3 – 117.2)	1.2 (0.4 – 38.2)	11.5 (8.3 – 15.8)	256 (87%)	45 (5 – 48)
R3	76	68 (89%)	3.8 (0.2 – 4.6)	44 (36 – 54)	2.9 (0.3 – 50.7)	1.7 (0.3 – 15.0)	26.5 (17.5 – 38.1)	61 (80%)	45 (12 – 48)
ReCap	200	176 (88%)	4.2 (1.0 – 8.4)	50 (38 – 60)	1.4 (0.2 – 29.4)	1.3 (0.5 – 11.5)	2.3 (0.9 – 5.7)	159 (80%)	44 (4 – 48)
Total	1177	1056 (90%)	4.7 (0.2 – 10.1)	46 (36 – 61)	2.3 (0.2 – 191.7)	1.6 (0.3 – 114.8)	17.4 (15.3 – 19.8)	971 (82%)	44 (1 – 48)

95% CI, 95% confidence interval; OHS, Oxford Hip Score.

Table 10. Univariate analysis (binary logistic regression) and multivariable analysis of variables predicting elevated whole blood cobalt or chromium levels (>7 ppb) in hip resurfacings.

	n	Univariate		Multivariable	
		Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Model					
ASR	293	ref		Ref	
BHR	228	0.45 (0.21 – 0.95)	0.037	0.25 (0.08 – 0.82)	0.022
Durom	100	0.20 (0.05 – 0.86)	0.031	0.36 (0.08 – 1.68)	0.192
ReCap	43	0.48 (0.11 – 2.10)	0.330	0.49 (0.10 – 2.33)	0.366
Other*	28	0.00	0.998	0.00	0.998
Gender					
Male	469	ref		Ref	
Female	223	4.48 (2.30 – 8.72)	<0.001	0.68 (0.23 – 2.04)	0.491
Age (years)**		0.95 (0.92 – 0.97)	<0.001	0.95 (0.91 – 0.98)	0.002
Time between index surgery and measurement (years)**		0.99 (0.87 – 1.13)	0.867	1.05 (0.83 – 1.32)	0.711
Headsizes (mm)**		0.79 (0.72 – 0.86)	<0.001	0.77 (0.67 – 0.89)	<0.001
Inclination (°)**		1.13 (1.08 – 1.19)	<0.001	1.15 (1.09 – 1.22)	<0.001

*Group “Other” includes 8 Conserve+, 4 Mitch, and 16 MMC MoM resurfacings **Increase in odds ratio per one unit increase.

Among patients with MoM THAs, univariate analysis showed a lower risk for elevated levels in patients with Pinnacle and ReCap implants compared with patients with ASRs. Also in the univariate model, female gender, large femoral head size and increasing time between surgery and blood metal ion measurement were risk factors for elevated levels. In multivariable analysis, no difference between Pinnacle and ASR THAs was seen (Table 11). All other risk factors remained as independent risk factors after applying the multivariable model. Also among THAs, in univariate analysis, high postoperative ROM was related to a slightly increased risk for elevated blood metal ions (OR 1.00 per degree increase, 95% CI 1.00 to 1.01, $p=0.023$), but not when included in the multivariable model (OR 1.00, 95% CI 1.00 to 1.01, $p=0.193$). No increased risk was related to BMI in either univariate (OR 0.98, 95% CI 0.95 to 1.01, $p=0.216$) or multivariable (OR 0.97, 95% CI 0.94 to 1.00, $p=0.061$) analysis. ROM and BMI were not included in the final multivariable model due to the substantial number of missing values.

Table 11. Univariate analysis (binary logistic regression) and multivariable analysis of variables predicting elevated whole blood cobalt or chromium levels (>7 ppb) in total hip arthroplasties.

	n	Univariate		Multivariable	
		Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Model					
ASR	341	ref		Ref	
BHR	82	0.89 (0.51 – 1.58)	0.700	0.63 (0.33 – 1.20)	0.158
Durom	36	1.14 (0.53 – 2.46)	0.738	0.93 (0.40 – 2.13)	0.861
M2A	51	0.82 (0.40 – 1.66)	0.574	0.79 (0.28 – 2.23)	0.651
Pinnacle	278	0.39 (0.25 – 0.60)	<0.001	0.46 (0.18 – 1.16)	0.100
R3	68	1.07 (0.59 – 1.93)	0.829	1.36 (0.68 – 2.72)	0.389
ReCap	176	0.07 (0.03 – 0.19)	<0.001	0.06 (0.02 – 0.16)	<0.001
Other*	24	0.59 (0.20 – 1.78)	0.352	0.62 (0.20 – 1.93)	0.410
Gender					
Male	564	ref		Ref	
Female	492	1.54 (1.12 – 2.12)	0.008	2.04 (1.35 – 3.06)	0.001
Age (years)**		1.00 (0.98 – 1.02)	0.901	1.01 (0.99 – 1.03)	0.215
Time between index surgery and measurement (years)**		0.99 (0.92 – 1.08)	0.855	1.19 (1.05 – 1.34)	0.007
Head size (mm)**		1.02 (1.00 – 1.04)	0.083	1.07 (1.01 – 1.13)	0.033
Inclination (°)**		1.03 (1.00 – 1.05)	0.023	1.02 (0.99 – 1.04)	0.153

*Group “Other” includes one Conserve+, 4 Continuum, 11 Mitch, and 8 MMC MoM total hip arthroplasties. **Increase in odds ratio per one unit increase.

5.2 MRI and ultrasound (Studies II and III)

In study II, pseudotumors were observed in 98 (59%) revision surgeries. There were 87 fluid-filled, two solid and nine mixed type pseudotumors. In MR images, a pseudotumor was seen in 79 (47%) hips (Table 12). Preoperative MRI provided sensitivity of 71% (95% CI, 62 to 79) and specificity of 87% (95% CI, 77 to 93) for detecting pseudotumours. A positive predictive value was 89% (95% CI, 80 to 94) and a negative predictive value was 68% (95% CI, 58 to 77). Sensitivity and specificity were similar in the groups of patients with hip resurfacings (68% and 70%) and THAs (72% and 89%).

Table 12. Magnetic Resonance Imaging (MRI) and revision findings crosstabulation. MRI classes that best resemble each revision finding type are bordered.

MRI class	Revision findings				Total
	No extracapsular pseudotumor	Fluid-filled pseudotumor	Mixed type pseudotumor	Solid pseudotumor	
No pseudotumour	60	27	1	0	88
Thin walled cystic appearing (1)	5	24	2	0	31
Thick or irregular walls, fluid signal (2a)	0	18	3	0	21
Thick or irregular walls with atypical contents (2b)	4	17	3	1	25
Solid pseudotumour (3)	0	1	0	1	2
Total	69	87	9	2	167

In study III, pseudotumors were seen in 46 of 82 (56%) revisions surgeries. A trochanteric region pseudotumor was found in 13 hips, an iliopsoas region pseudotumor in 23 and a pseudotumor in both regions in ten hips. Preoperative ultrasound showed 19 of the 23 posterolaterally located (trochanteric) pseudotumors (Table 13) and 26 of the 33 anteriorly located (iliopsoas) pseudotumors found in revision surgery (Table 14). Preoperative ultrasound had sensitivity of 83% (95% CI, 63 to 93) and specificity of 92% (95% CI, 82 to 96) in the trochanteric region. A positive predictive value was 79% (95% CI, 59 to 91) and a negative predictive value was 93% (95% CI, 84 to 97). In the iliopsoas region, ultrasound had sensitivity of 79% (95% CI 62 to 89), specificity of 94% (95% CI, 83 to 98), a positive predictive value of 90% (95% CI, 74 to 96) and a negative predictive value of 87% (95% CI, 76 to 94).

MRI did not detect twenty-eight pseudotumors seen in revision. Of these, twenty-seven were fluid-filled pseudotumors and one a mixed type. Eleven pseudotumors seen in revision were not detected by ultrasound, and of these four were fluid-filled and thin walled pseudotumors in the trochanteric region, and seven were fluid-filled and thin-walled in the iliopsoas region. Therefore, 38 out of the 39 pseudotumors missed in preoperative imaging (both studies) were fluid-filled. In the

MRI study, five fluid-filled and four pseudotumors with atypical content were seen in preoperative imaging but not in revision. The same was true in the ultrasound study with six fluid-filled pseudotumors, one mixed and one solid.

Table 13. Trochanteric region pseudotumors (PT): Ultrasound and revision findings crosstabulation.

Ultrasound findings	Revision findings				Total
	Only intracapsular	Fluid-filled PT	Mixed type PT	Solid PT	
No PT	54	4	0	0	58
Fluid-filled PT	4	14	2	0	20
Mixed type PT	1	0	0	0	1
Solid PT	0	0	2	1	3
Total	59	18	4	1	82

Table 14. Iliopsoas region pseudotumors (PT): Ultrasound and revision findings crosstabulation.

Ultrasound findings	Revision findings				Total
	Only intracapsular	Fluid-filled PT	Mixed type PT	Solid PT	
No PT	46	7	0	0	53
Fluid-filled PT	2	8	1	1	12
Mixed type PT	0	5	6	3	14
Solid PT	1	1	1	0	3
Total	49	21	8	4	82

In study II, 42 of the 87 revision-confirmed fluid-filled pseudotumors, three of nine mixed type and one of two solid type pseudotumors, were categorized correctly by MRI grading. In study III, 14 of 18 fluid-filled and none of the mixed type pseudotumors in the trochanteric region, and eight of 21 fluid-filled, six of eight mixed type and none of the four solid type in the iliopsoas region were correctly classified in preoperative ultrasound. The kappa-coefficient indicating agreement

between gradings was 0.40 (95% CI, 0.33 to 0.51, moderate agreement) for MRI compared to revision finding, 0.64 (95% CI, 0.47 to 0.80, good agreement) for ultrasound compared to revision findings in the trochanteric region and 0.52 (95% CI, 0.38 to 0.66, moderate agreement) for ultrasound compared to revision findings in the iliopsoas region.

In study II, we observed that the sensitivity of MRI was significantly lower when over one year had elapsed from preoperative imaging to revision surgery (Table 15). In study III, no difference in sensitivity or specificity was seen when patients were divided by the median time between ultrasound and revision (0 to 3.5 months and 3.5 to 12 months). For study II, exclusion of the 12 patients with bilateral hip resurfacings did not affect the results of any previous analyses.

Table 15. Effect of time on calculated sensitivity and specificity of magnetic resonance imaging (MRI).

Time between MRI and revision	N	Sensitivity	95% CI (%)	Specificity	95% CI (%)
Whole cohort	167	71% (70/98)	62 – 79	87% (60/69)	77 – 93
under 3 months	34	88% (22/25)	70 – 96	78% (7/9)	45 – 94
3 to 6 months	46	76% (26/34)	60 – 88	67% (8/12)	39 – 86
6 to 12 months	37	77% (17/22)	55 – 90	87% (13/15)	62 – 96
over 12 months	50	29% (5/17)	13 – 53	97% (32/33)	85 – 99

5.3 The effect of systematic screening (Study IV)

Before the beginning of intensified screening of MoM brands other than ASR in January 2012, the 9-year implant survival rate of the Pinnacle MoM THA cohort was 96% (95% CI, 95 to 98). Thirteen revisions had been performed by then: three for periprosthetic fracture, three for infection, one for aseptic loosening of the femoral component, one for aseptic loosening of the acetabular component, one for pain and subluxation, one for instability and three for ARMD. Before January 2012, two patients (three hips) died 6.1 and 7.3 years after the primary surgery due to causes unrelated to their MoM hips.

Twenty-three months after the start of our surveillance programme, 34 further hips (34 patients) were revised: 29 due to ARMD, three for infection, one for periprosthetic fracture and one for aseptic loosening of the femoral component. The 9-year implant survival rate of this cohort declined from 96% to 86% (95% CI, 82 to 90), with a 10-year implant survival rate of only 82% (95% CI, 77 to 87). In the implant survival figure describing the situation before and after 23 months of systematic screening, the effect of screening on implant survival is clearly demonstrated (Figure 6).

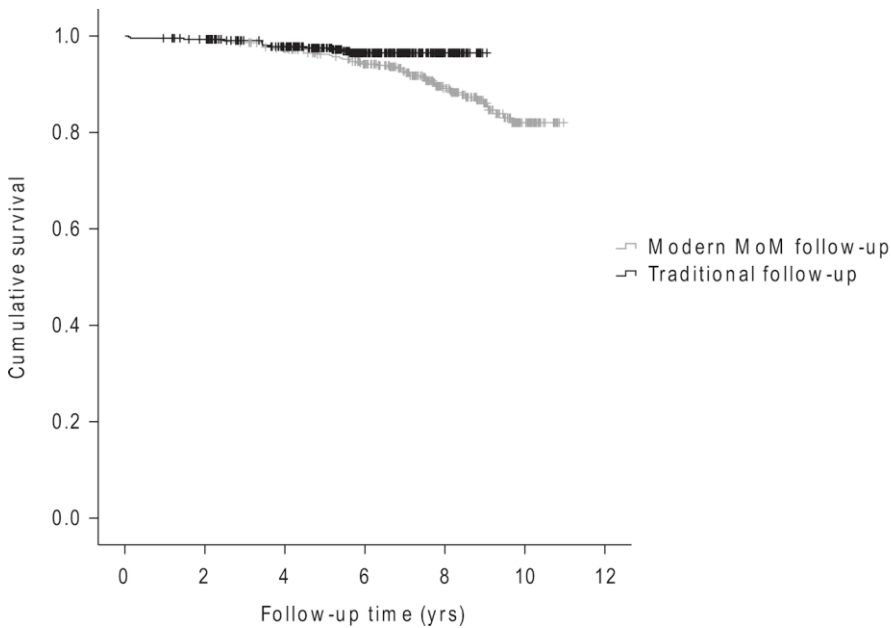


Figure 6. Graph showing implant survival before and after the introduction of the modern in-depth metal-on-metal (MoM) follow-up programme. *Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery: Lainiala O, Eskelinen A, Elo P, et al. Adverse reaction to metal debris is more common in patients following MoM total hip replacement with a 36 mm femoral head than previously thought: results from a modern MoM follow-up programme. Bone Joint J 2014;96-B:1610-1617. (Figure 3).*

At the time of submission of study IV, revision-confirmed prevalence of ARMD was 7%. Since the start of the surveillance, two patients (two hips) had died, 6.0 and 6.6 years after the primary surgery. Multivariable logistic regression adjusted for gender, age, uni-/bilaterality and brand of the femoral component showed a trend of female gender being a risk factor for revision for any reason (OR 1.80, $p=0.069$). For 88

revision with ARMD as the endpoint, the results were similar (OR 1.90, $p=0.083$). None of the other variables analyzed were significant risk factors.

OHS were available for 283 patients (87%). The median OHS was 45 (range 5 to 48) in the patients with unilateral and 44 (range 13 to 48) in those with bilateral THAs. The OHS was excellent (42 to 48) in 181 (64%), good (34 to 41) in 54 (19%), fair (27 to 33) in 27 (10%) and poor (0 to 26) in 21 (7%) of patients. Pain was severe or moderate in 29 patients (10%). Clanking or squeaking sounds were experienced by 34 patients (12%), sensation of subluxation by 28 (10%), sensation of pressure by 11 (4%) and numbness by 72 patients (26%).

Whole blood Co and Cr ion levels were available for all patients. The measurement was performed at a mean of 6.3 years (SD 1.8) after the primary surgery. Seventy-five patients were excluded from the analyses, as the contralateral arthroplasty was performed using an implant other than the Pinnacle MoM THA. Blood Co and Cr levels were significantly higher in the 52 patients with bilateral Pinnacle MoM THAs compared with those with unilateral arthroplasty (median Co 5.0 vs 1.5 ppb, and Cr 1.9 vs 1.1 ppb, $p<0.001$ for both comparisons). Of 199 patients with unilateral hip replacement, 32 (16%) had a blood Co level and eight (4%) had a blood Cr level higher than 5 ppb, and 19 (10%) and five (3%) had their levels higher than the MHRA 7 ppb cut-off value, respectively. Women with unilateral Pinnacle MoM hip replacements had higher blood Cr compared with men (median 1.2 vs 0.9 $p<0.001$), whereas there was no statistical significance between Co values (1.8 vs 1.1, $p=0.104$).

Plain radiographs were available for 363 hips (96%). In the proximal femur (Gruen 1 and 7), radiolucencies were seen in 35 hips (10%) and osteolysis in 28 (8%). In the distal femur, radiolucencies were seen in 11 hips (3%). One hip showed osteolysis in all Gruen zones, and in this hip the loose stem was replaced along with the acetabular component. Acetabular radiolucencies were seen in 15 hips (4%), and osteolysis in 13 (4%) hips. Of the hips revised due to ARMD, 14 out of 32 (44%) had inclination and version angles inside the Lewinnek's safe zone (Lewinnek et al. 1978), a figure similar to those who were not revised for ARMD (45%, $p=0.856$). Based on symptoms or elevated blood metal ion levels, 113 hips (30%) went through cross-sectional imaging with MRI or ultrasound, which showed a fluid-filled thin-walled pseudotumor in seven (6%), a fluid-filled pseudotumor with thick or irregular walls in five (4%), a pseudotumor with thick or irregular walls and atypical contents in eight (7%) and a solid pseudotumor in four (4%).

5.4 Results of revisions for ARMD (Study V)

At revision, an extracapsular pseudotumor was seen in 131 of 215 hips (61%) and osteolysis was seen in 88 of 215 hips (41%). The ALVAL score of the histopathologic samples obtained during the revision was low (0 to 4) in 49 of 161 hips (30%), moderate (5 to 8) in 98 of 161 hips (61%) and high (9 to 10) in 14 of 161 hips (9%) (Campbell et al. 2010).

Complete follow-up (preoperative, 2 months, 6 months and 12 months) data of blood Co and Cr levels were available for 180 of 198 patients (91%), and for 185 patients (93%) preoperative and 12-months blood metal ion measurements were available. Complete follow-up data of OHS were available for 104 of 198 patients (53%), and for 151 patients (76%) preoperative and 12-month OHS were available. For all hips, a 1-year postoperative radiograph was available.

After the revision of the MoM hip replacement, a clearly decreasing trend of whole blood Co and Cr levels was seen both in patients with unilateral and bilateral hip replacements, as well as in those with THAs and hip resurfacings. The percentage of elevated (≥ 7 ppb) Co levels among patients with unilateral THAs decreased from 73% (66 of 90, 95% CI 63 to 81) preoperatively to 0% (0 of 90, 95% CI 0 to 4) at one-year follow-up ($p < 0.001$, Figure 7A), and in patients with unilateral hip resurfacing from 56% (19 of 34, 95% CI 39 to 71) to 0% (0 of 34, 95% CI 0 to 10, $p < 0.001$, Figure 7B). The percentage of elevated blood Cr decreased from 31% (28 of 90, 95% CI 22 to 41) to 4% (four of 90, 95% CI 2 to 10) in the unilateral THA group ($p < 0.001$, Figure 7C), and from 56% (19 of 34, 95% CI 39 to 71) to 12% (four of 34, 95% CI 5 to 27) in the hip resurfacing group, $p < 0.001$, Figure 7D). In eight patients with ultra-high preoperative Cr values (median 85.6 ppb, range 40.6 to 125 ppb) the Cr level remained elevated at the 1-year follow-up (median 13.5 ppb, range 8 to 26 ppb). None of these patients had other metallic implants or other known sources of Co or Cr. Seven had normal and one had only mildly reduced renal function. Also, the revisions were performed using Ti sleeve adapters and with either CoC or CoP implants, which do not contain Co or Cr. Three years after the revision, Cr remained elevated in six of these patients (median 11.4 ppb, range 8.7 to 14.4 ppb).

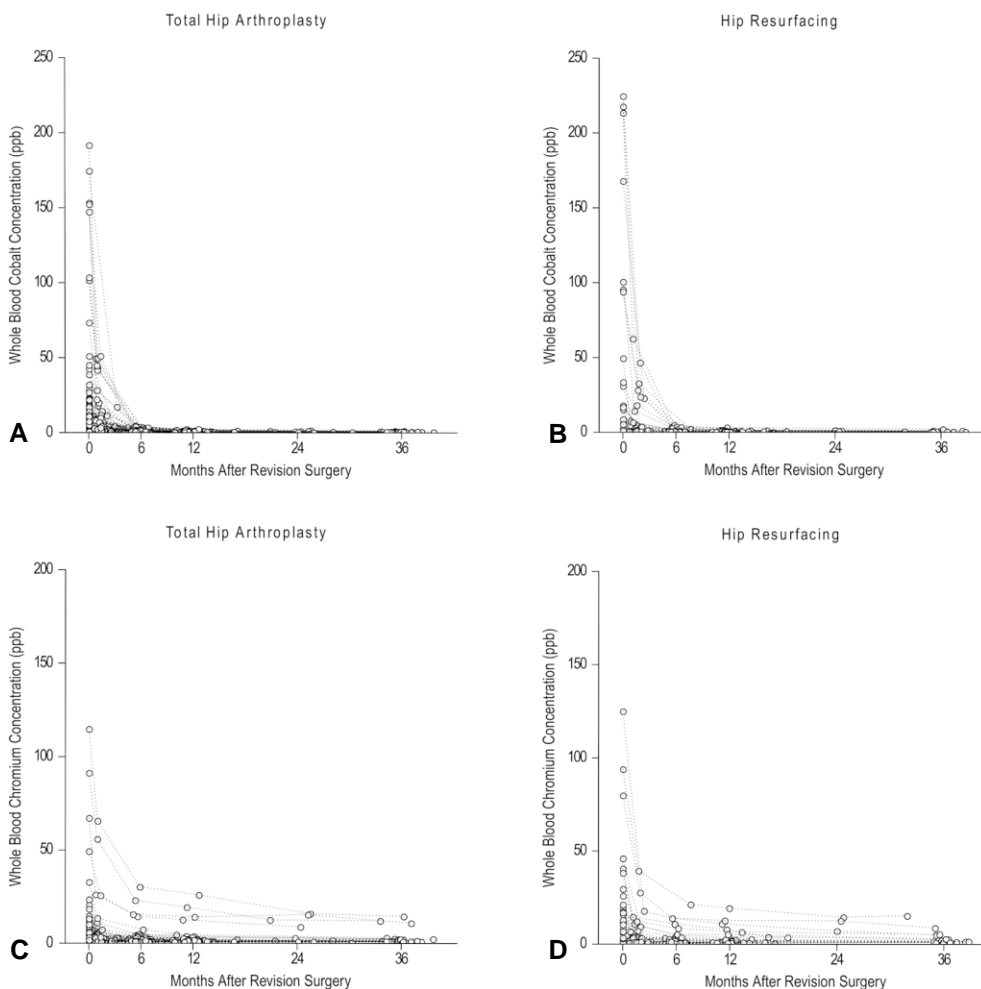


Figure 7. A decrease of blood Co was seen for patients who had unilateral THAs (A) and hip resurfacings (B). A decrease in Cr also was seen for patients who had unilateral THAs (C) and hip resurfacings (D). In both groups, four patients had greater than 7 ppb Cr remaining at 12 months. Patients with bilateral arthroplasties are not included owing to the confounding effect of the contralateral implants. *Reproduced with permission of Springer Publishing Company. Lainiala O, Reito A, Elo P, et al. Revision of Metal-on-metal Hip Prostheses Results in Marked Reduction of Blood Cobalt and Chromium Ion Concentrations. Clin Orthop Relat Res. 2015 Jul;473(7):2305-13. (Figure 2A-D).*

In patients with bilateral THAs, the percentage of patient with elevated blood Co decreased from 89% (47 of 53, 95% CI 77 to 95) to 13% (seven of 53, 95% CI 7 to

25, $p < 0.001$) and Cr levels from 34% (18 of 53, 95% CI 23 to 47) to 2% (one of 53, 95% CI 0 to 10, $p < 0.001$). All patients with elevated metal ion levels at 1-year follow-up had a contralateral MoM implant still in situ. Patients with bilateral hip resurfacings were not analyzed due to the small number of patients (eight).

A significant improvement of median OHS was seen in patients with a unilateral hip replacement. In the whole cohort, the median OHS improved from preoperative 37 (range, 4 to 48) to 40 (range, 9 to 48) at the time of the one-year follow-up ($p = 0.004$). In patients with unilateral THAs, improvement of the median OHS from 38 (range, 4 to 48) to 40 (range, 9 to 48) ($p = 0.049$) was seen, and in the group with unilateral hip resurfacings, the score improved from 37.5 (range, 9 to 48) to 44.0 (range, 13 to 48) ($p = 0.011$). In the THA group with bilateral involvement, the improvement seen in OHS was not statistically significant (37.0 [range, 14 to 48] to 41.0 [range, 9 to 48], $p = 0.196$). The percentage of patients with poor (0 to 26) or fair (27 to 33) OHS decreased from 39% (32 of 83; 95% CI 29 to 49) to 27% (22 of 83; 95% CI 18 to 37) in the unilateral THA group ($p = 0.031$), but no statistically significant change was seen in patients with unilateral hip resurfacings (39% [ten of 26; 95% CI 22 to 57] to 27% [seven of 26; 95% CI 14 to 46], $p = 0.453$) or in patients with bilateral THAs (40% [15 of 38, 95% CI 26 to 55] to 29% [11 of 38, 95% CI 17 to 45], $p = 0.344$). Patients with bilateral resurfacings were not analyzed (only four patients). The percentage of patients with either moderate or severe pain (OHS question 1) decreased from 37% (31 of 83; 95% CI 28 to 48) before revision to 16% (13 of 83; 95% CI 9 to 25) at 1-year follow-up after the revision ($p < 0.001$) in the unilateral THA group and from 54% (14 of 26, 95% CI 35 to 71) to 27% (seven of 26; 95% CI 14 to 46) in the unilateral hip resurfacing group ($p = 0.039$). No statistically significant change was seen in the bilateral THA group (32% [12 of 38, 95% CI, 19 to 47] to 18% [seven of 38, 95% CI, 9 to 33], $p = 0.227$).

Because of residual symptoms and/or elevated blood metal ions at the time of the 1-year follow-up visit, postoperative MRI was performed on 26 hips and ultrasound on 18 hips, respectively (20% of the hips postoperatively imaged). There was a normal finding in 15 MRIs, a cystic pseudotumor in five hips, a cystic pseudotumor with thick walls in one and a pseudotumor with atypical contents in five hips. A normal finding was seen in 15 ultrasound examinations and a cystic pseudotumor in three hips. Only minor radiographic abnormalities were observed at the one-year follow-up: acetabular radiolucency in seven (3%) hips and osteolysis in five (2%) hips, proximal femoral radiolucency in six (3%) and osteolysis in two (1%)

hips and distal femoral radiolucency in four (2%) hips. Distal femoral osteolysis was observed in none of the hips.

After the revision, deep vein thrombosis occurred in one patient, peroneal nerve palsy in one patient, and dislocations not leading to re-revision in two patients. Re-revision was performed for four patients due to recurrent dislocations, for one because of deep infection and for one because of an acetabular fracture. In one patient, a residual pseudotumor was removed through an ilioinguinal incision. Therefore, complications not leading to re-operation were seen in 2% of hips and complications leading to re-operation in 3%.

6 Discussion

6.1 Blood metal ion concentrations

Risk stratification of the screening protocols is based mainly on the clinical results of implant types (THA/resurfacing), various head sizes and hip replacement brands (MHRA 2012). Some guidelines recommend systematic blood Co and Cr measurements for risk implants including large diameter stemmed MoM THAs (MHRA 2012), and small head size (<45 mm) resurfacings (TGA 2012), although there is little published data to support this rationale. Blood metal ion data is scarcely reported in large unselected populations, with brand specific analysis allowing comparison of risk for elevated blood Co and Cr levels (Matharu et al. 2015a). In study I, 5.9% of patients with unilateral hip resurfacing and 17.4% with unilateral THA had blood metal ion levels greater than seven parts per billion (7 ppb) (MHRA 2012). In the resurfacing group, small head size, high cup inclination and young age were independent risk factors for elevated metal ion levels, and in the THA group female gender, large head size and longer time between surgery and ion measurement were independent risk factors for elevated ion levels.

In five out of seven THA brands, more than 20% of patients had elevated blood metal ion levels. In study I, the percentage of elevated blood metal ion levels in patients with large diameter MoM THA (17.4%) was almost identical to that reported in a recent study (17.9%) (Matharu et al. 2015a). Significantly higher Co levels have been reported for patients with large diameter head MoM THAs compared to patients with MoM hip resurfacings, but there is incongruity in the comparison of Cr levels in these patients (Garbuz et al. 2010, Johnson et al. 2013, Vendittoli et al. 2013). The rate of bearing surface wear in MoM THAs and resurfacings is similar (Matthies et al. 2011). Mechanical stress on the head-neck taper junction also results in the removal of the passive oxidative layer protecting the implant, which further leads to increased corrosion of the implant and is a likely explanation for the difference in blood metal ion levels between MoM THAs and resurfacings (Langton et al. 2012, Panagiotidou et al. 2015). In study I, blood metal ion levels were higher

in all MoM THAs compared to resurfacings with the same bearing surface (ASR, BHR, Durom), except with Biomet ReCaps. ReCap has a Ti sleeve between the head and the stem, resulting in a Ti-Ti-interface. Corrosion is more often seen in Ti-CoCr interphases compared to a Ti-Ti interface (Nassif et al. 2014). Lower Co release in Biomet MoM THAs with a Ti-sleeve compared to other MoM THAs has been reported, without higher Ti release (Lavigne et al. 2011a). It was speculated, that cold-welding would reduce micromotion and fretting corrosion, and that the large size of the sleeve may reduce deformation under load (Lavigne et al. 2011a). The wear of the inner surface of a Ti sleeve connected to a Ti stem has been documented (Witt et al. 2014), but to our knowledge the wear of the outer surface of a Ti sleeve connected to a CoCr head has not been determined. As cold-welding sometimes seen in Ti-Ti interfaces may lead to a more challenging revision (Mokka et al. 2013), the benefit of the Ti sleeve cannot be unambiguously determined. In disagreement with our results, a high percentage of elevated blood metal ion levels and pseudotumors have been reported in other ReCap cohorts (Bosker et al. 2012, Mokka et al. 2013).

Female gender is considered a risk factor for elevated blood metal ion levels (Vendittoli et al. 2007, Moroni et al. 2011, Bayley et al. 2015), although results that disagree exist as well (Beaule et al. 2011, Vendittoli et al. 2011, Hart et al. 2013). In study I, female gender was an independent risk factor for elevated blood metal ion levels in the THA group but not in the resurfacing group. Further, femoral head diameter has been described as an independent predictor of revision in MoM hips. In THAs, larger head sizes have been shown to be associated with higher risk for revision (Smith et al. 2012c), whereas the opposite findings have been reported in patients with resurfacings (Smith et al. 2012a, Canadian Arthroplasty Society 2013). Both positive and negative associations have been described between blood metal ions and femoral head size in THAs (Vendittoli et al. 2011, Bayley et al. 2015, Matharu et al. 2015a). An inverse relationship between femoral head size and blood Co and Cr concentrations has been reported for resurfacings (Sidaginamale et al. 2013). We found an increased risk for elevated blood metal ion levels in small head size resurfacings and THAs with large head size. We also observed an increased risk for elevated blood metal ions related to high cup inclination in the resurfacing group, but not in the THA group. As cup orientation has been reported to have negligible influence on taper wear (Langton et al. 2012, Elkins et al. 2014) and the material loss from the taper is of a similar magnitude to bearing surface wear (Matthies et al. 2013),

we believe that metal ions released from the trunnion-taper interface irrespective of inclination confound the relationship between inclination and metal ions in the THA population, and therefore inclination did not reach statistical significance in the THA group. The effect of acetabular component orientation on bearing surface wear has been well documented in previous studies (Langton et al. 2009, Matthies et al. 2014). We also observed that young age was a risk factor for elevated blood metal ions in the resurfacing group. Some studies have reported no, or only negligible association between age and blood metal ion levels in hip resurfacings (Desy et al. 2011, Hartmann et al. 2012). However, the association in our study may be explained by the higher physical activity of younger patients, as exercise has been shown to temporarily increase blood Co levels (Khan et al. 2006).

Our study provides valuable data about whole blood Co and Cr levels in MoM resurfacings and THAs with low risk of selection bias. This data can be further used with the clinical implant-specific track record of MoM hips to guide risk stratification and screening. Patients with certain stemmed MoM THA designs are clearly at higher risk for both the local and systemic adverse effects of Co and Cr. As elevated systemic metal ion concentrations are common, future work should investigate the significance of local and systemic Co and Cr burden, and more emphasis should be placed on the stemmed large head size designs.

6.1.1 Limitations of the blood metal ion study

Firstly, the number of hips varied between the brands, thus limiting the statistical power to analyse the differences between brands. For example, those brands with a low number of subjects are more prone to being classified as “not significantly better” based on our regression analysis. Therefore, the results of brands with advantageous, but statistically insignificant ORs should be interpreted more carefully. Secondly, the time from index surgery to blood ion measurement was not standardised, and the changes in blood metal ion levels over time may affect our results, although this has been taken into account by including the time from surgery to metal ion measurement in the multivariable analysis. Thirdly, while this study provides valuable information on the blood metal ion levels in patients with a variety of MoM hip brands, it should be emphasized that there is no clear consensus on the appropriate cut-off value for the blood metal ion levels predicting failure or increased wear (Hart et al. 2014, Paustenbach et al. 2014). However, it should be noted that

the cut-off value used in this study is actually the highest published cut-off value for MoM hips (Hart et al. 2011, Malek et al. 2012, Sidaginamale et al. 2013, Van Der Straeten et al. 2013, Hart et al. 2014), and therefore this study is more likely to underestimate than overestimate the prevalence of elevated blood metal ion levels in patients with MoM hip replacements. As the data are from a single hospital with systematic screening suggested for all patients with a MoM hip, the data can be considered to be highly representative and selection bias free. Acetabular inclinations were retrieved from various datasets, most of which did not include an acetabular version. Because the number of patients in the Study I was large, the version measurements were not performed. Without the acetabular version, only the two-dimensional effect of acetabular orientation could be assessed, and not the three-dimensional contact patch to rim distance, which would have been a better variable for the implant positioning (Matthies et al. 2014).

6.2 Imaging of pseudotumors

Both MRI and ultrasound had rather good sensitivity and specificity for detecting extracapsular pseudotumors. For ultrasound, we found no difference between the trochanteric and iliopsoas regions. Our study with MRI did not include a separate analysis of the location of the pseudotumor. Interestingly, in our study, the sensitivity of MRI for detecting pseudotumors was clearly lower when over one year had elapsed between imaging and revision compared to cases with imaging done less than a year before surgery. It is likely that the developing nature of the soft tissue pseudotumors explains the lower sensitivity in cases with a longer interval between imaging and the revision surgery. This implicates that imaging results more than one year old should not be used for preoperative planning.

When our results are scrutinized in comparison to several other recent papers (Garbuz et al. 2014, Muraoka et al. 2014, Nishii et al. 2014, Siddiqui et al. 2014, Robinson et al. 2014), neither MRI nor ultrasound can be unambiguously declared as “the gold standard” for the imaging of MoM hips based on diagnostic accuracy. Ultrasound is a significantly cheaper imaging modality compared with MRI (73 € vs 385-709 €, depending on the MRI sequences used [Marjut Keskinvinkka, Imaging Centre of Tampere University Hospital, personal communication, 18.8.2015]). However, as MRI provides better 3D-visualization, some orthopaedic surgeons

prefer MRI for preoperative planning in order to achieve optimal tissue resection (Liddle et al. 2013). As there is no definitive scientific evidence of either imaging modality being superior, the increased use of ultrasound as a primary screening modality due to lower cost seems justified. The screening of MoM hips costs approximately 350 € to 1245 € per patient, depending on the screening protocol, (Matharu et al. 2015b) annually. Therefore, the annual cost of the screening of the approximately 20 000 patients with MoM hips in Finland is 7 to 25 million €. This results in a large financial burden on Finnish hospitals, and attempts to reduce the cost of the screening have to be made. The costs of ultrasound are only 10% to 20% of the cost of MRI, and therefore the screening of a large number of patients with a few pseudotumors would seem reasonable. However, when considering a revision surgery for ARMD, orthopaedic surgeons often wish to have preoperative MRI for better 3D visualization and planning of the excision of the pathologic soft tissues, even when ultrasound images already exist. If the percentage of patients that are considered for revision after the primary imaging with ultrasound is large, the cost of double imaging might outweigh the benefit of a less expensive primary imaging modality. Further, one problem with ultrasound is that it is operator dependent: there is no option for re-evaluation of the images if the examination is performed poorly and significant changes may be missed.

6.2.1 Limitations of the imaging studies

In both of our studies, many of the misclassifications as well as false positives and negatives were related to cystic pseudotumors. Of course, this may partly reflect the high percentage of cystic lesions in our studies (89% in Study II and 70% in Study III). It is, however, likely that some of the misclassifications may be related to the nature of gradings used, as for example it was not clearly defined how thick the walls had to be in order to be classified as “thick-walled” and neither was there a clear cut-off on how much atypical content a pseudotumor had to contain in order to be classified as a mixed type. Also, using retrospective grading of the findings in operations performed by different orthopedic surgeons who may have described similar lesions in a somewhat different manner may have caused some discrepancy.

We used retrospective grading of revision findings based on descriptions in surgical notes, and also the ultrasound findings were retrospectively graded based on descriptions by radiologists. The most optimal study setting here would have

certainly been a prospective study with predefined systematic grading of all surgical findings accompanied by recently (days to weeks) performed imaging. The size of the pseudotumor seen in revision was reported only qualitatively and not quantitatively, so the correlation of size in imaging and revision could not be evaluated. With a retrospective study setting we were also unable to evaluate the imaging of the other ARMD pathologies such as degree of synovitis and osteolysis as these were not uniformly described and quantified during the revision. MRI offers the luxury of reliable re-grading of findings. However, ultrasound is operator dependent and in order to perform reliable retrospective re-grading, the examination should be performed using a pre-defined systematic approach that includes the whole examination being recorded on video. We did not evaluate the inter- and intraobserver reliability of our grading systems. This was omitted from our study due to limited resources. To define inter- and intra-observer reliability would have required fourfold assessment of the images (twice by two radiologists). Further, even if fourfold grading of the findings had been performed, it would have been impossible to retrospectively estimate the reliability of the surgical grading, as findings were not systematically photographed. As a result, some uncertainty on the analysis of diagnostic accuracy would have remained anyway.

6.3 Effect of systematic screening

Our study shows that an increase in the intensity of screening results in an increased rate of ARMD detected and revisions for ARMD performed, with significantly worse implant survival than in previous studies that lacked systematic screening (Engh et al. 2010, Barrett et al. 2012, Kindsfater et al. 2012, Bernasek et al. 2013, Liudahl et al. 2013). This would suggest that if it is desirable to detect all ARMD, systematic screening is the key. However, when mass screening programs are established, the benefit and harm to the patient should be carefully weighed. After all, the overall benefit has been questioned even in widely used screening protocols, such as breast cancer (Jorgensen et al. 2011) and prostate cancer (Chou et al. 2011), as the harm caused by the overdiagnosis of clinically insignificant diseases, the adverse effects of treatment and false-positive findings leading to psychological distress may overcome the benefits of treatment. It would seem that with ARMD,

we should move from asking: “Can we find all the ARMD lesions?” to “Do we want to find all the ARMD lesions?”

6.3.1 Screening of ARMD and World Health Organization criteria

The World Health Organization (WHO) has defined guidelines for justifiable screening that emphasize the significance of health problem, availability of treatment and proper tests, and the cost-effectiveness of the screening (Wilson and Jungner 1968). The WHO guidelines state that the condition should be an important health problem in order to justify screening (Wilson and Jungner 1968). This criterion is fulfilled in the case of ARMD, as the subjective symptoms may be difficult and in some cases devastating tissue destruction is seen (Gutman et al. 2013, Fu et al. 2015). Further, the criteria of available treatment and diagnostic equipment (Wilson and Jungner 1968) is fulfilled, as revision surgery is a widely used treatment (Griffin et al. 2012), and blood metal ion measurements (Sidaginamale et al. 2013) and cross-sectional imaging (Nam et al. 2014) are available, even though there is no exact consensus about the diagnostic criteria of ARMD. In addition, blood measurements and MRI/ultrasound do not cause significant harm, so their use as screening methods is acceptable. There is also known to be a clinically silent latent stage of ARMD (Wilson and Jungner 1968, Hart et al. 2012). However, only the short-term natural history of ARMD is known (Almoussa et al. 2013, Ebreo et al. 2013, van der Weegen et al. 2013a, Reito et al. 2014b), and there is no agreed policy on whom to treat and what is the cost-effectiveness of the treatment (Matharu et al. 2015b). It is therefore clear that these research questions need to be answered before systematic screening can be considered fully justified (Wilson and Jungner 1968).

6.3.2 Considerations about screening of ARMD

Study IV showed that the screening of patients with MoM hips reveals a high amount of ARMD and increases revision rates. The question raised from our results is “should all these cases of ARMD be treated with revision surgery”. The natural history of ARMD has been reported from only a few years of follow-up and there is no clear consensus about what should be done with asymptomatic patients with ARMD. The few studies about the natural history have reported no or only minor

changes in pseudotumors in the short-term (Almoussa et al. 2013, Ebreo et al. 2013, van der Weegen et al. 2013a, Reito et al. 2014b). On the other hand, case reports with massive pseudotumors leading to devastating outcomes have been described (Gutman et al. 2013, Fu et al. 2015), accompanied by poor revision results in MoM hips due to pseudotumors compared to other indications (Grammatopolous et al. 2009). Analogous to prostate cancer (Chou et al. 2011), an important question is are the ARMD lesions likely to progress to the stage where they become highly symptomatic or cause damage to surrounding tissues, or would most lesions go completely unnoticed for the life of the patients without screening. Excellent results up to 15-year follow-up with a minimal number of implant failures in some cohorts of 36 mm Pinnacle MoM THAs (Engh et al. 2010, Bernasek et al. 2013, Liudahl et al. 2013) and male patients with Birmingham Hip Resurfacings (Murray et al. 2012, Holland et al. 2012, Van Der Straeten et al. 2013, Mehra et al. 2015) would suggest that many patients with MoM hips remain asymptomatic. However, to date there is barely a decade of follow-up for patients with third generation MoM hips and some of these patients may live for another 40 to 60 years. Thus, the questions about lifelong clinical results and possible systemic adverse effects (cardiovascular, neurological, endocrinologic, reproductive health and cancer) by the Co and Cr burden are yet to be answered. Only long-term longitudinal cohort studies with repeated cross-sectional imaging can confirm whether ARMD is a continuously progressing disease or not, and to answer another clinically important question: how can those lesions that will progress and cause increasing soft-tissue destruction be identified?

There are possible harmful effects from screening. Firstly, overdiagnosis of ARMD would increase the risk of operative treatment applied to patients in whom the symptoms would have not progressed and the results would have been better using a conservative approach. Secondly, hearing about soft tissue abnormality in the hip region may lead to significant psychological distress and consumptive lawsuits (Dyer 2010), even though it might be possible that the lesion would have never progressed to the symptomatic stage. Thirdly, the cost-effectiveness of screening has not been defined, despite the enormously high cost of screening. As the cost of regular screening is from millions to tens of million euros annually in Finland (see 6.2.), the screening protocol has to be based on scientific evidence. Research should concentrate on identifying patient and surgical technique-related risk factors as well as high risk devices with an increased need for monitoring, and

low risk devices that could be monitored with follow-up comparable to traditional THAs. Further, the proper interval of repeated imaging and blood metal ion measurements is an important question. Since imaging studies have suggested that only a few new abnormalities are detected in imaging repeated at intervals of less than a few years (Almoussa et al. 2013, Ebreo et al. 2013, van der Weegen et al. 2013a, Reito et al. 2014b), it would seem that repeated imaging of all patients is not necessary. Asymptomatic patients with resurfacings, blood Co and Cr below 2 ppb and normal imaging findings are reported to have low risk for progression of ultrasound grade (2%) or developing pseudotumors (0%) at 3 to 5 years follow-up, and the authors suggest that no follow-up within an interval of 5 years is needed for these patients (Low et al. 2015). Annual measurement of blood metal ion levels in hip resurfacings is questionable since elevating levels are rarely seen, whereas in THAs blood metal ion levels elevating in one year follow-up are seen in almost one third of patients (Reito et al. 2014a). However, the clinically significant change of blood Co and Cr levels has not been determined, and it is not known if patients with slightly or moderately elevating metal ion levels warrant intensified follow-up. Studies with longer follow-up will show by how much the interval for blood metal ion measurements can be increased.

6.3.3 Limitations of the systematic screening study

Firstly, systematic cross-sectional imaging was not performed, but instead targeted imaging based on symptoms and blood Co and Cr measurements was used. Therefore, there may still be some cases of ARMD that were not detected. However, with this screening protocol, our study reflects more precisely the more common method as targeted screening is more widely used than systematic, and therefore the results may be appropriate to more institutions than with complete follow-up.

6.4 Results of revision of metal-on-metal hips

It has been estimated that more than 1,000,000 MoM hips have been implanted worldwide (AAOS 2012). High revision rates have been presented in registry-based data for MoM hips (AOANJRR 2014, NJR 2014), and manufacturers have recalled a few MoM implant brands (FDA 2012). In study V, we noticed a clear decreasing

trend of blood Co and Cr levels in virtually all patients undergoing revision surgery. The decreasing trend has been described earlier in smaller studies with shorter follow-up (Ball et al. 2013, Munro et al. 2013, Durrani et al. 2014). The decrease of blood Cr has been described as less predictable (Ball et al. 2013), whereas excretion of Co through the kidneys seems to be a more straightforward process (Newton et al. 2012). Other possible explanations for less predictable Cr decrement are accumulation of Cr in the liver and spleen (Urban et al. 2004) or adjacent tissues (Hart et al. 2010) or lesser renal clearance compared to Co (Newton et al. 2012). In study V, all eight patients with Cr levels that remained elevated received Ti-components with either CoC or CoP bearing surfaces, so metal ions released from the metallic head of MoP components does not explain the still elevated blood metal ion levels after revision surgery. Also, seven patients had normal renal function and only one had mildly reduced renal function measured in glomerular filtration rate. We noticed a statistically significant decrease in the number of patients with poor or fair OHS in patients with unilateral THAs, and a decrease in the number of patients with severe or moderate pain in patients with unilateral THAs or hip resurfacings. However, no statistically significant improvement was seen in patients with bilateral THAs. It should be noted that the absolute change in the percentages was of the same magnitude in patients with bilateral THAs as well, and the lack of statistical significance is probably due to the smaller number of patients in that group. A superior improvement in OHS compared with our results has been reported earlier (De Haan et al. 2008a, De Smet et al. 2011, Liddle et al. 2013, Pritchett. 2014). In many of the earlier studies, revision surgeries were performed for various indications, whereas our study included only hips revised due to ARMD. Unexplained pain, metallosis and pseudotumors have been reported to yield an inferior revision outcome compared to other indications (Grammatopolous et al. 2009, Su and Su. 2013). Therefore, the differences in the revision indications may explain the lesser improvement in our study. Further, median preoperative OHS was relatively good in our study, which partly explains the lesser increment seen in study V compared to previously published studies as OHS has a very strong ceiling effect, i.e., improvement of function cannot be measured after a certain point due to reaching the excellent/maximum score. The median preoperative OHS in study V was 37, and the range for good OHS was 34 to 41. The postoperative median of 40 is similar or even higher compared to other studies that report post-revision OHS (Eswaramoorthy et al. 2009, Grammatopolous et al. 2009, Ebreo et al. 2011, Liddle

et al. 2013). Radiographic evidence of acetabular loosening has been described in MoM THAs after revision (Munro et al. 2013), whereas component loosening has not been seen in resurfacings (Ball et al. 2007, Eswaramoorthy et al. 2009). In study V, only minor clinically insignificant radiolucencies were observed, and therefore post-revision loosening does not seem to be a common problem. No reliable conclusion can be drawn from post-revision cross-sectional imaging, as only 20% of the hips were imaged. A wide range of figures have been presented for post-revision complications not leading to revision (3% to 50%) and leading to revision (3% to 37%) after MoM revisions for ARMD (Grammatopolous et al. 2009, Munro et al. 2013, Matharu et al. 2014, Gross and Liu 2014, Pritchett 2014). In our study, complication not leading to re-operation was observed in 2% and complication leading to re-operation in 3%, which compare favourably to results from other centers.

There is no consensus on which patients would benefit most from the revision or to whom the revision should be recommended. It is clearly evident that revision of a MoM implant removes the source of Co and Cr ions and that the blood metal ion levels will degrade in virtually all patients. Slightly elevated whole blood metal ion levels in patients without symptoms or imaging findings are not generally considered as a revision indication (Kwon et al. 2014). Consideration for revision is sometimes recommended for patients with ultra-high whole blood Co and Cr levels, but it is not clear if these patients benefit from treatment. Further, it is unclear what would happen if the elevated metal ions were ignored. Would the levels keep on rising, and would the patients be vulnerable to systemic effects, delayed hypersensitivity or some unknown consequence associated with prolonged exposure to local or systemic metal ion exposure? Variable results about symptoms and hip function have been reported for MoM revisions. Even though there are several studies about the revision surgery of MoM hips, the methodology of these studies is highly incoherent. There is a large variation in indications for revision, the surgical approach used, components exchanged in revision (femoral only, acetabular only, both components), the components and bearing surfaces (MoM, CoC, CoP, MoP, etc.) used in revision and the follow up protocol.

In cases of periprosthetic fracture, aseptic loosening and infection, revision surgery is clearly indicated. Further, we can rightly say that revision surgery should be considered for patients with grave symptoms and/or large tissue abnormalities violating the adjacent muscles, vessels, nerves or bones. The actions at the other end

of the spectrum are easily determined as well: it is unlikely that for patients with only minor symptoms, marginally elevated blood metal ion levels or very locally limited mainly cystic soft tissue abnormality the outcome of the revision would be superior compared to the pre-revision situation. Unfortunately, there is a vast “gray zone” of patients with symptoms and clinical findings that are something between the two extremes. Based on the current literature, it is impossible to determine which patients with moderate symptoms and clinical findings of ARMD would benefit from the revision surgery and, on the other hand, at which point should revision be performed in order to avoid devastating soft tissue destruction. In study V, there were clearly patients who benefited from the surgery, which was seen in better postoperative OHS and milder pain, but unfortunately in some patients the postoperative performance was worse and pain was not relieved. To reliably assess the most suitable techniques and components for revisions of MoM hips, and to determine on which patients the revision should be performed, randomized controlled trials with specified inclusion of patients with suspected ARMD should be performed.

No official guidelines for the post-revision follow-up of patients with MoM hips exist. It has been suggested that blood metal ion measurements should be completely omitted after the revision, since there are no treatment options left even if the metal ion levels do not decrease (Gunther et al. 2013). However, the monitoring of patients with bilateral MoM implants may have to be continued after the first revision due to possible problems with the remaining implant. In our study, we observed blood Cr remaining elevated in a few patients even three years after the revision of the MoM implant. The clinical significance of this finding is unknown.

6.4.1 Limitations of the revision result study

There are clearly some limitations in this study. Firstly, there was only small lost-to-follow-up in blood metal ion measurements (7%) and radiographs (0%), but clearly higher in OHS (24%). It is possible that the patients not returning their questionnaires are more likely to be those not satisfied with the outcome of their hip operation, and therefore our study may give an over optimistic impression about the results of revisions due to ARMD. On the other hand, as we did not acquire immediate preoperative OHS, in some patients the preoperative OHS were recorded several months before the revision surgery. The symptoms that occurred after filling the questionnaire, but which eventually led to the decision for revision, would

therefore not affect the patients OHS. The true effect of both these factors is impossible to estimate retrospectively. Secondly, there were no strict institutional criteria for the revision surgery, but the patient-specific risk assessment and the patients and their surgeons made the final decision for revision. Therefore, the clinical status of patients was not standardized. Also, there was a wide range of bearing surfaces and implant brands used in the revisions. The use of only one revision component would have eliminated the component as a variable, and it would have been more reliable to study which patients benefited from the revision. On the other hand, with the use of two to three different types of revision components, we could have achieved valuable information about optimal components for the revision of MoM hips with ARMD. For example, is there a difference between metal-on-polyethylene and ceramic-on-ceramic in terms of functional outcome or the degradation of blood Co and Cr levels?

7 Conclusions and future prospects

The aim of this academic dissertation was to evaluate the usefulness of different methods used in the screening of patients with MoM hip replacements using blood metal ion measurements and cross-sectional imaging, and to study the results of revisions performed for ARMD in patients with MoM hip replacements.

Whole blood Co and Cr measurements are widely recommended for the screening of MoM hips. Study I showed a high percentage of elevated whole blood Co and Cr concentrations especially in patients with stemmed MoM hips. This is an important finding in terms of risk stratification for the screening of MoM hips.

Rather good sensitivity and specificity for the detection of pseudotumors were achieved with MRI and ultrasound. Based on our results and the current literature published on the imaging of ARMD, neither MRI nor ultrasound are superior imaging modalities compared to each other. However, as the cost of ultrasound is only 10% to 20% of MRI, the use of ultrasound as a primary screening modality should be considered in institutions with radiologists that are experienced in the imaging of ARMD. However, MRI should be obtained with low threshold if abnormalities are seen in ultrasound owing to its better 3D visualization. Also, imaging examinations that are more than a year old should not be used in preoperative surgical planning.

The systematic screening of patients with MoM hip replacements reveals a large number of new ARMDs. If the treatment policy of the institution is to aggressively revise ARMD, the revision rate will subsequently increase. However, even though we have shown that systematic screening reveals new cases of ARMD, we do not know if the systematic screening is cost-effective and in the best interest of patients with MoM hips in order to achieve the best possible quality of life. This issue certainly warrants further research.

Along with the question: “who should be intensively screened?” comes the question about which patients should go through revision surgery and the revision of their MoM implant. Our study showed that the revision surgery effectively removes the systemic burden of Co and Cr ions, but the results on clinical outcome

are harder to interpretate. Some patients clearly benefited from revision surgery. However, some did not gain any help for their symptoms and in some cases the functional outcome was actually worse when compared to the preoperative situation. Clearly, it is easy to conclude that patients who are asymptomatic and also have low blood metal ion levels and small or insignificant imaging findings should not be revised. On the other hand, symptomatic patients with grave imaging findings and/or high blood metal ions should be treated with revision surgery. However, there are many patients in the “gray zone” with moderate symptoms and findings, and we do not know for sure which of these patients will benefit from the revision. Thus, each such patient must be carefully informed about the possible benefits and risks of revision surgery.

Even though MoM hip replacements have been intensively studied, many questions still remain. Higher quality studies are needed about the clinical results of ARMD revisions. In such studies, the standardization of patient selection, revision indication, technique and implant is imperative in order to determine which patients should go through revision surgery and which would achieve the best outcome with a conservative line of treatment. Of course, a randomized controlled trial would be the optimal study setting, but also other prospective studies would help to gain more information. Based on multivariable analyses from registry data and high quality clinical studies, risk factors for ARMD and the failure of MoM hips should be clearly defined and used for stratification in order to improve the cost-effectiveness of MoM screening.

8 Errata

The title of Study III “Good sensitivity and specificity of ultrasound for detecting pseudotumors in 83 failed metal-on-metal hip replacements” should read “Good sensitivity and specificity of ultrasound for detecting pseudotumors in 82 failed metal-on-metal hip replacements”

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11 Original publications