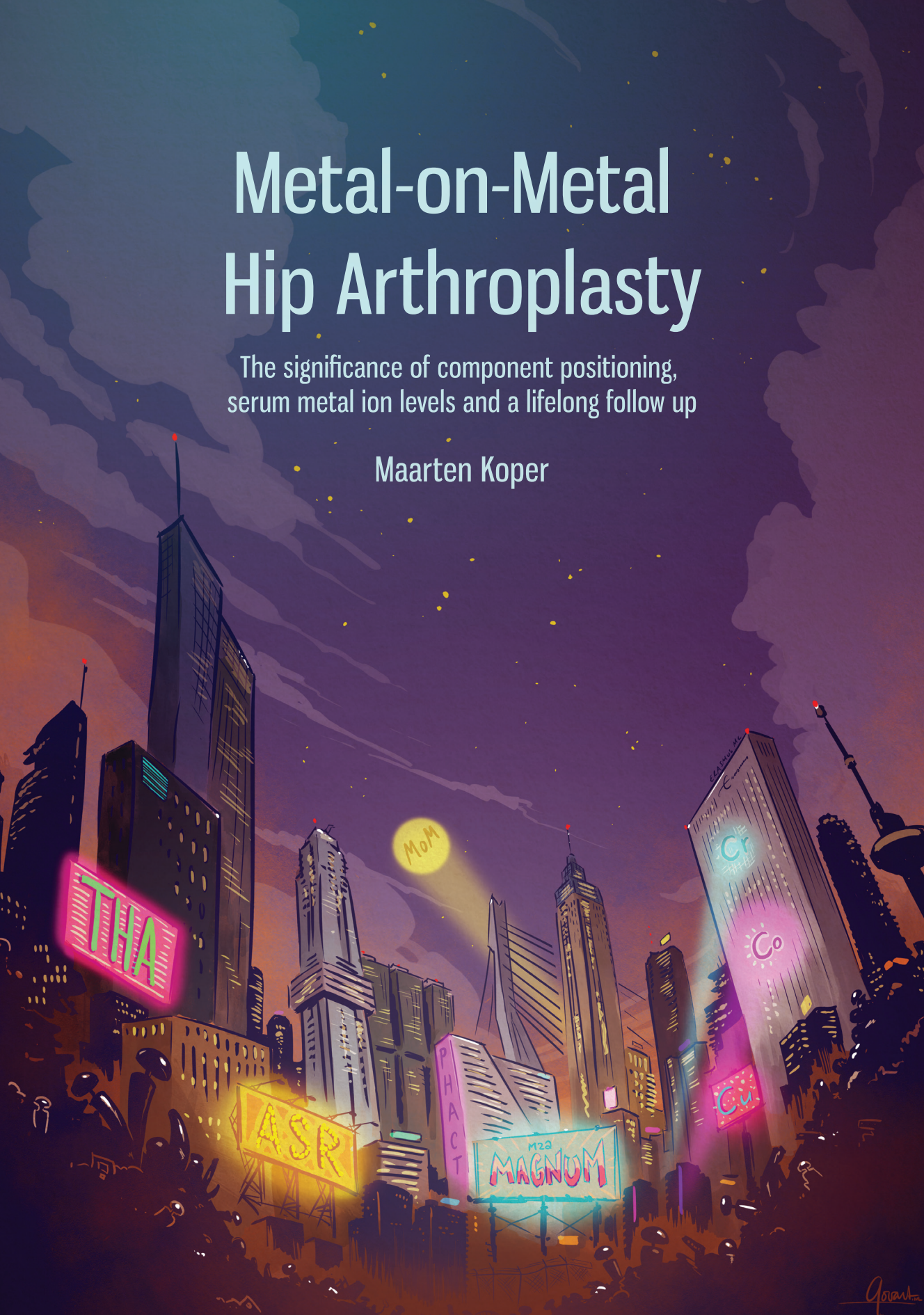
Metal-on-Metal Hip Arthroplasty

The significance of component positioning, serum metal ion levels and a lifelong follow up

Maarten Koper



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Maarten Cornelis Koper

Author: Maarten Cornelis Koper
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Metal-on-Metal Hip Arthroplasty: The significance of component positioning, serum metal ion levels and a lifelong follow up

Metaal-op-Metaal heup protheses: Het belang van component plaatsing, metaal levels in het bloed en een levenslange controle

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Erasmus University Rotterdam

Erasmus

Doctoral Committee

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CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION

1. Introduction

Patients with osteoarthritis of the hip can greatly benefit from one of the most successful surgical procedures available, a Total Hip Arthroplasty (THA). Due to its remarkable success rate, this operation was called "the operation of the century" in 2007 [1]. Initially, the THA was primarily performed on older patients, but over time it has been expanded to include younger individuals with severe osteoarthritis, or other hip pathology, who have higher functional demands. However, it has been observed that the long-term outcomes for younger patients undergoing THA are not as favorable as those for older patients. Multiple studies have reported 10-year implant survival rates ranging from 72% to 86% in patients under the age of 60, compared to over 90% revision-free survival rates for older patients (over 75 years) [2]. To further improve outcome of hip arthroplasty, also for the younger age groups, advancements in implantation technology, such as Computer-Assisted Surgery (CAS), and the development of improved bearing surfaces, such as Metal-on-Metal (MoM), emerged. These advancements had the potential to enhance the outcomes and longevity of THA in the younger, more physically demanding patients.

2. History

There are several historical reports on different treatment methods for osteoarthritic hip joints. However, it wasn't until 1930 when Philip Wiles described the first procedure that involved replacing both the femur and acetabulum with stainless steel components (figure 1) [3]. In the 1950s, McKee and Watson-Farrar further developed this concept, creating one of the first-generation Metal-on-Metal (MoM) Total Hip Arthroplasty (THA) using a cobalt-chromium (CoCr) alloy (figure 2) [4].

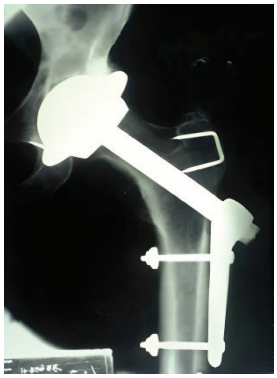

Figure 1: Wiles hip replacement [5].

Figure 2: The McKee-Farrar THA [6].

Around 1970, the use of MoM bearings declined rapidly due to the enormous success of Charnley's high-density polyethylene low friction arthroplasty [7]. Reports demonstrated better early results with the Charnley design, showing improved clinical outcomes and reduced component loosening [8,9]. Consequently, MoM bearings were phased out of the market without a comprehensive analysis and documentation of the reasons for failure [10].

However, Charnley's low friction arthroplasty design also faced challenges such aseptic loosening and osteolysis caused by polyethylene wear. This was referred to as 'polyethylene disease', primarily due to wear particles generated from polyethylene. As a result, the second and third generation MoM THAs were reintroduced in the early 1980s and 1990s to address the problems associated with polyethylene wear. These MoM bearings seemed to be effective in countering the issues related to 'polyethylene disease' [11]. During that same time, in the early 2000s, the "new" MoM Hip Resurfacing Arthroplasty (HRA) was introduced, providing benefits for young patients [12]. This type of bearing preserved more femoral bone, increased the range of motion, and caused less wear and fewer dislocations. These advantages made MoM bearings, compared to the "traditional" polyethylene bearings, particularly suitable for young and active patients.

3. Second and Third Generation Metal-on-Metal bearings

Early 90s, Weber developed one of the first second generation MoM bearings which was highly resistant to wear [13]. These second-generation MoM bearings were initially introduced to address the issues of "polyethylene disease" associated with Charnley's low friction arthroplasty. However, problems such as significant wear due to small diameter metal heads, radial clearance, and edge loading still persisted [14,15]. In order to address these difficulties, a third iteration of MoM arthroplasty emerged in 1998, recognized as the Weber-Metasul implant (figure 3). As indicated by Weber, this implant was proposed as a solution to the issues associated with both polyethylene and preceding metal bearings, achieved through a distinct design and the incorporation of alternative bearing materials [11]. Around the same time, the Birmingham Hip Resurfacing (BHR; Smith & Nephew, London, United Kingdom) was introduced to the European markets. The BHR and other MoM-HRA designs gained popularity among orthopedic surgeons as they provided a good bone-preserving solution with a reduced risk of dislocation due to the use of large femoral heads. Patients were promised long-term durability and the ability to return to sports activities [16]. The reduced dislocation risk also led implant manufacturers to develop "traditional" THAs with large metal head bearings, such as the M2a-Magnum THA (Biomet Inc., Warsaw, Indiana, USA, figure 4).

Figure 3: Weber-Metasul MoM THA [17].

Figure 4: Large head M2a-Magnum MoM THA with titanium sleeve [18].

Despite the lack of long-term follow-up results, the global popularity of MoM-HRAs and large head MoM-THAs increased in the early 2000s, with over one million patients receiving MoM bearings [12,19,20]. More than 20 different companies introduced various MoM bearings during this period, all without hardly any clinical proof of successful results. However, several known problems associated with hip arthroplasty, including fractures, dislocations, infections, implant failure, osteonecrosis of the head (HRA only), notching, and impingement with increased wear, persisted [21–24]. Some of these issues were more prominent in HRA due to the technically challenging nature of the procedure, limited visibility, and restricted exposure of the hip joint. Optimizing implant position was considered crucial to minimize these problems. In order to optimize surgical techniques and achieve precise component positioning in hip resurfacing arthroplasty (HRA), orthopedic surgeons adopted Computer-Assisted Surgery (CAS). Early literature suggested that CAS could lead to improved implant position and enhanced implant survival [25–27]. Additionally, CAS was believed to reduce the learning curve compared to other conventional surgical techniques [28].

To overcome some of the challenges associated with HRA (e.g., impingement, notching, wear), DePuy launched the Articular Surface Replacement (ASR, DePuy Orthopedics, Warsaw, Indiana, USA, figure 5) in 2003, six years after the introduction of the BHR. This next-generation MoM bearing was designed to compete with the BHR and promised to improve patient-reported outcome measures (PROMs) and implant survival. The ASR incorporated design modifications, advanced instrumentation, and a minimally invasive surgical technique to achieve these goals[29]. The changes in design of the acetabular cup and femoral component, along with simplified and precise instrumentation, were intended to overcome the earlier challenges associated with HRA.

Figure 5: ASR Hip Resurfacing Arthroplasty [30].

By 2009, the ASR had gained popularity and was the second most commonly used resurfacing bearing in England and Wales [31]. However, over time, it became evident that this particular MoM bearing, especially the ASR, failed to deliver on its promised improvements. Unfortunately, a similar trend was observed for all large head MoM bearings, as they exhibited also higher rates of revision surgery due to early aseptic loosening and Metal-on-Metal related complications.

4. Metal-on-Metal related complications

In the years following the re-introduction of MoM bearings, it became evident that implant failure, aseptic loosening, and local tissue reactions were common issues across all MoM bearings. Even manufacturers were aware of potential risks, as demonstrated by an internal memo from DePuy in July 2005, which expressed concerns about potential changes in immune function and the possible carcinogenicity of wear debris; *"In addition to inducing potential changes in immune function, there has been concern for some time that wear debris may be carcinogenic. The mechanism is not known and only 24 local malignancies have been reported in patients with joint replacements. Also worrying is the possibility of distant effects. One study suggested a threefold risk of lymphoma and leukemia 10 years after joint replacement. The metal to metal total hip appears to be quite promising and in the laboratory the data is (sic) definitely in its favor. However, the ultimate test is the long term human experience"* [19].

It was not until 2010 that the Medicines and Healthcare products Regulatory Agency (MHRA) recalled ASR hip bearings [32]. Subsequently, in the same year, DePuy issued a global recall of both ASR-HRA and ASR-THA bearings, withdrawing them from the market. This raised significant concerns among orthopedic clinicians and organizations, leading to stricter regulations for all MoM bearings. In 2011, the Dutch Orthopedic Association (NOV) recommended a national review of all implanted MoM bearings and advised annual follow-up examinations. One year later, the NOV advised against the implantation of MoM-HRAs and large head MoM-THAs altogether [33,34]. In the following years, multiple studies and data from national registries reported high failure rates of MoM-HRAs and large head MoM-THAs. Five-year revision rates were found to be as high as 8.3% for MoM-HRAs and 6.1% for MoM-THAs, compared to 1.6% for conventional metal-on-polyethylene THAs [35,36]. One of the primary causes of failure and revision was, and still is, a local tissue reaction due to small metal particles (±10 to 120 µm) [37]. These cobalt and chromium particles are approximately 13.500 times higher compared to metal-on-polyethylene particles and still soluble and bioactive in vivo [38]. An increasing number of publications have reported this specific complication associated with MoM bearings. Adverse Reaction to Metal Debris (ARMD) is the overarching term used to describe the various conditions around the hip joint [39]. These conditions include "Metallosis", which refers to the dark discoloration of soft tissue around the implant; "Pseudotumor", a solid or cystic mass of soft tissue that can cause local pain or swelling; and "Aseptic Lymphocytic Vasculitis-Associated Lesions" (ALVAL), a histological diagnosis of soft tissue characterized by the presence of giant cells and necrosis [40–42]. All of these conditions are associated with elevated levels of cobalt (Co) and chromium (Cr) ions in the local tissue or serum. Over the years risk factors for high levels of Co and Cr in MoM bearings have been identified and include small heads (28-32 mm), design factors, gender and acetabular cup inclination/anteversion [43–46].

5. Cobalt and Chromium

Cobalt (Co, atomic number 27, molar mass 58.8 gram) and chromium (Cr, atomic number 24, molar mass 51.9 gram) are both hard metals with high melting and boiling points, which makes them ideal for creating alloys. These metals have increased levels of ions in the serum and body of patients with MoM bearings. In HRA bearings, the elevated levels of Co and Cr are worn off from the bearing surface between the metal acetabular shell and metal femoral head. In large head MoM-THAs, wear can also occur in the metallic interface between the trunnion of the femoral stem and the taper of the femoral head, leading to a condition called trunnionosis or crevice corrosion (figure 6) [47–50].

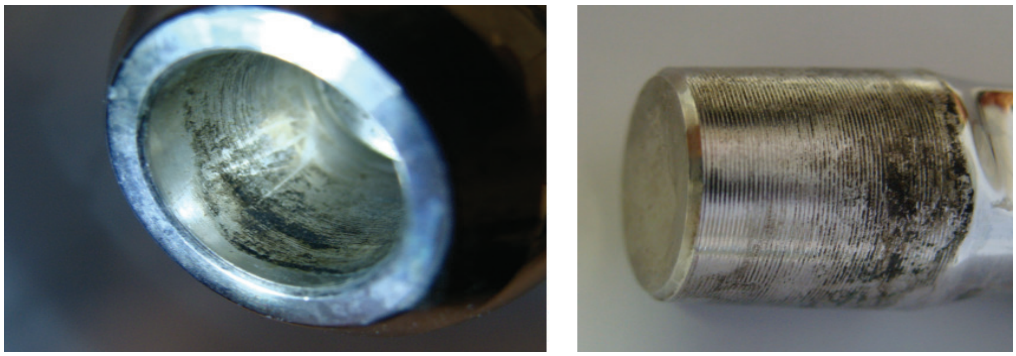

Figure 6: Crevice corrosion (trunnionosis) on the taper of the femoral head and trunnion of the stem [50].

The release of Co and Cr ions can cause both local and systemic problems. Local symptoms, known as ARMD, have been well-documented. However, the potential systemic issues and long-term exposure to high levels of Co and Cr are not fully understood. Systemic toxicity caused by Co release from hip bearings are referred to as prosthetic hip-associated cobalt toxicity (PHACT) [51,52]. Various systemic symptoms have been described in the current literature, including neuro-ocular toxicity (such as ototoxicity, tinnitus, vertigo, and blindness), cardiotoxicity, nausea, anorexia, and thyroid toxicity [53–56]. Although Co is classified as "possibly carcinogenic to humans" by the International Agency for Research on Cancer, there is currently no evidence of any carcinogenic toxicity associated with Co [57–59].

Increased serum levels of Co and Cr are used in national follow-up protocols as a screening tool to assess the risk of ARMD and implant failure. Different safe upper limit (SUL) levels of Co and Cr have been proposed and utilized, but there is no global consensus on the maximum acceptable level [60]. Additionally, SULs can be specific to the type of bearing and the patient, making it challenging to establish a single guideline for all MoM bearings. Co and Cr results are typically expressed in either parts per billion (ppb = micrograms/liter) or nanomoles (nmol). To convert between these units, the molar mass can be utilized, where 1 nmol/L of Co is equivalent to 0.059 ppb (µg/L), and 1 nmol/L of Cr is equivalent to 0.052 ppb (µg/L) [38]

	Cobalt	Chromium
Molar mass (g/mol)	58.993	51.996
Molar mass (nmol/L)	0.059	0.052
nmol/L	= 1 µg/L / 0.059	= 1 µg/L / 0.052
µg/L (parts per billion)	= 1nmol/L x 0.059	= 1nmol/L x 0.052

Unit conversion table.
Abbreviations: g = gram; nmol = nano mol; L = liter; µg = microgram

6. Present use of Metal-on-Metal Bearings

The use of MoM bearings has significantly declined since the recall of the ASR-bearings and the associated concerns of all MoM bearings. The Dutch Orthopedic Association advised orthopaedic surgeons to discontinue the use of large head MoM bearings [33].

Currently, the Birmingham Hip Resurfacing (BHR) is the only MoM bearing that is still used for a specific group of patients. Several studies have demonstrated favourable functional outcomes and survival rates of the BHR in young, active men (under 65 years of age with a femoral-head diameter > 50mm) [61,62]. However, with the excellent performance of the latest highly-crosslinked polyethylene THAs, the use of the BHR needs to be reassessed in large-scale trials [63]. The main concern with all implanted MoM bearings that remain in situ is the elevated levels of Co and Cr. The long-term effects of chronic Co and Cr ion release, even in well-functioning MoM-bearings, are unpredictable and unknown. Lifelong follow-up with regular clinical monitoring and assessment of Co and Cr levels is recommended.

AIMS OF THE THESIS

This thesis comprehensively explores two distinct cohorts, which involve different Metal-on-Metal (MoM) hip designs;

- the ASR Hip Resurfacing Arthroplasty (DePuy International Ltd. Leeds, UK)
- the large head M2a-Magnum Total Hip Arthroplasty (Biomet Inc. Warsaw, Indiana, USA).

The objectives of this thesis are as follows:

1. To evaluate the mid- and long-term outcomes of two distinct MoM bearing types, with a special focus on implant positioning and monitoring serum metal ion levels.
2. To evaluate the efficacy of Computer-Assisted Surgery (CAS) for optimizing implant positioning and examine its influence on Patient Reported Outcome Measures (PROMs) and overall implant survival.
3. To conduct wear analyses and highlight the importance of regular follow-up protocols, integrating serum metal ion control and PROMs, to provide a comprehensive evaluation of MoM implants.

These research objectives are divided into the following three parts:

Part 1: Optimizing component positioning in Metal-on-Metal Hip Arthroplasty

- Evaluate the effects of Computer-Assisted Surgery on component positioning in Metal-on-Metal Hip Resurfacing Arthroplasty.

Part 2: Survival and Failure Analysis of a Metal-on-Metal Hip Arthroplasty

- Determine the early clinical outcome and survival of a large head Metal-on-Metal Total Hip Arthroplasty.
- Study the causes of early failure and perform wear analysis on revised Metal-on-Metal bearings.

Part 3: Significance of Serum Cobalt and Chromium in Metal-on-Metal Hip Arthroplasty

- Investigate the differences in serum metal ion levels during long-term follow-up.
- Evaluate the utility and predictive significance of routine monitoring of serum metal ion levels.

OUTLINE OF THE THESIS

Part 1: Optimizing component positioning in Metal-on-Metal Hip Arthroplasty

The **2nd Chapter** presents the results of a multi-centre, randomized controlled trial on the use of imageless Computer-Assisted Surgery (CAS) for the implantation of the ASR-HRA. The objective of the study was to assess whether CAS could achieve a more accurate position of the femoral component compared to the conventional surgical technique. Additionally, the study investigated the differences in PROMs between the CAS group and the conventional group. It is important to note that during the trial, a global recall of the ASR-HRA was announced due to early failures and issues related to metal wear. Among the various factors contributing to this failure, incorrect positioning of the components emerged as one of the primary causes.

Part 2: Survival and Failure Analysis of a Metal-on-Metal Hip Arthroplasty

After the global recall, all patients with a MoM bearing were advised to undergo frequent outpatient controls and follow-up with their orthopaedic surgeon. **Chapter 3** presents the findings of the first 5-year follow-up of 160 patients who received a large head M2a-Magnum MoM-THA. Following the review issued by the Dutch Orthopaedic Association in 2012, all patients with a large head MoM-THA were closely monitored in the outpatient clinic. The chapter offers a comprehensive description of the various aspects evaluated during the follow-up, including physical examinations, clinical outcomes, serum metal ion levels, radiographs, ultrasonography, and other additional investigations. Furthermore, a survival analysis was conducted to assess the early survival rate of the prosthesis.

The **4th Chapter** presents clinical and wear analyses of 9 revised large head MoM bearings from the cohort described in Chapter 3. The objective of this analysis is to gain insights into different wear patterns, which can help in understanding the mechanisms of failure and predicting possible complications or failures.

Part 3: Significance of Serum Cobalt and Chromium in Metal-on-Metal Hip Arthroplasty

As is known from earlier generations of MoM bearings, wear-related failure and increased metal ion levels can be observed in patients with this type of bearing. High levels of serum metal ions, such as Co, are recognized for their toxic effects on the human body, causing both local and systemic problems. **Chapter 5** of this thesis presents a systematic review on Prosthetic Hip-Associated Cobalt Toxicity (PHACT), focusing on the systemic symptoms associated with Co levels in relation to any type of hip bearing.

In **Chapter 6**, a safe upper limit (SUL) for serum Co and Cr levels is calculated based on the cohort of 160 large head diameter MoM-THAs described in Chapter 3. The establishment of a bearing-specific SUL could assist in developing patient-specific follow-up protocols. Additionally, this chapter includes a 10-year survival analysis and examines the correlation between annually measured serum levels of Co and Cr with variables such as gender, prosthesis size, cup inclination angle, and revision surgery.

The final chapter, **Chapter 7**, highlights the predictive value of serum Co and Cr levels in relation to different PROMs in the HRA patients. Using the unique 10-year follow-up data from a subset of the cohort described in Chapter 2, the annually measured serum Co and Cr levels are correlated with the Harris Hip Score and Hip Disability and Osteoarthritis Outcome Score, providing valuable insights into the relationship between metal ion levels and patient-reported outcomes.

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PART 1

Optimizing component positioning in Metal-on-Metal Hip Arthroplasty.

CHAPTER 2

No added value for Computer- Assisted Surgery to improve femoral component positioning and Patient Reported Outcomes in Hip Resurfacing Arthroplasty.

A multi-center randomized controlled trail.

M.C. Koper1, M. Reijman[1], E.M. van Es[1], J.H. Waarsing[1], H.W.J. Koot[2], S.B. Keizer[3], I. Jansen[4], F.C. van Biezen[1], J.A.N. Verhaar[1], P. K. Bos1

[1] Department of Orthopedics, Erasmus University Medical Center Rotterdam, The Netherlands.

[2] Department of Orthopedics, Maxima Medical Center Eindhoven, The Netherlands.

[3] Department of Orthopedics, Medical Center Haaglanden Den Haag, The Netherlands.

[4] Department of Orthopedics, Admiraal de Ruyter Hospital Goes, The Netherlands.

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ABSTRACT

Background: Computer Assisted Surgery (CAS) has proven to improve the accuracy in several orthopedic procedures. Therefore we used this technique to evaluate femoral component positioning in Hip Resurfacing Arthroplasty (HRA). The aim of this study was to evaluate imageless CAS compared to manually implanted femoral components and subsequently evaluates Patient Related Outcome Measures (PROMs). We hypothesized that the use of CAS optimizes the position of the femoral component and improves PROMs.

Methods: This is a multicenter, single-blinded, randomized, controlled trial of two groups. In the CAS group guiding of the femoral component was done with imageless navigation. In the Conventional (control) group the femoral component was placed manually according to the preplanned position. The primary outcome measure consists of a maximum of 3 degrees difference between the postoperative Stem Shaft Angle (SSA) and preplanned SSA. Secondary outcome measures consist of the Hip disability and Osteoarthritis Outcome Scale (HOOS), the Harris Hip Score (HHS) and Visual Analogue Scale (VAS) pain score.

Results: A total of 122 patients were randomized, 61 in the CAS group and 61 in the conventional group. There was no significant difference in accuracy of femoral implant position. The mean difference between the postoperative- and preplanned SSA was -2.26 and -1.75 degrees (more varus) respectively in the CAS and Conventional group. After surgery both groups show significant improvement in all PROMs compared to the baseline measurements, with no significant differences between the groups.

Conclusion: Our cohort indicates no benefit for the use of CAS in accuracy of placement of the femoral component in HRA compared to manual implantation. There are no clinical differences in PROMs after 1 year follow up. This study showed no added value and no justification for the use of CAS in femoral component positioning in HRA.

Introduction

Hip Resurfacing Arthroplasty (HRA) is still considered a viable treatment option for young and active patients with end-stage osteoarthritis of the hip. Initially, this Metal-on-Metal (MoM) articulation showed promising short-term results, with high early return to work rates and high rates of participation in sports activities [1-3]. However, there have been a high number of early failures and a high revision rates [4-8]. This led to a recall of several MoM hip bearings, a more frequent follow-up of patients, and finally to a reduced use of HRA's worldwide. Nevertheless, several HRA's, are still used and reasonable survival rates have been reported. For some implants and patient categories equal to Total Hip Arthroplasty [9, 10].

The implantation of a HRA is a challenging procedure, due to reduced visibility and little exposure of the hip joint. A non-optimal placement of the femoral component is related to early femoral neck fractures, loosening, notching and higher risk of impingement with increased wear [11-14]. Therefore, an optimization of positioning of the femoral component in HRA could increase the survival of this bearing and possibly improve Patient Reported Outcomes (PROs).

Computer-Assisted-Surgery (CAS) was introduced to improve the accuracy of component positioning and survival of orthopedic implants. CAS has shown to result in an optimization of implant positioning in total hip arthroplasty [15-17] and an accurate component positioning in HRA's [18-22]. However, there is no clear evidence that CAS improves the femoral positioning in HRA compared to manual placement.

Therefore, in this multi-center, patient-blinded, randomized controlled trail (RCT) we compared femoral component positioning between CAS and manual placement. The primary outcome measure was ability to achieve a postoperative Stem-Shaft Angle (SSA) within 3 degrees of the preplanned SSA. Secondly, we compared different PROMs between the two groups. We hypothesized that CAS results in a more accurate femoral component position and improves PROMs within one-year follow-up.

Methods

Study design

All consecutive patients who received an Articular Surface Replacement (ASR) prosthesis (DePuy International Ltd, Leeds, UK) were recruited between October 2006 and January 2010. Patients under the age of 60 (men) and 55 (women) years with nocturnal pain and/or limited walking distance, osteoarthritis (Kellgren Lawrence grade ≥2) of the hip, resistant to conservative treatment and eligible for a resurfacing hip prosthesis were asked to participate. Exclusion criteria consisted of a contralateral total hip prosthesis, body mass index >30 kg/m^2, request to correct an existing leg length discrepancy, not willing to participate in follow-up, proven metal allergy, evident osteoporosis, pathology of the acetabulum (evident acetabular dysplasia: CE angle of < 15 degrees, hip dysplasia, slipped capital femoral epiphysis and Legg-Calve-Perthes disease), previous hip surgery, vascular deficiency of the lower extremity, renal deficiency, active local or systemic infection, use of steroids and/or immunosuppression, femoral anatomic anomaly, femoral head neck ratio <1, and extreme varus position(neck-shaft angle <110 degrees). Conservative treated acetabular fractures were not excluded.

Patients were randomized using concealed allocation via a specifically designed website. Stratification took place per orthopaedic surgeon. All patients were blinded for the allocation, whereas the surgeon could not be blinded for the procedure. A standardized anteroposterior (AP) pelvic X-ray was used for calculation of the Centrum-Collum-Diaphysis (CCD)-angle and for preplanning of the femoral component. The software used for the preplanning was OrthoView (OrthoView, Meridian Technique Limited, Southampton, United Kingdom). Power analysis calculated a minimal of 117 patients per group in order to show a mean absolute difference of minimally 3 degrees between the postoperative SSA and preplanned SSA (one-side testing alpha = 0.05 and beta = 0.80). This sample size calculation is based on the study of Beaule et al., were they investigated the relation between the orientation of the femoral component and outcome of an ASR prosthesis [12]. With a follow-up period of three years, a 20% dropout was calculated and an inclusion of a total of 280 patients (140 each group) needed.

Surgical planning and technique

Eleven experienced orthopedic hip replacement surgeons were trained to use the CAS-system. They attended an obligatory hands-on instructional cadaver course and a saw bone training. All operations were performed using a standard posterolateral approach. In the CAS group, surgical guiding of the femoral component was done with BrainLab Ci™ ASR System 1.0 (BrainLAB AG, Feldkirchen, Germany). There was no additional dissection necessary for CAS compared to the standard hip resurfacing surgery. Both groups received identical antibiotic prophylaxis with Cephalosporin (1000 milligram) direct preoperatively and 24-hours postoperatively. Thrombosis prophylaxis with Nadroparine was given until 6 weeks postoperatively. A standardized pain medication protocol was used postoperatively. Patients were rehabilitated under the guidance of the physiotherapist with immediate unrestricted weight bearing.

Radiological evaluation

To calculate the CCD-angle, the preoperative standardized AP-pelvic X-ray was analyzed in a blinded manner by two of the authors (MCK, EvE) using GeoGebra (International GeoGebra Institute and GeoGebra GmbH, freeware). Figure 1a demonstrates the use of GeoGebra where multiple marks are placed on the collum and the shaft to calculate the CCD angle. The SSA, defined as the angle between the stem of the femoral HR component and the axis of the femoral diaphysis in the AP projection, was measured on the preplanned AP-pelvic X-ray and direct postoperative AP-pelvic X-ray (figure 1b).

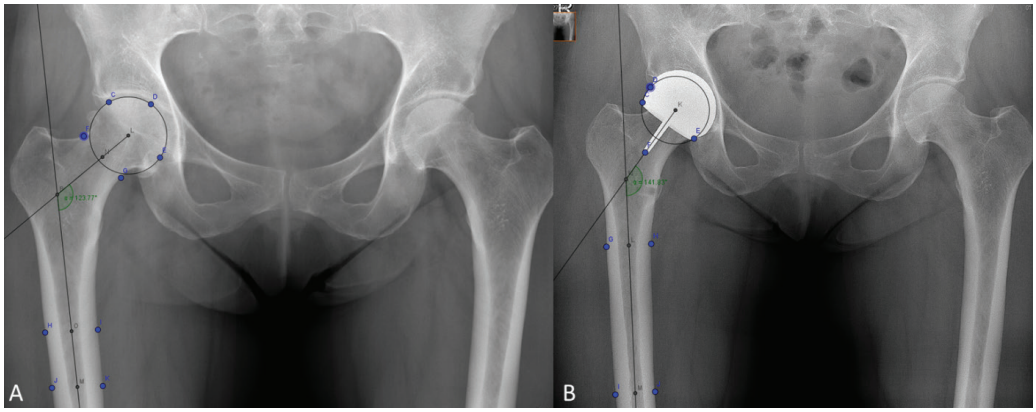

Figure 1. Examples of the use of GeoGebra (International GeoGebra Institute and GeoGebra GmbH, freeware) to calculate the Center-Collum-Diaphysis (A) and the postoperative Stem-Shaft-Angle (B).

Clinical evaluation

The Hip disability and Osteoarthritis Outcome Scale (HOOS), the Visual-Analogue-Scale (VAS) pain score and the Harris-Hip-Score (HHS) were used to evaluate relevant patient-centered outcomes. The HOOS is subcategorized in five domains; pain, symptoms, function in daily life, sports and hip related quality of life. Scores on the HOOS range from 0 to 100, where 0 indicates the worst possible outcome and 100 the best possible [23]. The VAS pain is a validated tool to evaluate pain perception of a patient, and scores range from 0 to 10, with 0 indicating no pain an 10 being the worst pain experienced [24]. At each outpatient visit the HHS was completed by the orthopedic surgeon and used to score the hip function[25]. The survey has 10 questions and score a range from 0 to 100 with higher scores represent less dysfunction and better outcome.

Data collection

Surgical blood loss and surgery duration were logged by the anesthesiologist and written on the surgery evaluation form. Each adverse event was classified as 'surgical' when it occurred in the operation room, as 'early' when it occurred within three months after surgery, and as 'late' when it occurred more than three months postoperatively. At the end of the trial, all hospital records of the participating patients were retrieved and checked to verify the adverse events and their extensiveness. Baseline questionnaires were administered before surgery, and subsequently at 6 weeks, 3 and 12 months postoperative. At each outpatient visit, the HHS was completed by

the orthopedic surgeon. The other questionnaires were patient-reported and were sent out electronically (web-based or via email) or sent on paper by post.

Statistical analysis

Descriptive statistics including means, standard deviations, frequencies and percentages were used to describe the patient characteristics. For all X-ray measurements the intra-observer and inter-observer reliability were evaluated using the intra-class correlation coefficient (ICC). We used a two-way mixed model with absolute agreement and a confidence interval of 95%. The ICC values range from 0 to 1, in which 1 indicates perfect reliability and an ICC greater than 0.75 considered acceptable [26].

Intention-to-treat analyses were used for all variables. However, due to some protocol violations, all data were also analyzed per protocol. The independent t-test was used to assess differences between groups for continuous data, while the Chi-square test was used to assess differences in categorical data. To assess differences in continuous data over time within the same treatment group, a paired t-test was used. For the implant survival analysis, a Kaplan-Meier was used to compare treatment groups. Events were defined as revisions of the femoral and/or acetabular component for any reason, and patients without an event were censored at 3 year postoperative. All analyses were performed using SPSS 20 (IBM Corporation, Armonk, NY). All tests were two-sided and a p-value <0.05 was considered significant.

Results

During the trial period, a total of 125 patients (133 hips) were included, 67 hips were randomized to the conventional group and 66 hips to the CAS group. The study flowchart is depicted in figure 2 and patient characteristics in table 1. A total of 11 randomized patients were excluded due to primary missing data and loss of follow up, five patients in the conventional group and six patients in the CAS group. These patients showed no difference in baseline characteristics. In general, patients in both groups were similar, except for BMI, which was significantly higher in the CAS group (26.9 versus 25.5, p=0.003), which can be explained by a higher body weight (table 1). Unfortunately, due to an international recall of the ASR prosthesis after publications of high complication and failure rates the study was prematurely ended. This resulted in a lower number of inclusions needed and incompleteness of data gathered by the participated orthopedic surgeons.

Table 1. Baseline patient characteristics for the CAS and Conventional group.

	CAS (n = 61)	Conventional (n = 61)	P-value	Excluded hips (n=11)
Age (years)	50 (6.3: 22-60)	50 (6.4: 29-60)	0.887	45.64 (6.9: 37-59)
Weight (kg)	85.6 (11.3: 62-107)	79.7 (12.27 : 53-110)	0.006*	77.9 (11.5: 55-95)
Length (cm)	178.3 (8.9: 161-196)	176.2 (9.2: 157-196)	0.210	175.2 (11.5: 164-197)
BMI (kg/m^2)	26.9 (2.6: 20.3-30.1)	25.5 (20.4-29.4)	0.003*	25.3 (2.9: 19.0-29.8)
Gender (Men : Women)	39 : 22	42 : 19	0.702	6 : 5
Side (L : R)	25 : 36	29 : 32	0.585	7 : 3

Abbreviations: CAS = Computer Assisted Surgery, BMI = Body Mass Index.
Age, Weight, Length and BMI are presented as means (SD: range). Gender and Side are given as a ratio.
* Significant difference

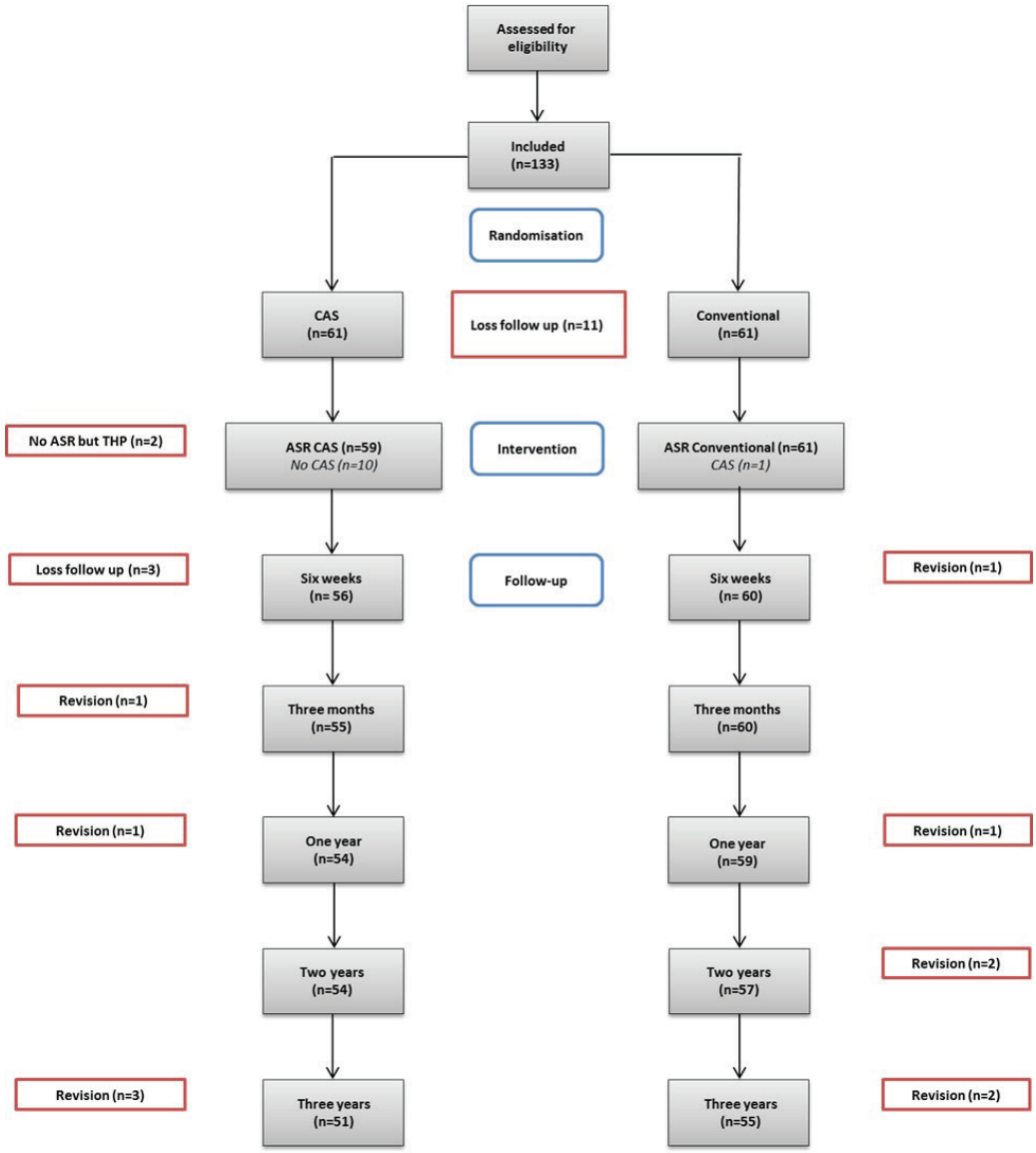

Figure 2. Study flowchart.

Surgical details

Table 2 shows the details on the surgical procedure for each group. The mean operation time in the CAS group was significantly (p<0.001) longer, i.e. 19 minutes. Three minor 'early' adverse events were reported, all in the conventional group. One patient had minor cardiac ischemia, the second patient complained of a painful lower leg and swelling, but thrombosis was excluded. The third patient had a superficial skin infection and required oral antibiotics. All resolved without further problems.

Protocol violations occurred thirteen times. Ten of the CAS randomized patients were operated without CAS due to no CAS system availability during surgery. Two patients in the CAS group were excluded because safe femoral component placement was considered not possible and a total hip prosthesis was implanted. One conventional randomized patient was operated with CAS.

Table 2. Surgery details of the CAS and Conventional groups.

	CAS (61)	Conventional (61)	P-value
Surgery time (min)	116 (30:65-240)	97 (24: 60-180)	0.000*
Blood loss (mL)	645 (276: 200-1500)	573 (282: 150-1500)	0.171
Component size (mm)	49 (3: 43-57)	49 (3: 41-57)	0.635
CAS protocol deviations	12	1	
- Conventional/CAS	10	1	
- Total Hip Prosthesis	2	0	

Abbreviations: CAS = Computer -Assisted Surgery.
Surgery time, Blood loss and Component size are given as means (SD: range). CAS protocol deviations are given as counts.
* Significant difference

Radiographic evaluation

The intra-observer reliability for the two readers was excellent: 0.98, 95% CI 0.94-0.996 for reader 1, and 0.96, 95% CI 0.91-0.99 for reader 2. The ICC for the inter-observer reliability was 0.95, 95% CI 0.89-0.99. The mean native CCD-angle was 129 degrees in both groups, with no significant difference between the groups. We did find a significant difference (P=0.033) in the preplanned SSA within the intention to treat analysis. This is a baseline difference and we do not have a clear explanation for this and believe this is not of any clinical relevance for the outcome of this study. The mean postoperative SSA minus the preplanned SSA showed no significant difference between the two groups (p=0.636). A slightly more varus position was found in both groups with -2.26 and -1.75 degrees deviation respectively in the CAS and conventional group. Analysis of patients with more than 3 degrees, 7 degrees or 10 degrees deviation also showed no significant difference. Table 3 shows all measured data calculated as intention to treat, as well as calculations per protocol.

Table 3 Radiographic evaluation of the angles

	Radiographic evaluation angles (shown as intention to treat)			Radiographic evaluation angles (shown per protocol)		
	CAS (n = 61)	Conventional (n = 61)	P-Value	CAS (n = 50)	Conventional (n = 70)	P-Value
CCD-Angle, degrees (SD: range)	129.5 (6.1: 117-143)	128.6 (6.5: 115-149)	0.443	1292 (6.1: 117-143)	128.9 (6.5: 115-149)	0.78
Preplanned SSA, degrees (SD: range)	138.3 (3.8: 128-148)	136.6 (4.8: 127-152)	0.033*	138.0 (3.8: 128-148)	137.1 (4.7: 127-152)	0.281
Post-operative SSA, degrees (SD: range)	136.0 (5.7: 124-150)	134.9 (6.7: 119-153)	0.311	136.3 (5.6: 124-150)	134.8 (6.6: 119-153)	0.196
Difference postoperative SSA minus preplanned SSA						
Mean, degrees (SD: range)	-2.26 (5.8: -15.25-12.11)	-1.75 (5.9: -13.14 -16.21)	0.636	-1.7 (5.9: -15.25-12.11)	-2.2 (5.8: -13.14-16.21)	0.592
Absolute, degrees (SD: range)	5.14 (3.5: 0.0-15.25)	4.94 (3.5: 0.04-16.21)	0.768	5.0 (3.5)	5.0 (3.5)	0.932
> 3 degrees, n (%)	44 (72%)	40 (66%)	0.558	35 (70%)	44 (61%)	0.692
> 7 degrees, n (%)	18 (29%)	19 (31%)	0.884	12 (24%)	20 (28%)	0.534
> 10 degrees, n (%)	6 (10%)	4 (7%)	0.517	05 (10%)	10 (14%)	0.586

Abbreviations: CAS = Computer-Assisted Surgery, CCD = Centrum-Collum-Diaphysis, SSA = Stem-Shaft-Angle.* Significant difference

Table 4 Patient Reported Outcomes with one year follow up. Calculated per protocol.

	Baseline		Six weeks		Three months		One year		P-value (LMM)
	CAS	Conventional	CAS	Conventional	CAS	Conventional	CAS	Conventional	
VAS	5.7 (1.9)	5.4 (2.0)	1.3 (2.0)	1.3 (1.8)	0.8 (1.3)	0.8 (1.3)	0.4 (1.0)	0.5 (1.2)	0.688
HOOS Pain	38.4 (13.0)	40.5 (15.4)	81.1 (15.5)	79.2 (13.3)	87.0 (15.6)	86.5 (14.7)	91.1 (11.2)	88.0 (16.7)	0.432
Other symptoms	35.0 (14.4)	35.7 (14.2)	67.2 (16.7)	69.0 (15.5)	72.5 (16.1)	72.2 (16.1)	74.5 (18.0)	75.9 (19.6)	0.914
Activities of daily living	38.2 (14.9) *	42.7 (16.4) *	72.8 (17.3)	71.2 (13.5)	83.2 (17.6)	82.2 (15.2)	89.6 (11.7)	87.3 (16.3)	0.333
Sport	16.6 (14.0) **	22.8 (18.3) **	53.6 (29.2)	46.2 (25.6)	69.9 (26.0)	65.8 (25.6)	73.8 (24.2)	76.6 (23.2)	0.444
Hip-related QoL	21.7 (12.3)	24.5 (11.7)	51.9 (16.1)	48.4 (16.7)	66.5 (20.2)	59.6 (17.9)	71.9 (14.6)	69.0 (20.9)	0.309
HHS Total	57.1 (10.6)	60.6 (10.6)	79.1 (16.6)	80.2 (11.5)	91.0 (12.8)	93.7 (8.7)	96.3 (7.1)	97.8 (4.0)	0.537

Abbreviations: CAS = Computer-Assisted-Surgery, LMM = linear mixed-model, VAS = visual analogue scale, HOOS = Hip disability and Osteoarthritis Outcome Scale, HHS = Harris Hip Score. All data are presented as means (SD). * Significant difference (p = 0.028), ** Significant difference (p = 0.021).

Clinical evaluation

Compliance rates for the different questionnaires ranged between 87-100% at baseline, 70-90% after 6 weeks, 70-90% after 3 months and 67-90% after 12 months of follow-up. Reasons for missing data are the international recall of the prosthesis and shutdown of the study website. Table 4 describes all results of the questionnaires during the one year follow-up visits, separately for the two groups. The baseline mean VAS score in both groups decreased significantly(P=0.000) after 6 weeks of surgery. Between both groups no significant difference at any time point was observed. The HOOS questionnaire at baseline showed no differences between the CAS and conventional group in pain, hip-related quality of life and other symptoms. The conventional group showed significant higher scores in the subscales activities of daily living(P= 0.028) and sport(P=0.021) at baseline. After 6 weeks, 3 months and one year follow up, no significant differences between the two groups were observed. The mean HHS was significantly increased in both groups after six weeks(P=0.000), three months(P=0.000) and 1 year(P=0.026) of surgery.

Survival Analysis

During a three-year follow-up period, 11 revisions were performed. An overall survival of 91% in three years was calculated in the entire group. Table 5 shows the revision characteristic between the two groups. All late events in our clinics were managed with a conventional total hip arthroplasty. With per protocol analysis we found more revisions in the conventional group versus the CAS group(8 versus 3) in the three-year follow-up period, this difference was not significant. Figure 3 shows the Kaplan-Meier survival curve between the two groups.

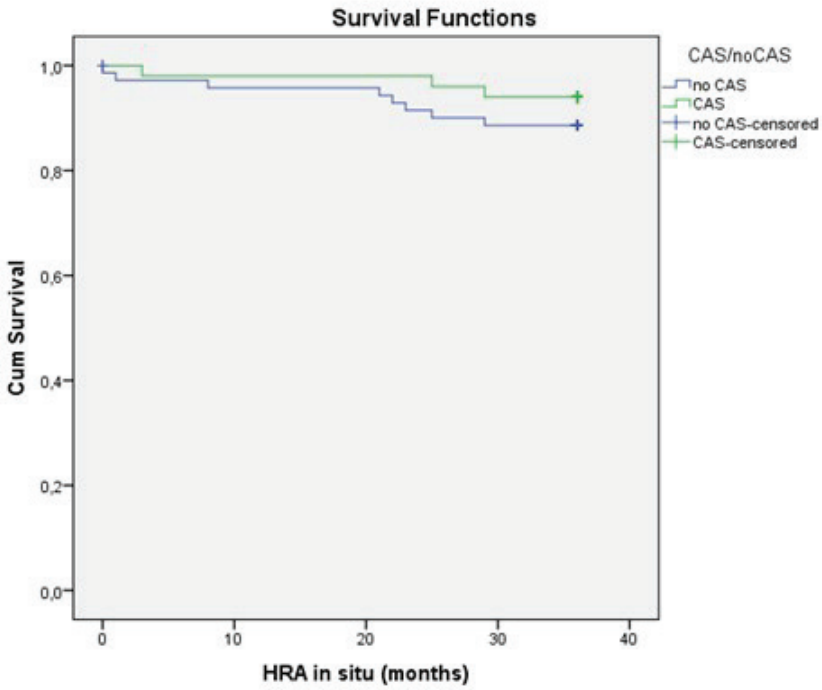

Figure 3. The 3 year survival Kaplan-Meier curve between the CAS and Conventional group. No significant difference (p=0.304) in survival was found.

Table 5 Revision characteristics for the CAS and Conventional group

	Age/Gender	Size component (mm)	Revision indication	Time to revision (months)	Component revised	Anatomy (degrees)	Angle planned (degrees)	Angle post (degrees)
CAS randomized	46/Female	46	Collum fracture	3	Femur	Normal (128)	133	124
	56/Male	49	Collum fracture	25	Femur	Coxa Valga (136)	142	135
	51/Male	53	ARMD, high cobalt/ chromium	29	Femur + Acetabulum	Normal (130)	136	142
	54/Female (no CAS)	47	Aseptic loosening	30	Femur + Acetabulum	Normal (129)	134	131
	53/Female (no CAS)	46	Collum fracture	1,5	Femur	Coxa Valga (141)	143	–
Conventional randomized	52/Male	49	Pain	25	Femur	Normal (122)	137	133
	55/Female	45	Aseptic loosening	8	Femur + acetabulum	Normal (127)	133	141
	53/Female	43	Aseptic loosening	21	Femur + Acetabulum	Normal (126)	136	140
	59/Male	51	Pain, high cobalt/ chromium	23	Femur + Acetabulum	Normal (127)	138	136
	54/Female	41	ARMD	22	Femur + Acetabulum	Coxa Valga (135)	132	149
	48/Male	51	Aseptic loosening	0.5	Acetabulum	Normal (134)	138	134

Abbreviations: CAS = Computer-Assisted Surgery, ARMD = Adverse Reaction to Metal Debris

Discussion

In this multi-center, patient-blinded, randomized controlled study we compared imageless CAS versus manual placement of the femoral component in HRA. The primary endpoint of this study was an accurate placement of the femoral component within 3 degrees difference between the postoperative SSA and preplanned SSA. We did not find a difference in accuracy between the CAS and conventional group.

An accurate positioning of the femoral component in HRAs remains a critical step during surgery. A non-optimal placement of the femoral component is related to early failure. An excessive valgus position results is an increased risk of femoral notching and weakening of the bone with possible avascular necrosis, while a varus position leads to increased femoral neck fractures and aseptic loosening [11, 13, 14, 27, 28]. Increased metal ion levels, adverse reaction to metal debris (ARMD) and pseudotumor formation also seem related to a suboptimal position of components, which may result in increased revision rates [5, 29, 30]. The importance of CAS in component placement in HRA is already shown in preclinical and clinical studies [18, 31-36]. However, most of these clinical studies retrospectively evaluated case series. In this RCT the CCD-angle, preplanned SSA and postoperative SSA were all determined with high intra- and interobserver reproducibility, showing the accuracy of our measurements. The CCD angle in our study was similar for the two treatment groups. We only found a small but significant difference in the preplanned SSA (P=0.003) between the two groups; 138 degrees in the CAS group compared to 137 degrees in the conventional group. However, we consider this difference not of clinical significance. We did not observe any difference in the mean postoperative SSA between the two treatment groups, nor in the number of hips with a postoperative difference in SSA of ≥3, ≥7 or ≥10 degrees from the preplanned SSA. These results show that CAS did not result in an increased accuracy in placement of the femoral component. In contrast to our results, Stiehler et al, did show a significant improvement in placement of the femoral component with the use of CAS. Fewer femoral components were positioned in ≥5 degrees absolute deviation compared to preplanning in the CAS group [19]. In another, retrospective study, they showed a more accurate placement of the femoral component and less deviations from the planned SSA was accomplished with the use of CAS [37].

The impact of CAS on several aspects of patients' functioning (HHS, HOOS and VAS) was evaluated during a one-year follow-up period. Although the patients differed in their level of activities of daily living and sport at baseline, these differences were not clinically relevant. We did observe an overall improvement of patients' functioning over time, but this was similar for the two treatment groups. All results are consistent with previous studies [9, 19, 37].

Our study has several limitations. Unfortunately due to recall of the ASR system, the study was prematurely terminated, resulting in a lower number of patients than needed, possibly hampering our statistical analysis. Selective protocol deviations due to incidentally unavailability of the CAS system in certain surgeries possibly influenced our study outcome. In this case, per protocol analysis would provide a better estimate of the effects of this method. Lastly, our longitudinal analysis of PROs was hampered by missing data. As missing data occurred due to termination of the study, selective bias will be limited, as patients who completed the data are representative of the study population.

Conclusions

Despite the limitations and recall of the ASR prosthesis we feel obligated to present our results. As orthopedic surgeons we have to strive to perform better and always search for optimization of a procedure. In our study, we show no added value for the use of imageless CAS in placement of the femoral component. In addition, CAS also did not improve any of the Patient-Centered Outcomes after one year follow up. Therefore we do not expect that CAS will result in long-term event-free survival, but this remains to be determined in long-term follow up.

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MoM
PHACT
M2a
MAGNUM

PART 2

Survival and Failure Analysis of a Metal-on-Metal Hip Arthroplasty

CHAPTER 3

A 5-year survival analysis of 160 Biomet Magnum M2 metal-on-metal total hip prostheses.

M.C. Koper, N.M.C. Mathijssen, S.B.W. Vehmeijer

Department of Orthopaedics, Reinier de Graaf Hospital, Delft - The Netherlands

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ABSTRACT

Background: Large-head metal-on-metal (MoM) total hip arthroplasties (THA) are associated with high failure rates and possible pseudotumour formation. This study reports the first results of 160 Biomet Magnum M2 large head MoM total hip articulations.

Patients and methods: From 2006 to 2010 the Reinier de Graaf Hospital implanted 160 large-head Magnum M2 MoM THAs (Biomet Inc. Warsaw, Indiana, USA) in 150 patients. These patients were recalled after a warning from the Dutch Orthopaedic Association. Patients were offered a clinical and radiographic assessment of the hip prosthesis, serum control on cobalt and chromium ions, and an ultrasound of the hip. If indicated, additional MARS-MRI or CT scan was performed. Descriptive statistical analysis, correlations, t-tests, non-parametric tests and implant survival were calculated.

Results: The mean follow-up was 6.1 years (4.8-8.4). A cumulative survival rate of 93.1% (95% CI: 88.3-98%) was found after 5 years. Reasons for revision were loosening, pain, infection and pseudotumour formation. The prevalence of pseudotumour formation around the prostheses was 8.75%.

Conclusions: This study reports the first results of 160 MoM THAs implanted in our clinic from 2006-2010. In total, 13 (8.1%) of the THAs were eligible for revision after the recall. In most patients the reason for revision was pseudotumour formation. A total of 14 (8.75%) pseudotumours were diagnosed at the first recall. These results show that a comprehensive follow-up strategy is essential for MoM THAs to promptly identify and manage early complications.

Introduction

Metal-on-metal (MoM) total hip arthroplasties (THA) were introduced as long-lasting total hip prostheses, especially for young patients. Better function, decreased implant wear and higher survival rates were expected [1, 2]. In England, more than 60,000 patients have received a MoM THA since 2003 [3]. However, since the safety alert from the Medicines and Healthcare product Regulatory Agency [4], the use of these articulations has decreased both in relative and absolute terms. Multiple studies have shown high revision rates with the MoM resurfacing prostheses as well as with the MoM THAs by early failures and pseudotumour formation [2, 5-7]. Metal debris due to high wear can lead to elevated serum levels of cobalt and chromium which may result in local tissue reactions around the prostheses causing the formation of pseudotumours. Histological characteristics of the pseudotumour tissue are described as 'aseptic lymphocyte dominated vasculitis associated lesion' (ALVAL) [5]. Pseudotumour formation can results in early failure of the MoM articulations, their prevalence however, is still unknown [8]. Design characteristics, component size, surgical implant factors, such as inclination of the acetabular component and female gender have already been documented as risk factors for pseudotumour formation and early failure of the MoM articulations [9, 10] . In 2011 the Dutch Orthopaedic Association (Nederlandse Orthopedische Vereniging) began a recall of all MoM articulations in The Netherlands. Their advice included an active recall of all MoM articulations as well as active follow-up. This study reports the first results of this recall of all large head MoM THA implanted in our clinic from 2006 to 2010.

Materials and methods

Patient demographics

In the Reinier de Graaf Hospital (Delft, The Netherlands) 160 primary large-head MoM THA were implanted in 150 patients between 2006 and 2010. The THAs were performed by 2 surgeons and implant selection was based on surgeon experience.

Implants and operative technique

All patients received the Biomet Magnum (M2a-Magnum) prostheses with Recap cup and Taperloc (Taperloc®Hip Stem) or Mallory stem (Mallory®) (all Biomet Inc. Warsaw Indiana, USA). Surgery was performed through either an anterior supine intermuscular (ASI) approach or through a straight lateral approach. All ASI-patients were study patients for a prospective ASI-study while the Mallory stems were used in an RSA Mallory study. During the first 24 hours postoperatively antibiotic prophylaxis was given. Low-molecular-weight heparin was given for 6 weeks postoperatively.

Metal ion analysis

Whole blood samples were obtained from all patients in trace-element free tubes. Whole blood cobalt (Co) and chromium (Cr) ion levels (nmol/l) were measured by mass spectrometry. Advised by the Dutch Orthopeadic Association, the cobalt ranges were set as normal <40 nmol/l (< 2mmg/L), normal high 40-85 nmol/l (2-5mmg/L), high 85-170 nmol/l (5-10mmg/L) and extreme high >170 nmol/l (> 10mmg/L). Patients with a bilateral MoM THA were excluded in measurements.

Clinical analysis

All patients were asked if they experienced pain in the groin, suffered from deafness, dizziness, fear behaviour/depression or neurological problems after the surgery. Moreover, the Harris Hip score was used to evaluate all various hip disabilities in patients. The HHS was divided into 5 categories (90 > 100 excellent, 80 > 90 good, 70 > 80 fair, 60 > 70 poor, <60 really poor). Anteroposterior pelvic and lateral hip radiographs were obtained and reviewed by a specialized radiologist. Radiographs were assessed for osteolysis, bone resorption, radiolucency's and component migration. The angle of inclination of the acetabular component was measured by two authors (MCK, NM) by using the transischial line and a second line drawn across the rims of the cup. Also, all patients received an ultrasound exam of the hip by a specialized radiologist. Features of liquid in or around the joint as well as space occupying masses were measured.

Additional analysis

If the patient experienced pain in the hip, blood samples showed elevated levels of cobalt > 40nmol/l or if radiographic imaging and/or ultrasound analysis were abnormal, a Metal Artefact Reduction Sequence (MARS)- Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) was obtained. The diagnosis pseudotumor was based on a combination of clinical presentation, ultrasound, MARS-MRI and/or CT (Figure 1).

Statistical analysis

Descriptive statistical analysis, correlations, t-test, non-parametric tests and an implant survival were conducted using statistical software (PSAW 18.0, Chicago, Illinois). Confidence intervals for the Kaplan-Meier method were set on 95%. Revision for any reason was defined as implant failure, and calculated as the time between 'date of operation' and 'date of revision'. Patients who died without revision were censored at the date of death.

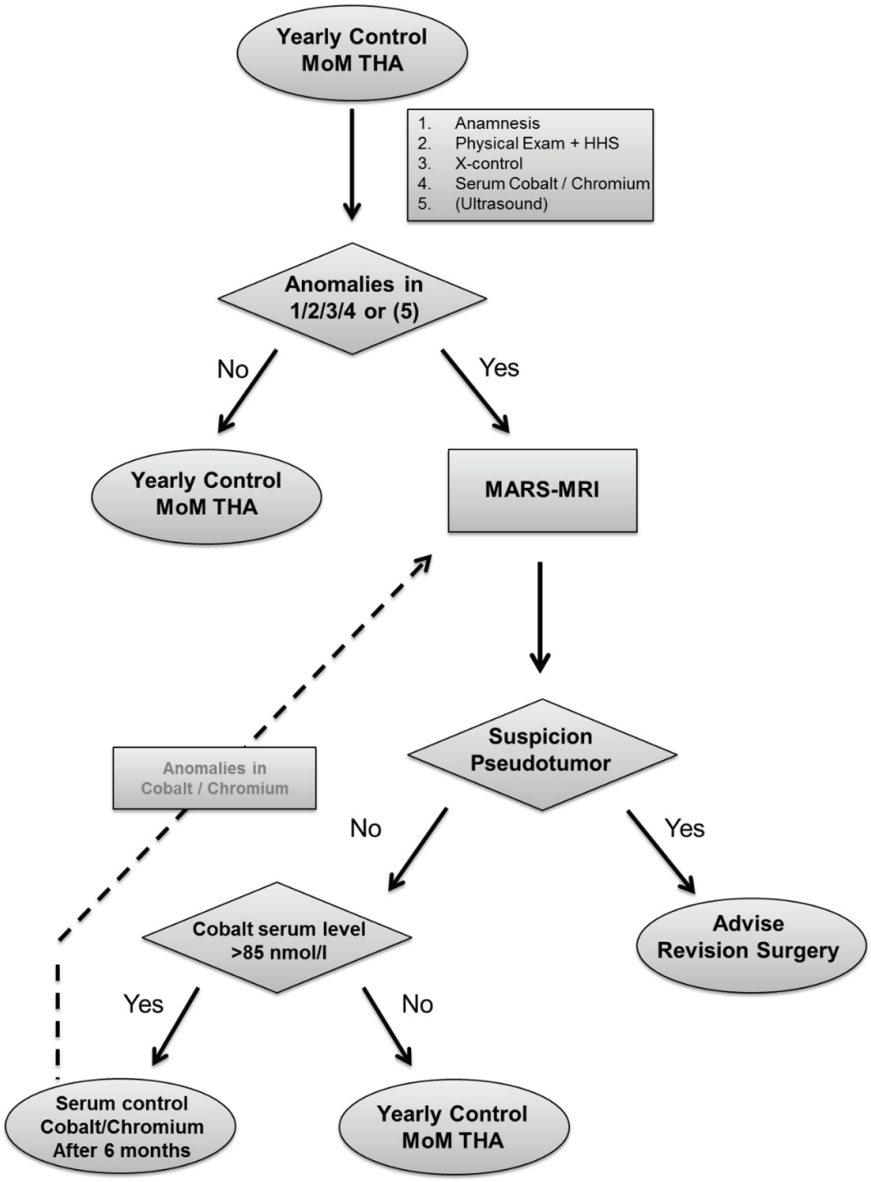

Figure 1. Flowchart created in the Reinier de Graaf Hospital for control and follow-up of MoM articulations. The yearly control includes anamnesis, physical exam, radiographic control and serum tests. Ultrasound was only done during our recall. If any anomalies were found we suggest a MARS-MRI and with suspicion of pseudotumor we advise revision surgery.

Results

Patients and Demographics

In total, 160 MoM THAs were evaluated of which 10 patients had bilateral MoM articulations. Nine patients died of unrelated causes, one had a bilateral MoM articulation. Four patients were lost to follow up or refused to participate. A total of 152 hips were diagnosed with primary osteoarthritis, other demographic features are shown in table 1. The cohort contained 82 women (89 hips) and 68 men (71 hips) with a mean age at surgery of 62 years (range 22 to 85 years). The mean follow up is 6.1 years (4.8-8.4) with an overall survival of 90.6% (CI:82.9% - 98.7%).

Until July 2014, a total of 15 hips (9.4%) has been revised, of which 13 after the recall. The mean time to revision was 3.7 years (range 0.5 to 5.4 years). The two earlier performed revisions were due to infection and loosening. Of the later 13 revised prostheses, 7 (53.8 %) patients experienced pain, 2 (22.2%) were revised due to loosening, and a total of 10 (76.9%) patients were positive for pseudotumor formation. Within the revised prostheses, there was no significant difference in component size ($p = 0.29$).

Four patients with a possible pseudotumor refused revision surgery and are closely monitored. One patient died, unrelated to the pseudotumor. After the recall, a total of 12 patients, 14 prostheses (8.75%),were diagnosed with pseudotumor formation with a mean implantation time of 4.9 years (2.8 –6.7). The cumulative survival rate of the large head Biomet MoM THA at five years is 93.1% (CI: 88.3% - 98%). There was no significant difference in survival between the two used stems nor in gender (data not shown).

Clinical analysis

The patients with revised hip prostheses scored a mean Harris Hip score in the group 'fair' (70 > 80). The mean HHS for the total group was excellent. Pearson Chi-square tests showed patients with pseudotumor formation had a significant ($p=0.007$) lower HHS compared to the patients not diagnosed with pseudotumor. Seven patients of the 13 revised prostheses (53.8%) experienced pain in the groin, compared to 21 (18.3%) of the non-revised patients ($p<0.001$).

Of the 12 patients (14 hips) diagnosed with pseudotumor, 6 (46.2%) experienced pain in the groin, compared to 20% of the patients not diagnosed with pseudotumor formation ($p = 0.054$). No significant differences were found between the revised patients or pseudotumor formation group and the total cohort concerning deafness, dizziness, fear behaviour or neurological problems.

Radiographic analysis

None of the antero-posterior pelvic and lateral hip radiographs showed signs of bone resorption, lysis or fractures. Loosening of the cup was seen in one patient. The lateral cup inclination had a mean (SD) angle of 44.3 (9.4) degrees in the revised patients and 40.9 (7.3) degrees in the total group (table 2). Patients diagnosed with pseudotumor formation scored a mean inclination angle of 45.6 (7.0) degrees. T-test showed in both groups a significant differences of respectively $p = 0.005$ and $p = 0.061$. The intra-observer and inter-observer reliability was evaluated using the intra-class correlation coefficient (ICC) and calculated 98.5% (95%CI 98.0% - 98.8%) within the measurements.

Metal ion analysis

The mean (SD) level of serum cobalt was 42.3 nmol/l (127.7) and of serum chromium 43.7 nmol/l (52.8) (table 2). The median (IQR) level of serum cobalt was 23.8nmol/l (14.1-39.0) and of serum chromium 31.7nmol/l (19.3-54.6).

There was a significant increase in cobalt level in the pseudotumor patients ($p< 0.05$), however no significant difference was found in chromium level (table 2). There were no differences in the revised group.

The median cobalt level for males was 16.7nmol/l (8.5-32.6) and a median chromium level of 22.2 nmol/l (15.4-37.8). For females, the median level of cobalt in serum was 26.7nmol/l (19.4-44.6) and the median chromium serum was 38.0nmol/l (23.4-64.2). No significant differences in cobalt or chromium level between men and women were found.

Ultrasound analysis

In 19 (14.1%) of the totally 135 performed ultrasounds aspects of possible pseudotumor formation were seen. A total of 26 (19,3%) patients was diagnosed after ultrasound with fluid around the joint or capsule. After performing an MRI, 2 of the 19 diagnosed pseudotumors were positive and revised. Eight patients (10 hips) did not have ultrasound, but MRI or CT was performed immediately. The ultrasound was not conclusive in 3 patients because of overweight (Table 2).

CT and MARS-MRI

A total of 47 MARS-MRI's and 28 CT-scans were obtained of 72 hips. 11 hips (23.4%) were positive for pseudotumor formation on the MARS-MRI of which 6 prostheses have been revised. 4 patients refused revision and 1 patient died during follow up. In 13 patients (27.7%) the MARS-MRI showed 'fluid around the joint', 2 of them were revised and appeared to be positive for pseudotumor tissue. In 23 patients (48.9%) the MRI showed no sign of pseudotumor formation. CT-scan investigation of 28 hips showed a pseudotumor in 2 (7.1%) patients and underwent revision. In 24 hips (85.7%) no pseudotumor was found and 2 (7.1%) hips showed fluid around the joint or capsule. Table 3 shows the MARS-MRI findings of the revised and monitored patients in relation to the mean serum levels of cobalt and chromium (nmol/l). The groups are too small for any significant differences.

Table 1: Patient demographic features and radiological parameters.

	All patients	Revised	Pseudotumor
Number of hips (patients)	160 (150)	15 (14)	14 (12 patients)
Deceased	10 (9)	1 (1)	1 (1)
Mean Age in years date of operation (range)	62 (22-85)	60 (22-83)	61 (22-78)
Median	63	60	65
SD	10.1	13.0	13.0
Number of men/women (%)	Male 71 (44) Female 89 (56)	Male 4 (27) Female 11 (73)	Male 4 (29) Female 10 (71)
Side (%)			
Left	76 (47.5)	10 (66.7)	6 (43)
Right	84 (52.5)	5 (33.3)	8 (57)
Diagnosis (%)			
Primary osteoarthritis	152 (95)	13 (86.6)	13 (93)
Avascular Necrosis	5 (3.1)	1 (6.7)	0
Others	3 (1.8)	1 (6.7)	1 (7)
Approach (%)			
ASI	95 (59.4)	10(66.7)	9 (64)
Straight lateral	65 (40.6)	5(33.3)	5 (36)
Component sizes in mm			
Mean Cup (range)	54 (46-64)	54(50-62)	54 (52-60)
Median	54	52	54
Mean Head (range)	48 (40-58)	48 (44-56)	48 (46-54)
Median	48	46	48

Abbreviations: SD = Standard Deviation, ASI = Anterior Supine Intermuscular

Table 2. Clinical outcome; all patients and all revised patients.

	All patients (n=150)	Revised (n=13)	Pseudotumor (n=14)
Clinical outcome			
Mean HHS (range)	90>100 'excellent' (90>100 - < 60)	70 > 80 'fair' (90>100 - <60)	80>90 'good' (90>100- 60)
Painfull hip, no. (%)	28 (18.6%)	7 (53,8%)	6 (46.2%)
Deafness, no .(%)	9 (6%)	0	0
Fear, no .(%)	7 (4.7%)	2 (15,4%)	2 (15.4%)
Dizzyness, no .(%)	6 (4.0%)	0	0
Neurological signs, no .(%)	0	0	0
Radiological results			
Inclination angle in degrees	40.9(10.5– 61.7)	44.3(26.6 – 59.4)	45.6 (35.8-59.4)
Mean	41.4	44.7	42.7
SD	7.3	9.4	7
Ultrasound (n = 135 (%))			
No pseudotumor,	87 (64.4%)	4 (30,8%)	2 (14.3%)
Aspect of pseudotumor	19 (14.1%)	3 (23,1%)	5 (35.7%)
Liquid	26 (19,3%)	4 (30,8%)	5 (35.7%)
No ultrasound performed	10 (7.4%)	2 (15,4%)	2 (14.3%)
Unknown	3 (2.2%)	-	-
Serum cobalt (nmol/l) Mean(range)	42.3 (8.5-1431.2)	179.7(13.6-1431.2)	202.9 (13.6 – 1431.2)
SD	127.7	440.5	461.3
<40	97 (77.0%)	5 (38%)	3 (21%)
40-85	25 (19.8%)	4 (31%)	6 (43%)
85-170	2 (1.6%)	0 (0%)	0 (0%)
170	2 (1.6%)	4 (31%)	5 (36%)
Serum chromium (nmol/l)			
Mean (range)	43.7 (2.0-510.9)	107.2(6.5-511)	98.0 (6.5 – 511)
SD	52.8	150.6	461.3
CT-results	(n=28)	(n=5)	(n=3)
No pseudotumor	24 (85.7%)	2(40%)	1 (33.3%)
Aspect of pseudotumor	2 (7.1%)	2 (40%)	2 (66.7%)
Liquid	2 (7.1%)	1 (20%)	-
Other	0	0	-
MRI-results	(n=47)	(n=8)	(n=13)
No pseudotumor	23 (48.9%)	-	-
Aspect of pseudotumor	11 (23.4%)	6(75%)	11 (84.6%)
Liquid	13 (27.7%)	2 (25%)	2 (15.4%)
Other	0	-	0

Abbreviations: HHS = Harris Hip Score, SD = Standard Deviation

Table 3. MARS-MRI findings of the revised and monitored patients.

	MARS-MRI findings	Mean Co levels (nmol/l)	Mean Cr levels (nmol/l)
Revised patients	Tumor (n = 7)	366	188.8
(n13)	Liquid (n = 3)	37.2	37
	No tumor (n= 3)	13.6	14
Monitored patients	Tumor (n = 5)	130.3	106.9
(n=39)	Liquid (n = 11)	38.6	60
	No tumor (n = 23)	39.2	60.4

Results of the MARS-MRI are presented in relation to the mean serum levels of cobalt and chromium. The 5 patients positive for pseudotumor and no revision are closely monitored. 1 patient died, unrelated to the tumor.

Discussion

Multiple studies on survival of the large head MoM THA have shown early failures, pseudotumor formation and high revision rates [2, 4, 6]. Since the warning of the National Joint Registry of England and Wales in 2010 the MoM articulations have been clearly monitored [2]. The Dutch Orthopeadic Society advised centres in the Netherlands to recall all patients who had received a MoM articulation. Clinical control of the hip, control of serum infection markers, serum cobalt and chromium levels as well as a radiographic control and ultrasound of the hip were advised.

This study reports the first results after the recall of all large head MoM THA implanted in our clinic. In total, 160 MoM THA were implanted from 2006 till 2010 and a total of 150 articulations were evaluated. The cumulative survival rate in our cohort after five years is 93.1% (95%CI: 88.3% - 98%). A total of 15 revisions (9.4%) were performed of which 13 after the recall.

Results of survival studies of the Biomet MoM prostheses vary widely. Puolakka et al. showed a poor survival of Biomet cementless prostheses, mostly related to a poor cup survival [11]. The Mallory head cup had a survival of 98% after 5 years. Bosker et al showed a survival of 88% of the M2a-Magnum articulation after a mean follow up of 3.6 years [12]. Contrary, Meding et al. and Sturup et al. both showed a low incidence of groin pain, adverse reactions and no early failure of the prostheses [13, 14]. However they show no exact survival rate.

A study of Bolland et al. reported a cumulative survival rate (with revision for any reason) of 92.4% at five years for a large hybrid MoM THA [15], a survival rate comparable to the survival rate of metal-on-polyethylene bearings and our results.

The exact incidence and prevalence of pseudotumors around MoM articulations is still unknown and varies widely [8, 16, 17]. Some believe early revision of the MoM THA is recommended when diagnosed with pseudotumor formations [7, 18]. Contrary, Hart el al state that pseudotumor formation alone is no reason for revision. In their cohort, the prevalence of pseudotumor formation in patients with a painful hip is 57% compared to a prevalence of 61% in the control group [19, 20]. Kwon et al. found a prevalence of pseudotumor formation of 5% in screened asymptomatic patients with a hip resurfacing with a mean follow-up of 61 months [20].

Our study showed a prevalence of pseudotumor formation of 8.75% (14 hips) after a mean follow up of 6.1 years (4.8-8.4). The first clinical signs of pseudotumor formation are pain, mostly starting in the groin, and discomfort [7, 21]. Other possible signs are deafness, fear or dizziness [16]. In our cohort, the number of patients experiencing pain in the groin was significant higher ($p<0.001$) in patients with a pseudotumor (46.2%) when compared to patients without pseudotumor formation (20%). Patients with pseudotumor formation had a significant ($p=0.007$) lower HHS and experienced significant more pain in the groin. We did not find any relation between pseudotumor formation and deafness, fear or dizziness. However, only 47 (31.3%) MARS-MRI's and 28 (18.7%) CT-scans were obtained in 72 (48%) patients, meaning possible asymptomatic patients with pseudotumor formation can be missed. Of the 13 revised prostheses in our cohort, 10 (77%) were positive for pseudotumor formation.

Pseudotumor formation seems also to be associated with a significant elevated cobalt and chromium serum level [22-24]. The high levels of cobalt and chromium are especially found in large-diameter MoM articulations, suggesting that pseudotumor formation is associated with high wear and corrosion [25-27]. The high wear and edge loading might be the result of suboptimal

positioning or poor design of the components [16, 28]. Especially excessive inclination, with an inclination angle greater than 55 degrees and a small size, enlarges the edge loading and might lead to high wear and local debris [29, 30]. An inclination of the acetabular component of more than 55 degrees is related to increased serum cobalt and chromium levels. A study of Kwon et al report in all revised prostheses due to pseudotumor formation signs of edge loading [31]. Pandit et al. even claimed that metal wear particles were detected in every case, even with well positioned implants [7].
We found a mean inclination angle of 40.9 degrees in the total cohort. Revised patients had a mean inclination angle of 44.3 degrees and patients diagnosed with pseudotumor a mean of 45.6 degrees (table 2). In both groups this was a significant difference.
The effects of metal wear particles and elevated serum metal have been documented but are still not understood [8]. High serum levels of cobalt and chromium were known and evolved during the running-in phase of the prostheses [32]. However, these elevated levels still persist at long-term follow up [33]. During the steady state phase, when wear rate is constant, metal ion levels seem to reach a steady state [8]. Healthy controls have a mean serum cobalt level of 4.07nmol/L and a mean serum chromium level of 5.38nmol/L [34]. We only found a significant increased ($p< 0.05$) serum cobalt in patients with a pseudotumor. However, in literature, no relation between increased metal ion levels and risk of revision can be found [8]. Moreover, a high serum level of cobalt and chromium is not per definition caused by pseudotumor formation [35].
Glyn-Jones et al. even reported women are more at risk to develop pseudotumors than men [17]. Mont et al. even showed that pseudotumors develop more often in women after hip resurfacing arthroplasty [36]. The exact reason is still unknown, however the naturally small acetabulum in women requires small sized components with a greater change of malposition and thereby a greater change of high wear and elevated ion levels. Venditolli et al. reported higher serum levels cobalt and chrome in women [37], other articles also relate the high levels of cobalt and chromium with increased pain [26]. Our cohort showed no relation of serum level of cobalt and chromium between gender or with increased pain. There is also no difference in HHS.

We described the first results of large head Biomet Magnum M2 MoM THA placed in our facility, including the short term survival, complications and failures during the first recall. It seems that cobalt and chromium are important metal ions related to the formation of pseudotumors and are useful markers for follow up. Although pseudotumor formation in normal functioning hip prostheses is not a clear statement for revision, we do recommend considering a revision in order to prevent future complications. The patients in our cohort, diagnosed with pseudotumor formation and a poor HHS, were offered revision surgery. Patients with pain, however without anomalies were offered active physiotherapy and close follow-up (figure 1). We also recommend a close follow up in other hard-on-hard bearings as they can give adverse local tissue responses as seen in MoM THA. Concerning the MoM articulation placements, we suggest the placement of these prostheses only in a research setting with informed consent of the patient.

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CHAPTER 4

Clinical and Wear Analyses of 9 Large Metal- on-Metal Total Hip Prostheses

M.C. Koper[1], N.M.C. Mathijssen[1], F.Witt[2]
M.M. Morlock[2], S.B.W. Vehmeijer[1]

[1] Department of Orthopaedics, Reinier de Graaf Hospital
Reinier de Graafweg 3, 2625 AD, Delft, the Netherlands

[2] Biomechanics Section, Hamburg University of Technology
Denickestraße 15, 21073, Hamburg, Germany

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ABSTRACT

Background: Metal-on-Metal (MoM) total hip arthroplasties (THA) are associated with pseudotumor formation and high revision rates. This prospective study analyzed the clinical and wear analyses of 9 large Metal-on-Metal (MoM) total hip arthroplasties (THA) to understand the underlying mechanisms of failure. The MoM bearings were revised for multiple reasons; the main reason was pseudotumor formation.

Materials and Methods: From 2006 till 2010 the Reinier de Graaf Hospital implanted 160 large head M2a-Magnum™ (Biomet Inc. Warsaw, Indiana, USA) THAs in 150 patients. The first year, 9 bearings were revised and analyzed at the Biomechanics Section, Hamburg University of Technology, Germany. We performed clinical (Harris Hip Score, radiographic analysis, blood cobalt and chromium) and wear analysis (implant, tissue and fluid) of the 9 bearings. Since this study did not fall under the scope of the Medical Research Involving Human Subjects Act in The Netherlands, no ethical approval was necessary. In this prospective study all patient details were anonymized by the corresponding author, all other authors were blinded during the research and wear analyses. Patients with bilateral MoM implants were excluded.

Results: The 9 bearings had a median (IQR) survival of 41.0 (25) months in situ. From these bearings, three showed no noticeable wear. The median (IQR) head wear volume was 3.2 (3.6) mm^3 and maximum wear depth 0.02 (0.02) mm. For the cup the median (IQR) wear volume was 0.23 (0.3) mm^3 with a maximum wear depth of 0.03 (0.05) mm.

Conclusions: An early identification of parameters related to failure of the MoM THA, such as pain, decreased range of motion, radiographic changes and high levels of blood cobalt and chromium is of great importance for patient's quality of life. Especially now patients and surgeons face the long term effects of all these bearings still in situ. This study reports the clinical and wear analyses of 9 MoM THA. In the majority of this group the reason for revision was pseudotumor formation. Most bearings showed signs of wear, however with a great diversity in clinical analysis, in inclination angle, serum cobalt and chromium levels as well as wear analysis. For a better understanding of the underlying mechanisms related with failure, more wear analyses of revised MoM bearings are necessary as well as a frequent follow-up of the patients with a MoM bearing.

Introduction

The Dutch Orthopaedic Association (Nederlandse Orthopedische Vereniging) decided in the beginning of 2011 to do a recall of all MoM articulations in The Netherlands. Their advice included active recall of all MoM hip implants as well as an active follow–up. This decision was made after multiple studies had shown high revision rates with the MoM THA by early failures and pseudotumor formation due to metal debris by high wear and edge loading [1–4]. In 2009 almost 35% of the 270.000 hip replacements in the USA were MoM bearings [1, 5]. In England, an estimated number of more than 60.000 patients have received a MoM THA since 2003 [6]. The metal debris can lead to elevated serum levels of cobalt and chromium and tissue reactions around the prosthesis, described as 'Aseptic Lymphocyte dominated Vasculitis Associated Lesion' (ALVAL), also known as pseudotumor [2]. The high wear and edge loading might be the result of suboptimal positioning or poor design of the components [7, 8]. Especially excessive inclination, with an inclination angle greater than 55 degrees as well as a small size of the cup, increases the edge loading. This edge loading might lead to high wear and local debris and is related to increased serum cobalt and chromium levels [9, 10]. Furthermore, edge loading is proposed to have a relation to wear of modular taper interfaces [11].

The wear rates of the retrieved MoM bearings vary widely. First reports showed a low wear rate of 0.3 mm^3 per year [12 13]. However, latest reports of MoM hip resurfacings and total hip prosthesis show high wear rates up to 6 mm^3 per year [14, 15].

This study describes the clinical and biological analysis of 9 patients with revised MoM THAs. We performed wear analysis of the 9 revised implants to relate the wear rate to our clinical and biological findings to help understanding the underlying mechanisms of failure.

Materials and methods

Patient demographics

In the Reinier de Graaf Hospital (Delft, The Netherlands) 160 primary large head MoM articulations were implanted in 150 patients between 2006 till 2010. Data and survival analysis of our cohort are written elsewhere [16]. From the 160 bearings placed in our facility, fifteen were revised of which two patients had bilateral MoM bearings. Thirteen of these implants were revised after the recall and 9 of these bearings were analyzed for this prospective study at the Biomechanics Section, Hamburg University of Technology, Germany. From these 9 bearings, seven were revised due to pseudotumor formation and in two cases progressive pain was the indication. Six of the patients were female and the mean age at primary surgery was 57 years (range 22–72 years). The median (IQR) time in situ was 41.0 (25) months. All components; cup, head and insert were revised, in one case the stem was also revised. The median (IQR) cup size was 52 (2) mm and head size 46 (2) mm. All patient demographic features are shown in Table 1. Patient no 9 had bilateral MoM THA, of which the right hip is revised. Since this prospective study did not fall under the scope of the Medical Research Involving Human Subjects Act in The Netherlands, no ethical approval was necessary. In this study all patient details were anonymized by the corresponding author, all other authors were blinded during the research and wear analyses. Patients with bilateral MoM implants were excluded in measurements.

Table 1. Patient demographics of the 9 revised bearings.

Patient	Age	Gender	YoO	Indication	Head size	Stem name	Pain	HHS	Diagnosis	Inclination angle (degrees)	Co levels (nmol/l)	Cr levels (nmol/l)	Histology
1.	57	F	2007	OA	46	Mallory	no	70>80	Tumor	47.69	22,9	18,4	Pseudotumor
2.	58	F	2007	OA	48	Taperloc	yes	60>70	Tumor/ Loosening	59.11	1431,2	510,9	Not performed
3.	60	F	2007	OA	46	Taperloc	yes	90>100	Tumor	59.44	80,9	67,4	Not performed
4.	65	F	2008	OA	46	Mallory	yes	60>70	Tumor	35.81	13,6	6,5	Not performed
5.	57	F	2009	OA	46	Taperloc	no	80>90	Tumor	52.07	80,8	100,1	Pseudotumor
6*	59	M	2009	AVN	56	Taperloc	yes	70>80	Loosening	32.49	22,1	35,9	Pseudotumor
7*	72	M	2009	OA	46	Taperloc	yes	<60	Pain	26.62	13,6	14	Pseudotumor
8.	22	M	2009	Pseudoarthrosis	46	Mallory	yes	70>80	Tumor	41.59	26,8	58,6	No clear diagnose
9**	67	F	2009	OA	48	Taperloc	no	90>100	Tumor	40.14	283,9	149,6	Pseudotumor

Abbreviations: YoO = Year of Operation, HHS = Harris Hip Score, Co = Cobalt, Cr = Chromium, OA = Osteoarthritis
Patients * marked had no pseudotumor. ** Bilateral MoM THA.

Implants and operative technique

All patients received the Biomet Magnum (M2a-Magnum™) prostheses with Recap cup and Taperloc (Taperloc® Hip Stem) or Mallory stem (Mallory®) (Biomet inc. Warsaw Indiana, USA). The implants were implanted by two surgeons (one of the co-authors) and the selection of the type of implant was based on experience of the surgeon. Seven operations were performed through an anterior supine intermuscular approach and two (patient 1 and 8) through a straight lateral approach. During the first twenty four hours postoperatively antibiotic prophylaxis was given and patients received low-molecular-weight heparin for 6 weeks.

Clinical analysis

All patients were examined clinically and asked if they experienced pain in the groin, suffer from deafness, dizziness, fear behavior/depression or experienced neurological problems after surgery. Additionally, the Harris Hip Score (HHS), a score to assess the results of hip replacement, and physical examination, all taken by one doctor, were used to evaluate all patients (S1 Fig). The HHS was divided into 5 categories (90 > 100 excellent, 80 > 90 good, 70 > 80 fair, 60 > 70 poor, <60 really poor) and used as one of our outcome measurements.

Anteroposterior pelvic and lateral hip radiographs were obtained and criticized by a specialized one radiologist. Radiographs were assessed for radiolucency, component migration, osteolysis and/or bone resorption. Lateral cup inclination was measured by two authors (MCK, NM) by using the transischial line and a second line drawn across the rims of the cup. Also, all patients had received an ultrasound exam of the hip by one specialized radiologist and additional MARS-MRI or CT-scan. Fluid components or mass on ultrasound or reactive masses on MARS-MRI /CT-scan were highly suspected for pseudotumor formation.

Metal ion analysis

Blood was sampled from all patients in trace-element free tubes. Whole blood Cobalt (Co) and Chromium (Cr) levels (nmol/l) were measured by mass spectrometry (Atomaire Absorption Spectrometry, Thermo Elemental, Solaar M6, 2001, England). Advised by the Dutch Orthopeadic Association, the cobalt ranges were set as normal <40 nmol/l (< 2 mmg/L), normal high 40–85 nmol/l (2–5 mmg/L), high 85–170 nmol/l (5–10 mmg/L) and extreme high >170 nmol/l (> 10 mmg/L).

Wear Measurement

Analysis of the bearings consisted of digital photographs and wear measurements. The surface geometry of each component was determined with the use of a coordinate measurement machine Mitutoyo BHN 305 (Mitutoyo Deutschland GmbH, Neuss, Germany). By using a 2 mm ruby tip all surfaces were scanned. The original surfaces were estimated by fitting unworn surfaces to regions of the measured surface which is unworn. For assessing bearing wear the geometrical from of a sphere was applied for fitting. Conical surface was calculated the same way, whereby the geometrical form of a cone was applied. Volumetric wear was quantified by comparison with an assumed initial geometry. Mathematical methods used are described in detail elsewhere [17, 18]. The red marked bearing and taper surfaces (Fig 1) were analysed.

Figure 1. The red marked bearing and taper surfaces in the picture bellow were analyzed

Tissue and Fluid analysis

During revision surgery, tissue and liquid samples around the joint of 6 patients were taken to determine cobalt, chromium and titanium concentrations. Samples were freeze-dried and crushed with a scalpel. 100 mg samples were digested by microwaves (ELAN DRC II and Optima7000DV ICP-OES, PerkinElmer, Inc. Waltham, MA, USA). Two samples were taken from the solution, separately analyzed and the results averaged.

Results

Clinical analysis

The mean Harris Hip Score was 'fair' (70 > 80). Patients revised because of pain scored a lower HHS (60>70) compared to the other revisions. Seven patients (77.8%) experienced pain in the groin, and 2 (22.2%) patients noted a swelling around the joint. None of the analyzed patients showed neurological signs, signs of deafness or dizziness. Only one patient complained of fear during mobilization which was related to the pain in the groin. Six patients complained of groin pain of which only four had pseudotumor formation. Three patients, all female, with pseudotumor tissue had no groin pain. This despite their serum increased ion level of cobalt and chromium and the wear in both cup and head.

Radiographic analysis

The anteroposterior pelvic and lateral hip radiographs of patient 2 and 6 showed signs of loosening of the cup. All the other anteroposterior pelvic and lateral hip radiographs showed no signs of bone resorption, lysis or fractures. The lateral cup inclination had a median (IQR) angle of 41.2 (21.4) degrees. Patients diagnosed with pseudotumor formation scored a median (IQR) inclination angle of 47.7 (23.3) degrees. In our total cohort of 160 prostheses the mean (SD) inclination angle was 40.9 (7.3) degrees [16].

Ultrasound analysis

Ultrasound was performed in 8 patients from our study group. Signs of pseudotumor were observed in 2 of these patients. Moreover, four patients showed liquid accumulation inside the joint or capsule. In one patient ultrasound was not performed, but CT and MRI was done immediately.

Metal ion analysis

The median level of serum cobalt was 24.9 nmol/l with an interquartile range (IQR) of 65.15 nmol/l. For chromium a median of 47.3 nmol/l (IQR 76.8 nmol/l) was found. Patients with a pseudotumor showed a median level of serum cobalt of 53.8 nmol/l (IQR 397.9 nmol/l) and chromium of 63.0 nmol/l (IQR 187.4 nmol/l).

CT and MARS-MRI

A total of 6 MARS-MRI's and 3 CT-scans were obtained of which 1 patient had both (patient no 9). In two cases CT-scan showed a possible pseudotumor. MARS-MRI showed in 5 cases a possible pseudotumor (see Table 1). CT-scan of patient number 7 showed no signs of pseudotumor. Patient no 6 had no CT or MRI investigation.

Wear Analysis

Table 2 shows the wear analyses of all nine bearings. In three bearings no noticeable head wear was found. The median (IQR) head wear volume was 3.2 (3.6) mm^3 and maximum wear depth 0.02 (0.02) mm. For the cup the median (IQR) wear volume was 0.23 (0.3) mm^3 with a maximum wear depth of 0.03 (0.05) mm. Only one bearing, no 2, showed massive bearing wear. Notable cup wear of 28 mm^3 and head wear 24.4mm^3. Figure 2 shows the wear plots of this bearing. Clear inner sleeve taper wear was only seen in patient 9 (Table 2).

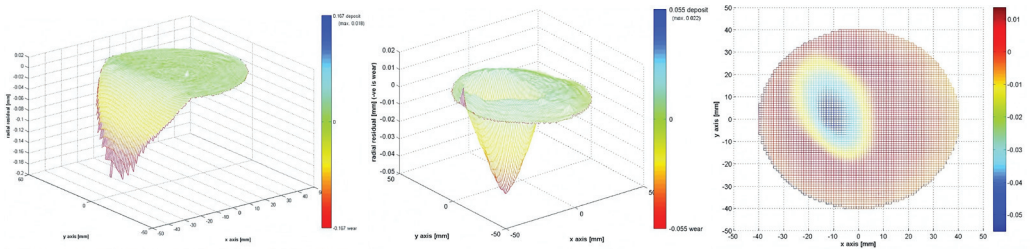

Figure 2. Wear plot graphs of the cup (most left) and head (middle and right) of patient no 2. 70% points used for estimation of wear. The green area represents the estimated original surface. The red area represents the wear and is defined as a negative deviation from the original surface

Table 2. Head, cup and taper wear in the revised bearings.

	Head wear			Cup wear			Inner Sleeve Taper wear		
Patient	Wear Area Ratio [%]	Wear Volume [mm^3]	Wear per Year [mm^3]	Wear Area Ratio [%]	Wear Volume [mm^3]	Wear per Year [mm^3]	Deposits [mm^3]	Wear Volume [mm^3]	Wear per Year [mm^3]
1.	6.382	1.209	0.2267	2.910	0.315	0.0591	0.078	0.000	0.000
2.	24.561	24.424	4.8047	20.575	27.998	5.5078	0.208	0.000	0.000
3.	13.042	4.486	0.9444	1.884	0.302	0.0636	0.002	0.000	0.000
4.	0.035	0.004	0.0009	0.000	0.000	0.000	0.041	0.000	0.000
5.	11.910	3.657	1.0703	0.000	0.000	0.000	0.118	0.000	0.000
6*	13.701	3.281	1.1931	0.000	0.000	0.000	0.266	0.041	0.0149
7*	0.000	0.000	0.000	1.825	0.178	0.0548	0.078	0.000	0.000
8.	6.484	0.930	0.310	2.302	0.260	0.0867	0.166	0.000	0.000
9**	9.210	3.204	1.1651	1.060	0.232	0.0844	3.074	0.172	0.0625

Patients * marked had no pseudotumor. ** Bilateral MoM THA.

Tissue and Fluid Analysis

The tissue and fluid analysis shows a great diversity between the bearings (Table 3). The largest difference is seen in the titanium tissue samples. The median (IQR) amount of titanium in the tissue is 168.5 (3327.2) mg/kg. Tissue analysis also showed a large amount of chromium with a great diversity between the samples. The median (IQR) of chromium was 6.9 (744.3)mg/kg. The other results are shown in Table 3.

Table 3. Tissue and fluid analyses of 6 revised bearings.

Patient	Type	Co (mg/Kg)	Cr (mg/Kg)	Ti (mg/Kg)
1.	Tissue	44.3	29.8	1347
	Fluid	1.11	0.77	<10
2.	Tissue	204	2945	9468
	Fluid	3.97	26.37	<10
3.	Tissue	7.90	36.35	182
	Fluid	0.52	1.74	<10
4.	Tissue	5.34	24.4	155
	Fluid	<0.1	0.27	<10
5.	Tissue	9.69	48.7	<50
	Fluid	1.56	4.24	<10
7*	Tissue	15.6	37.5	<50
	Fluid	0.13	0.27	<10
Median (IQR)	Tissue	12.6 (77.0)	36.9 (744.3)	168.5 (3327.2)
	Fluid	0.8 (2.0)	1.3 (9.5)	10 (0)

Abbreviations: Co = Cobalt, Cr = Chromium, Ti = Titanium, IQR = Interquartile Range
Patient * marked had no pseudotumor.

Discussion

Survival of large MoM THAs has decreased by early failures and pseudotumor formation. Analysis of revised MoM THA shows a wide variation in wear rates and also pseudotumor formation in the absence of high wear [2, 4, 19]. A better understanding of failure, wear rate and clinical presentation is relevant to predict the outcome of MoM THA's. We described the clinical and wear analysis of a small group of 9 MoM THA implanted in our clinic from 2007 till 2009. Seven prostheses were revised due to pseudotumor formation, two other prostheses because of pain and loosening.

Pseudotumors seem to be associated with high wear and metal hypersensitivity [20, 21], however a clear association has not been seen yet. According to Edward et al. the histopathological changes in the tissue cannot be explained by high wear alone [19]. There are also several reports of MoM THA failure and adverse local tissue reactions in patients with the absence of high wear [2, 4, 22]. In these patients a hypersensitivity reaction to the metal is more likely and results in aseptic lymphocytic vasculitis-associated lesions [23]. However, reducing the amount of wear might prevent this reaction and possibly reduce the formation of pseudotumors. This is also of importance for all other bearings. The most important predictor of wear rate is edge loading [24]. Edge loading is caused by high cup inclination, cup version, cup and head version, head-neck ratio, cup design and more variables. Some studies show excessive inclination, with an inclination angle greater than 55 degrees and a small size, increases the edge loading and might lead to high wear and local debris. An inclination of the acetabular component of more than 55 degrees is also related to increased serum cobalt and chromium levels [9, 10]. According to Hart et al, high cup inclination can even be a predictor of high wear rate [24]. The effects of metal wear particles and elevated serum metal have been documented but are still not under- stood [25]. High serum levels of cobalt and chromium were known and evolved during the running-in phase of the prostheses [26].

A clear correlation between the serum ion levels of cobalt and chromium and wear rate was not found in this study. This is in accordance with the findings of de Smet et al and Hart et al. [24, 27]. However, a trend in high inclination and increased metal ion levels could be observed (Table 1).

In our small group, two patients (patient no 2 and 3) had a cup inclination angle over the 55 degrees. Both patients also show the highest cup wear area ratio (Table 2). However, high wear was also seen with an inclination angle of 47.7 and 32.5 degrees. The patients with high head wear ratio also showed an increased serum level of cobalt and chromium. Especially patient no 2 with an inclination angle of 60 degrees (Fig 3), a head wear ratio of 24.4 mm^3 and a cup wear ratio of 28.0 mm^3 showed highly increased cobalt and chromium levels (Table 1). These results show again the importance of a good positioned acetabular component especially to prevent the high edge loading and increase in serum and tissue ion levels as mentioned above.

The fluid and tissue analysis showed highly increased levels of cobalt and chromium in all patients. Thereby, even more striking is the high titanium level in the tissue of patient 1 and 2. These high levels of titanium indicate "trunniosis" in the taper-stem junction because only these two components consist of titanium alloys. Trunniosis, or cold-welding, is a phenomenon seen in the large head bearings, mostly above the 40mm [28–30]. More stress load on the modular interface at the larger head bearings implies more corrosion and debris, especially titanium. In our cases,

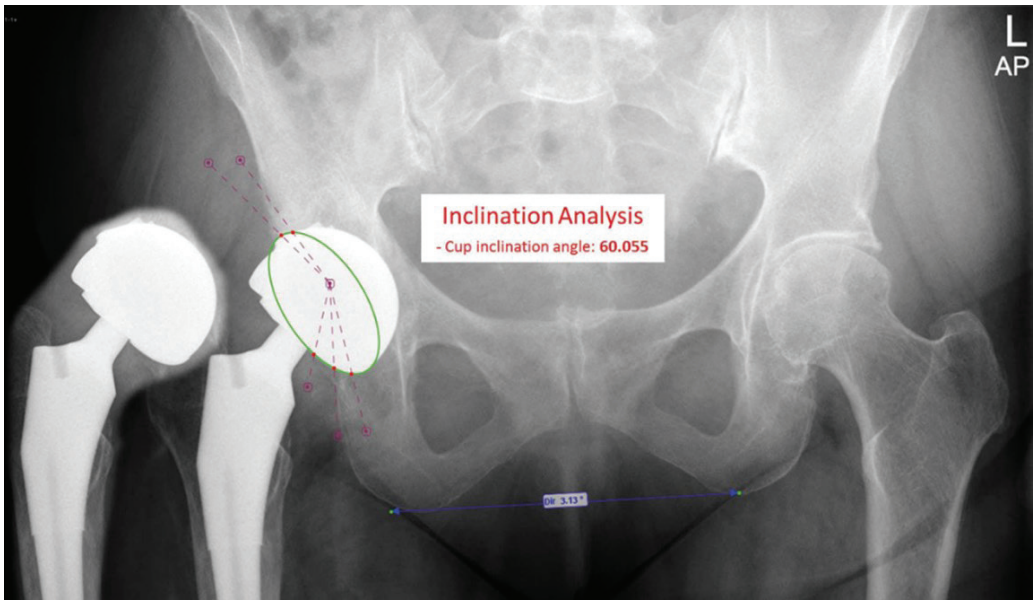

Fig 3. Anteroposterior radiograph of the pelvic from patient no 2 with the MoM total hip replacement on the right. The acetabular inclination angle was estimated 60 degrees and the anteversion angle 31 degrees.

no clear wear at the inner sleeve taper was found and stem wear analyses were not performed because the stem stayed in situ during the revision surgery. However, the large amount of titanium in fluid and tissue suggests wear at the taper-stem junction.

As shown above, the exact mechanisms for failure and pseudotumor formation are still not completely understood. Whether the failure is due to high cup inclination, edge loading, trunniosis, due to patient characteristics or a combination of all above, more wear analyses of revised bearings might help finding the answers. This study has several limitations. The clinical analyses as well as the wear analyses differs greatly. Furthermore, the gender ratio, age as well as the surgical technique varies within this small group. We also used two different stem types in our analysis. These sources may all bias the clinical and wear analysis and therefore limit the results of this study.

However, we can state all precautions should be taken for close monitoring and frequent control of MoM THA. Focussing on the clinical presentation can be misleading in decision making. Serum ion levels of cobalt, chromium (and titanium), radiographic control and MARS-MRI are all necessary for close monitoring. An example and flowchart for close monitoring and follow up is described earlier by our research group [16]. A better understanding of the process after implant placement in relation to clinical features, serum ion levels, pseudotumor formation and failure of the implant is necessary. Especially now we are facing the long term effects of the MoM THA's still in situ.

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PART 3

Significance of Serum Cobalt and Chromium in Metal-on-Metal Hip Arthroplasty

CHAPTER 5

Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports.

J.R.W. Crutsen[1,*], M.C. Koper[2,*]
J.Jelsma[3], M.Heymans[4], I.C. Heyligers[3,5], B. Grimm[6]
N.M.C. Mathijssen[2] and M.G.M. Schotanus[3, 7]

[1] Department of Orthopaedic Surgery
VieCuri Medical Center, Venlo, the Netherlands

[2] Department of Orthopaedic Surgery
Reinier HAGA Orthopaedic Center, Zoetermeer, the Netherlands

[3] Department of Orthopaedic Surgery and Traumatology
Zuyderland Medical Center, Sittard-Geleen-Heerlen, the Netherlands

[4] Zuyderland Academy, Centre of Knowledge and Information (KIC)
Zuyderland Medical Centre, Sittard-Geleen, the Netherlands

[5] School of Health Professions Education (SHE)
Maastricht University, Maastricht, the Netherlands

[6] Luxembourg Institute Health, Human Motion, Orthopaedics
Sports Medicine, Digital Methods (HOSD), Luxembourg, Luxembourg

[7] School of Care and Public Health Research Institute (CAPHRI)
Faculty of Health, Medicine and Life Sciences
Maastricht University, Maastricht, the Netherlands

*The first two authors contributed equally to this manuscript

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ABSTRACT

Background: Prosthetic hip-associated cobalt toxicity (PHACT) is caused by elevated blood cobalt concentrations after hip arthroplasty. The aim of this study is to determine which symptoms are reported most frequently and in what type of bearing. We also try to determine the blood level of cobalt concentrations associated with toxicological symptoms.

Materials and Methods: A systematic review was conducted on the 10th of July according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A methodological quality assessment (risk of bias (RoB)) was performed. Primary outcomes were the reported symptoms of cobalt toxicity and the level of cobalt concentrations in blood. These levels were associated with toxicological symptoms.

Results: A total of 7645 references were found of which 67 relevant reports describing 79 patients. The two most used bearings in which PHACT was described were metal-on-metal (MoM) bearings (38 cases) and revised (fractured) ceramic-on-ceramic (CoC) bearings where the former ceramic head was replaced by a metal head (32 cases). Of all reported symptoms, most were seen in the neurological system, of which 24% were in the sensory system and 19.3% were in central/peripheral system, followed by the cardiovascular (22.1%) system. The mean cobalt concentration for MoM-bearings was 123.7 ± 96.8 ppb and 1078.2 ± 1267.5 ppb for the revised fractured CoC-bearings.

Conclusions: We recommend not to use a metal-based articulation in the revision of a fractured CoC bearing and suggest close follow-up with yearly blood cobalt concentration controls in patients with a MoM bearing or a revised fractured CoC bearing.

Introduction

Exposure to metal ions after hip arthroplasty surgery is a widely reported phenomenon. Multiple studies have shown that an increase in metal ions can result in local soft tissue reactions described as an adverse reaction to metal debris (ARMD) [1, 2, 3, 4]. There is also an increasing number of case reports describing systemic reactions in relation to elevated blood cobalt concentrations known as prosthetic hip-associated cobalt toxicity (PHACT) [5, 6]. Increased cobalt concentrations are often seen after implantation of metal-on-metal (MoM) hip bearings [7]. This can be due to the release of ions from the metal (cobalt–chromium) surface either directly (corrosion) or during sliding under load, which may create wear particles (adhesion). Another source of significant metal particle release is the application of a metal component for the revision of a fractured ceramic head and/or a fractured ceramic acetabular liner. In this scenario, massive three- body abrasive wear can be created, as small remaining particles of the fractured ceramic bearing lead to abrasion of the metal surface [8, 9]. The systemic effects of cobalt toxicity are historically well documented from industrial exposure, iatrogenic use of oral cobalt chloride tablets and from the beer industry as a foam stabilizing agent [10, 11, 12]. The toxicity of cobalt is related to the unbound (free) form of cobalt (Co2+) and certain patient conditions. Unice et al. [13] stated that kidney failure, iron deficiencies, sepsis, malnutrition and use of certain medication increased the toxicity of cobalt at lower concentrations. The systemic complaints in patients with PHACT may lead to a variety of symptoms: neuro- ocular toxicity (e.g. tinnitus, vertigo, deafness, blindness, convulsions, headaches and peripheral neuropathy), cardiotoxicity and thyroid toxicity [14]. Nausea, anorexia and unexplained weight loss have also been described [6, 15, 16, 17]. Initially, there were concerns that high cobalt and chromium concentrations increased the risk of cancer; however, this was not proven in large comparative studies [18, 19].
It is still unknown which of these systemic symptoms are mostly reported in PHACT and at what blood cobalt concentration toxicity occurs. The present study is a systematic review of the current literature reporting systemic cobalt toxicity symptoms after any type of hip arthroplasty. The aim is to define and present the most reported systemic symptoms related to PHACT and to determine blood cobalt levels associated with toxicity.

Methods

The study protocol of this systematic review on case reports was registered in PROSPERO, the international prospective register of systematic review, with registration number: CRD42020215827.

Criteria for considering studies for this review

Types of studies and participants

Case reports concerning cobalt toxicity after hip arthroplasty were included. Patients with any type of bearing (MoM, CoC, metal-on-polyethylene (MoP) and ceramic-on-polyethylene (CoP)) and any type of hip arthroplasty design (hip resurfacing arthroplasty (HRA), short stem hip arthroplasty, and 'conventional' stemmed total hip arthroplasty, both uncemented and cemented) were included. Articles describing allergic reactions on hip prosthesis and/or cobalt and articles reporting only local problems around the hip such as adverse local tissue reactions (ALTR), ARMD and aseptic lymphocytic vasculitis- associated lesion (ALVAL) were excluded.

Types of interventions

The description of intervention was not necessary for inclusion, as patients may have died from cobalt toxicity before intervention could be initiated. In some cases, a revision arthroplasty or chelation therapy was the intervention of choice of the attending physicians.

Types of outcome measures

Primary outcomes were the reported symptoms of cobalt toxicity and the blood cobalt concentration at which these symptoms were seen. All reported symptoms were counted and divided into nine different categories based on the physiological system related to the occurrence of the symptoms. We followed the categories used in the study of Devlin et al., with some minor adjustments [6]. Cobalt concentrations in blood were reported in nmol/L, µg/L and parts per billion (ppb). Cobalt concentrations in nmol/L were converted to ppb where 1 nmol/L = 0.059 ppb.

Search methods for identification of studies

The search was performed on July 10, 2020, in PubMed, EMBASE, Cochrane Library/Wiley, CINAHL (EBSCO), Web of Science (Clarivate Analytics) and Trial registers (PROSPERO by one author (JJ). The following (MeSH) search terms were used: 'Hip Prosthesis', 'Arthroplasty', 'Replacement', 'Hip and Cobalt'. The full search strategy and terms can be found in Supplementary data 3 (see section on supplementary materials given at the end of this article). Articles published in Dutch, English, German or Spanish were included. There were no further restrictions for publication type or date. Reference lists of included articles were screened for missing items. In addition, also posters presented at congresses and published abstracts were included. Duplicates were identified by one author (JJ) in RefWorks. All records were independently screened on the title and abstract by two authors (JJ, MGMS) and disagreement was resolved by mutual discussion. Full- text articles were assessed for eligibility by two authors (JRWC, MCK), differences were resolved in a consensus meeting and if necessary, through discussion with another author (JJ).

Data collection and analysis

Data were extracted and stored in a Microsoft Excel 2019 file (Microsoft). The following data of the included studies were extracted: study ID (author, year of online publication), number of patients (n), patient characteristics at onset of symptoms (age in years, sex), primary intervention and indication for the primary procedure, secondary intervention and indication (if applicable), follow-up (in months) since surgery, cobalt ion concentration in any type of amount (e.g. nmol/L, µg/L, ppb) when symptoms were seen, symptoms reported and outcome after treatment, regardless of the type of treatment. All results are presented as total (percentage) or as mean (s.d.).

Quality assessment

The risk of bias (RoB) tool of the Cochrane Handbook for Systematic Reviews of Interventions was used and the Newcastle–Ottawa Scale (NOS) was chosen to assess the quality of the articles [20, 21, 22]. This checklist was used to determine quality of non-randomized studies, including case-controlled and cohort studies, in three areas: selection, comparability and the ascertainment of either the exposure or outcome of interest. An assessment scale was available to award stars

with a maximum score of 9: 1 for each question in the selection and outcome scale and 2 for the comparability domain (Supplementary data 1) [21]. The follow-up as described in question 6 was determined to be at least 3 months in agreement with all authors. A score of less than 5 stars represents a high RoB [23].

In addition, a checklist suggested by Murad et al. was also used to obtain RoB [24]. This checklist is especially designed for case reports and exists of an eight-item tool categorized in four domains: selection, ascertainment, causality and reporting. It is a modification of the tools by Pierson, Bradford Hills and the NOS (Supplementary data 2) [24]. The eight items of the tool were scored yes or no. Like the NOS, the adequate follow-up was determined to be 3 months. Questions 5 and 6 of the questionnaire were not taken into account since they were mostly relevant to cases of adverse drug events. Quality of the articles was defined 'good' when 'yes' was scored ≥4 times, 3–2 times 'yes' was defined 'moderate' and ≤1 time 'yes' as 'poor'. All eligible case reports were included in the review irrespective of their methodological quality.

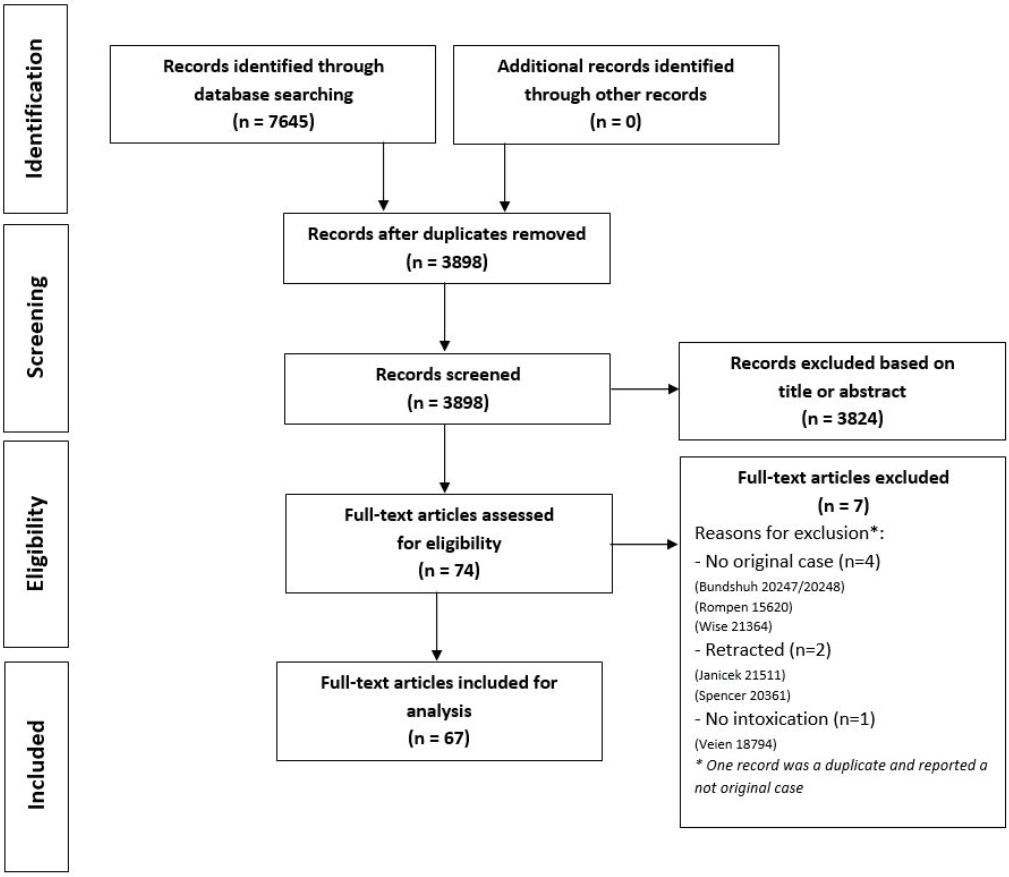

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart.

Results

Our search identified 7645 references of which 3898 were screened after removal of duplicates (Supplementary data 3). A total of 3824 were excluded based on title or abstract, resulting in 74 eligible articles. Of these, a total of 67 were included for analysis after excluding another 7 studies, due to no original case description, retraction and no described toxicity (Fig. 1). The RoB classification according to the NOS checklist resulted in a 98.5% (n = 66) of low RoB and 1.5% (n = 1) of high-risk bias of the case reports (see Supplementary data 4). According to the checklist of Murad et al., 76.1% (n = 51) of the studies were classified as having good methodological quality. A full review of the Murad checklist is found in Supplementary data 5. We identified a total of 79 patients with reported PHACT. Table 1 presents the most important data of all articles and methodological quality assessment score. The full overview is shown in Supplementary data 6. A total of 46 (58.2%) patients were male and 27 (34.2%) were female. Sex was not mentioned in six patients. The mean age at primary surgery was 53.2 ± 14.2 years. The main known reason for primary surgery was osteoarthritis (n = 28; 35.4%); however, in most reports, the primary indication was unknown (n = 36; 45.6%). Table 2 presents the demographic data of the entire group.

Table 1: Most important details of the reviewed articles and quality assessment score results. For a complete overview see appendix 2.

Reference	Patients, n	Major Reported Systemic Symptoms (classified)	Cobalt in ppb (sample)	Primary intervention	Secondary intervention	Indication revision	Quality score	
							NOS	Murad
Allen et al. [32]	1	Cardiovascular	287.6 (S)	MoM	CoP	Systemic symptoms	Low	Good
Apel et al. [33]	1	Neurological (Sensory and C/P) Cardiovascular	355 (S)	CoC	MoC	Fracture CoC implant	Low	Good
Austin et al. [34]	1	Neurological (Sensory) Cardiovascular	1351.4 (WB)	-	-	Systemic symptoms	Low	Good
Balbouzis et al.[35]	1	Cardiovascular	22.2 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Bartholomeu et al. [36]	1	Neurological (Sensory)	-	-	-	Systemic symptoms	Low	Good
Biglia et al.[37]	1	Metal/Psychosocial	14 (WB)	CoC	MoM	Fracture CoC implant	Low	Good
Bonilla & Bhimaray [38]	1	Cardiovascular (shock)	100 (WB)		-	Systemic symptoms	Low	Good
Briani et al.[39]	1	Neurological (C/P)	14.3 (WB)	CoC	-	Systemic symptoms	Low	Good
Charette et al. [40]	1	Cardiovascular	156 (S)	MoM bilateral	CoP	Systemic symptoms	Low	Good
Choi et al. [41]	2	Cardiovascular Neurological (Sensory)	489.5 (S)	CoP	MoP	Fracture CoC implant	Low	Good
		Cardiovascular	111.9 (S)	CoC bilateral	CoM	Fracture CoC implant		
Citak et al. [42]	1	Cardiovascular Neurological (Sensory)	-	CoC	MoP	Fracture CoC implant	Low	Poor
Czekaj et al. [43]	1	Neurological (Sensory and C/P)	206 (WB)	MoM	CoP	Systemic symptoms	Low	Good
Dahms et al. [44]	1	Neurological (Sensory) Cardiovascular	885 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Davies & Chareonthaitawee [45]	1	Neurological (Sensory) Cardiovascular	953 (S)	CoC	MoP	Fracture CoC implant	Low	Poor
Dolliana & Nüesch [46]	1	Neurological (Sensory) Gastroenterology	819.2 (WB)	CoC	MoM	Fracture CoC implant	Low	Moderate
Enseleit et al. [47]	1	Neurological (Sensory) Cardiovascular	-	Bilateral	-	Systemic symptoms	Low	Poor
Sánchez & Cardona [48]	1	Neurological (Sensory and C/P) Cardiovascular	1036 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Fox [29]	1	Neurological (Sensory and C/P) Cardiovascular	817 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Garcia et al. [49]	1	Neurological (Sensory and C/P) Cardiovascular	1000 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Gautam et al. [50]	1	Cardiovascular	373 (S)	CoC	MoP	Fracture CoC implant	Low	Good

Giampreti et al. [51]	1	Neurological (C/P)	352.6 (S)	MoM	CoP	Hip pain	Low	Moderate
Giampreti et al. [52]	4	Neurological (Sensory and C/P) Cardiovascular	50 (WB)	MoM	-	Systemic symptoms	Low	Moderate
			352.6 (WB)	MoM	-	Systemic symptoms		
			201.3 (WB)	MoM	-	Systemic symptoms		
			201.3 (WB)	MoM	-	Systemic symptoms		
Gilbert et al. [53]	1	Cardiovascular	1085 (S)	CoC bilateral	MoP	Fracture CoC implant	Low	Good
Goel & Hoskote [54]	1	Cardiovascular (shock)	25 (S)	MoM bilateral		Systemic symptoms	Low	Moderate
Grant et al. [55]	1	Neurological (Sensory and C/P)	2148(P)	CoC	MoM	Fracture CoC implant	Low	Good
Griffiths et al. [56]	1	Neurological (Sensory and C/P) Cardiovascular	2006 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Grillo et al. [57]	1	Neurological (Sensory) Cardiovascular	107.8 (S)	CoC	MoM	Fracture CoC implant	Low	Good
Grosso et al. [58]	1	Neurological (Sensory)	1076 (WB)	CoC	MoM	Fracture CoC implant	Low	Poor
Guevara et al. [59]	1	Neurological (Sensory) Cardiovascular	-	-	-	Systemic symptoms	Low	Poor
Harris et al. [60]	1	Neurological (Sensory and C/P) Cardiovascular	788.1 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Ho et al. [61]	1	Neurological (Sensory and C/P) Cardiovascular	799 (S)	CoC	-	Systemic symptoms	Low	Moderate
Ikeda et al. [62]	1	Neurological (C/P)	400 (WB)	CoC bilateral	MoP	Fracture CoC implant	Low	Good
Jones et al. [25]	7	Not classified		McKee hip	Girdlestone	Recurrent dislocations	Low	Good
		Not classified		McKee hip	MoP	Possible fracture		
		Not classified		McKee hip	MoP	Persistent pain		
		Skin/hair		McKee hip bilateral	Girdlestone	Protrusion acetabulum		
		Not classified		McKee hip	None described	Hip pain		
		Not classified		McKee hip	Recemented prosthesis	-		
		Not classified		McKee hip	MoP	Recurrent dislocations		
Kao & Bunning [63]	1	Neurological (C/P)	20 (WB)	Bilateral MoP	-	Systemic symptoms	Low	Moderate
Kim et al. [64]	1	Neurological (Sensory and C/P) Cardiovascular	397.8 (WB)	CoP bilateral	MoP	Fracture CoP implant	Low	Good
Lapena Motilva et al. [65]	1	Neurological (Sensory and C/P)	892.8 (WB)	-	-	Systemic symptoms	Low	Good
Lecoanet et al. [66]	1	Neurological (Sensory and C/P) Cardiovascular	1463.7 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Leikin et al. [67]	1	Neurological (Sensory and C/P)	1096.5 (S)	CoC	MoM	Fracture CoC implant	Low	Poor
Machado et al. [68]	1	Cardiovascular	13.6 (P)	MoM	-	Systemic symptoms	Low	Poor

Mao et al. [69]	2	Neurological (Sensory and C/P)	24.2 (S)	MoM	CoP	Systemic symptoms	Low	Good
		Neurological (Sensory and C/P)	15.2 (S)	MoM	CoP	Systemic symptoms		
Marcus & Woodkotch [70]	1	Neurological (Sensory and C/P)	-	MoM	MoP	Systemic symptoms	Low	Moderate
Martin et al. [71]	1	Cardiovascular	192 (S)	MoM bilateral	Bilateral CoP	Systemic symptoms	Low	Good
Moniz et al. [72]	1	Cardiovascular	169 (S)	MoM	CoP	Systemic symptoms	Low	Good
Mosier et al. [73]	1	Cardiovascular	189 (S)	MoM bilateral	Dual Mobility CoP	Systemic symptoms	Low	Good
Ng et al. [74]	1	Neurological (Sensory and C/P)	44.7 (S)	MoM bilateral	-	Systemic symptoms	Low	Good
Nogar & Bells[75]	1	Neurological (C/P) Cardiovascular	208 (S)	MoM	-	Systemic symptoms	Low	Good
Oldenburg et al. [26]	1	Neurological (Sensory and C/P) Cardiovascular	625 (S)	CoP	MoP	Fracture CoP implant	Low	Good
Payen et al. [76]	1	Cardiovascular (shock)	267.2 (WB)	MoM bilateral	-	Systemic symptoms	Low	Good
Pelayo-de Tomas et al. [77]	1	Neurological (Sensory and C/P) Cardiovascular	651.2 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Pelclova et al. [78]	1	Neurological (Sensory and C/P)	506 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Peters et al. [79]	1	Neurological (Sensory and C/P)	596.5 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Reich et al. [80]	1	Neurological (C/P)	10.1 (S)	Revision MoM	2nd revision MoP	Acetabular osteolysis	Low	Good
Reid et al. [81]	1	Cardiovascular	-	MoM	Unstable	Systemic symptoms	Low	Good
Rizzetti et al. [27]	1	Neurological (Sensory and C/P)	549 (WB)	CoC	MoP	Fracture CoC implant	Low	Good
Sanches Dalmau et al. [82]	1	Neurological (Sensory and C/P)	259 (P)	MoP bilateral	Chelationtherapy	Systemic symptoms	High	Poor
Sanz Perez et al. [83]	1	Cardiovascular (shock)	652 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Shapiro et al. [84]	1	Neurological (C/P)	39 (S)	MoM	CoP	Systemic symptoms	Low	Good
Sotos et al. [85]	1	Neurological (Sensory and C/P)	122 (S)	MoM	CoP	Systemic symptoms	Low	Good
Steens et al. [28]	1	Neurological (Sensory and C/P)	-	CoC	CoM	Chronic pain	Low	Good
Tilney et al. [86]	1	Cardiovascular	246.3(WB)	MoM	-	Systemic symptoms	Low	Good
Tower [87]	1	Neurological (Sensory and C/P)	74 (S)	MoM	-	Systemic symptoms	Low	Poor
Tower [88]	2	Neurological (Sensory and C/P) Cardiovascular	122 (S)	MoM	-	Systemic symptoms	Low	Good
			23 (S)	MoM	-	Systemic symptoms		
Vasukutty et al. [89]	1	Cardiovascular	44.9 (S)	CoC	MoP	Fracture CoC implant	Low	Good
Woelber et al. [90]	1	Neurological (Sensory and C/P)	116 (S)	MoM bilateral	BilateralCoP	Systemic symptoms	Low	Good
Wong & Nixon [91]	1	Skin/hair	57.1 (S)	MoM	ToP	Systemic symptoms	Low	Good
Zeynalov et al. [92]	1	Metal/Psychosocial	1.6 (S)	MoM	CoM	Systemic symptoms	Low	Good
Zywiel et al. [93]	1	Cardiovascular	6521 (WB)	CoC	MoP	Fracture CoC implant	Low	Good

Abbreviations: No = number, C/P = central and peripheral, ppb = parts per billion, S = serum, WB = whole blood, P = plasma, NOS = Newcastle-Ottawa Scale, MoM = Metal-on-Metal, CoC = Ceramic-on-Ceramic, CoP = Ceramic-on-Polyethylene, MoP = Metal-on-Polyethylene, ToP = Titanium-on- Polyethylene

Table 2. Demographics of all patients (n=79)

Demographics	Values
Primary surgery	
Mean age at primary surgery*	53.2 (14.2)
Indications for primary surgery±	
Primary osteoarthritis	28 (35.4)
Avascular necrosis	9 (11.4)
Fracture	3 (3.8)
Dysplasia	2 (2.5)
Hip pain	1 (1.3)
Unknown	36 (45.6)
Male/Female±	46/27 (58.2/34.2)
Primary bearing±	
MoM	38 (48)
CoC	32 (40.5)
MoP	2 (2.5)
CoP	2 (2.5)
Unknown	5 (6.5)
Revision surgery	
Mean age at revision surgery*	58.6 (11.1)
Indication for revision surgery±	
Systemic symptoms	38 (48.1)
Fracture CoC	31 (39.2)
(chronic) Pain	4 (5.1)
Recurrent dislocations	2 (2.5)
Protrusion acetabulum	1 (1.3)
Fracture	1 (1.3)
Osteolysis	1 (1.3)
Unknown	1 (1.3)
Male/Female±	26/15 (63.4/36.6)
Cobalt toxicity	
Mean age at onset of symptoms*	59.0 (11.5)
Primary PHACT complaints±	38 (48)
Revision PHACT complaints±	41 (52)
Mean cobalt toxicitylevel in ppb*	572 (962.1)
Mean follow up time in months*	12.7 (14.2)

Abbreviations: SD = standard deviation, MoM = Metal-on-Metal, CoC = Ceramic-on-Ceramic, MoP = Metal-on-Polyethylene, CoP = Ceramic-on- Polyethylene, PHACT = Prosthetic Hip Associated Cobalt Toxicity, ppb = parts per billion.
*mean (SD)
± n (%)

PHACT related to type of bearing

The two most used bearings in the primary surgery were MoM (n = 38; 48.0%) and CoC (n = 32; 40.5%). Also, MoP (n = 2; 2.5%) and CoP (n = 2; 2.5%) were reported; in five cases (6.5%), no primary bearing was reported.

In 38 (48.0%) patients, the PHACT symptoms occurred after primary surgery; of which, in 34 (89.5%) after a primary MoM bearing. The mean time between the primary surgery and onset of symptoms was 2.1 (range: 0–13) years. A total of 41 (52.0%) patients developed PHACT symptoms after they had revision surgery. Especially, revision of a (fractured) CoC bearing for a MoP (n = 21) or MoM bearing (n = 6) caused the onset of cobalt toxicity symptoms. In this group, the mean time of developing PHACT was 8.8 (range: 4–15) years after the primary surgery and 2.4 (range: 0–9) years after the revision surgery (Table 3).

Table 3. Demographics of all bearings (n= 79)

	Primary Bearing		
Demographics	MoM (n= 38)	CoC (n= 32)	Others (9)#
Primary surgery			
Mean age at primary surgery in years*	56.2 (14.9)	50.5 (13.1)	54.4 (19.9)
Indications for primary surgery±			
Primary osteoarthritis	16 (42.1)	11 (34.4)	3 (33.3)
Avascular necrosis	2 (5.3)	4 (12.5)	1 (11.1)
Fracture	3 (7.9)	1 (3.1)	0 (0)
Dysplasia	2 (5.3)	0 (0)	0 (0)
Hip pain	0 (0)	1 (3.1)	0 (0)
Unknown	15 (39.5)	15 (46.9)	5 (55.6)
Male/Female±	20/13 (52.6/34.2)	20/12 (62.5/37.5)	6/2 (66.7/22.2)
Primary PHACT complaints±	34 (89.5)	1 (3.1)	3 (33.3)
Revision PHACT complaints±	4 (10.5)	31 (96.9)	6 (66.7)
Cobalt toxicity level in ppb±	123.7 (96.8)	1,078.2 (1,267.5)	379.4 (369.3)
Mean age at onset of symptoms in years*	58.3 (12.9)	59.3 (10.9)	58.5 (11.5)
Mean time in years at onset of symptoms after primary surgery*	2.1 (0-13)	8.8 (4-15)	4.1 (2-12)
Revision surgery			
Mean age at revision surgery in years*	60.7 (11.2)	56.9 (11.4)	58.5 (8.8)
Indication for revision surgery±			
Systemic symptoms	29 (76.3)	1 (3.1)	2 (22.2)
Fracture CoC	0 (0)	29(90.6)	2 (22.2)
(chronic) Pain	3 (7.9)	1 (3.1)	0 (0)
Recurrent dislocations	2 (5.3)	0 (0)	0 (0)
Protrusion acetabulum	1 (2.6)	0 (0)	0 (0)
Fracture	1 (2.6)	0 (0)	0 (0)
Osteolysis	1 (2.6)	0 (0)	0 (0)
Unknown	1 (2.6)	1 (3.1)	5 (55.6)
Bearing after revision±			
MoM	0 (0)	6 (18.8)	0 (0)
CoC	0 (0)	0 (0)	0 (0)
MoP	5 (13.2)	21 (65.6)	2 (22.2)
CoP	12 (31.6)	0 (0)	0 (0)
ToP	1 (2.6)	0 (0)	0 (0)
CoM / MoC	1 (2.6)	3 (9.4)	0 (0)
Girdlestone	2 (5.3)	0 (0)	0 (0)
Not suitable	16 (42.1)	0 (0)	0 (0)
Unknown	1 (2.6)	2 (6.25)	6 (66.7)
Mean follow up time in months*	13 (12.2)	11 (13.5)	15 (25.3)

Abbreviations: SD = standard deviation, MoM = Metal-on-Metal, CoC = Ceramic-on-Ceramic, MoP = Metal-on-Polyethylene, CoP = Ceramic-on- Polyethylene, PHACT = Prosthetic Hip Associated Cobalt Toxicity, ppb = parts per billion, ToP = Titanium-on-Polyethylene, CoM = Ceramic-on-Metal, MoC = Metal-on-Ceramic.
(MoP (n= 2), CoP, (n= 2), unknown (n= 5)
*mean (SD / range)
± n (%)

PHACT related systemic symptoms

A total of 321 symptoms were scored and divided into nine different categories: neurological, cardiovascular, gastroenterology, musculoskeletal, skin/hair, thyroid, mental/psychosocial and others. The neurological symptoms were subcategorized in central/peripheral and sensory. Some patients had more than one reported symptom during the first presentation. All documented symptoms were considered and scored as possible PHACT. Table 4 shows all the different symptoms in the nine different categories. The most identified symptoms were neurological related. Since most symptoms were especially related to the sensory system, we divided them into sensory system (n = 77; 24.0%) and central/peripheral-related symptoms (n = 62; 19.3%) .

Hearing impairment/loss and visual impairment/retinal dysfunction were the most mentioned problems in the sensory system, with a total of 34 (44.2%) and 25 (32.5%), respectively. Within the 79 described patients, hearing impairment/loss encounters for a total of 43.0% and visual impairment/retinal dysfunction for 31.6%. In the central/ peripheral group, the most described symptoms were cognitive, memory, or concentration problems (n = 16; 12.6%) and paresthesia/ anesthesia (n = 13; 16.5%).

The second most reported complaints were grouped in the cardiovascular origin. We found 71 suspected cobalt-induced cardiovascular complaints after primary and/or revision hip surgery. The described cardiovascular symptoms divers from dyspnea (n = 25; 31.6%), cardiomyopathy (n = 12; 15.2%), heart failure (n = 10; 12.7%) to cardiogenic shock (n = 4; 5.1%) (Table 3).

Another systemic problem, often related to cobalt toxicity, is hypothyroidism or thyroid dysfunction. We found nine patients (11.4%) with proven thyroid abnormalities. A total of 17 (21.5%) patients described fatigue and nine had thyroid dysfunction. Of these nine patients, only three patients had also proven thyroid dysfunction, whereas in all other patients, the cause of fatigue had not been investigated or described.

A total of 32 (40.5%) patients were recorded with hip pain as one of the symptoms. Despite this being no systemic complaint, we felt obligated to describe this symptom as it is most likely related to the (early) failure of the hip prosthesis. In all patients who received treatment for the symptoms, by either removing the prosthesis or by medication, the symptoms reduced considerably.

Table 4. All Systemic symptoms (n = 321; 100.0%) reported in 79 patients

Symptoms	Patients (n, (%))
Neurological	
Central and Peripheral	62 (19.3)
Cognitive/memory/concentration	16 (20.3)
Paraesthesia/Anesthesia	13 (16.5)
(Poly)Neuropathy	8 (10.1)
Proprioception loss / difficulty walking	7 (8.9)
Headache	4 (5.1)
Hyposthenia / Asthenia	3 (3.8)
Spasm / Musclecramps	3 (3.8)
Lower motor neuron syndromes	2 (2.5)
Axonopathy	1 (1.3)
Bulbarpalsy	1 (1.3)
Convulsions	1 (1.3)
Neuropaticpain	1 (1.3)
Parkinson	1 (1.3)
Tremors	1 (1.3)
Sensory#	77 (24.0)
Hearing impairment / loss	34 (43.0)
Visualimpairment / Retina ldysfunction	25 (31.6)
Dysgeusia / Metallic taste	9 (11.4)
Tinnitus	5 (6.3)
Vertigo	2 (2.5)
Loss of smell / Anosmia	1 (1.3)
Opticnervearthrophy	1 (1.3)
Cardiovasculair	71 (22.1)
Dyspnoe/Apnoe/Orthopnea	25 (31.6)
(Peri)Cardiomyopathie	12 (15.2)
Heart failure	10 (12.7)
Tachycardia	5 (6.3)
Cardiogenic shock	4 (5.1)
Exertionalchest tightness /pain	4 (5.1)
Oedema	4 (5.1)
Pericarditis	2 (2.5)
Hypertension	2 (2.5)
Syncope	2 (2.5)
Pericardialeffusion	1 (1.3)
Gastroenterology	12 (3.7)
Diarrhea	3 (3.8)
Nausea	3 (3.8)
Vomiting	3 (3.8)
Anorexia	2 (2.5)
Liver failure	1 (1.3)
Musculoskeletal	37 (11.5)
Arthromyalgia	1 (1.3)

Decreasedmusclemass	1 (1.3)
Polyarthralgia	1 (1.3)
Polymyalgia	1 (1.3)
General stiffness	1 (1.3)
Skin / Hair	8(2.5)
Rash/dermatitis/sarcoid-like	6 (7.6)
Diaphoresis	1 (1.3)
Hair loss	1 (1.3)
Thyroid	9 (2.8)
Hypothyroidism/Thyroiddysfunction	9 (11.4)
Mental / Pschosocial	25 (7.8)
Fatigue	17 (21.5)
Depression	4 (5.1)
Anxious	2 (2.5)
Insomnia	2 (2.5)
Other	20 (6.2)
Weight loss	7 (8.9)
Weakness	4 (5.1)
Fever	2 (2.5)
Malaise	2 (2.5)
Polydipsia	2 (2.5)
Multi-organ failure	1 (1.3)
Polycythemia	1 (1.3)
Uncontrolled diabetes	1 (1.3)

visual, and vestibular, auditory, gustatory olfactory, somatosensory

PHACT and blood cobalt concentrations

The mean cobalt concentration in blood at which the systemic symptoms were related was 572.0 ± 962.2 ppb for the total group. However, these concentrations differ greatly between the different bearings. The mean cobalt toxicity level for specific MoM, revised CoC, and other bearings were respectively 123.7 ± 96.8, 1078.2 ± 1267.5 and 379.4 ± 369.3 ppb. Table 5 described the mean cobalt concentration between the MoM and revised CoC bearings and three major systemic symptoms: neurological, central/peripheral and sensory and cardiovascular. There was no noticeable difference between the cobalt toxicity concentrations and the developed symptoms in the two bearings. After revision of the MoM bearing or a second revision of the earlier fractured CoC bearing, cobalt concentrations decreased in almost all reported patients.

Table 5. The total number of the three most presented systemic symptoms in relation with the cobalt toxicity level in the two most reported bearings (MoM and CoC).

	Bearing-type and Cobalt Level			
Major Systemic Symptoms	MoM, n	Cobalt*	CoC, n	Cobalt*
Neurological C/P	17	127.2 (110.9)	16	889.1 (574.9)
Neurological Sensory	13	119.4 (98.7)	19	1000.1 (517.9)
Cardiovascular	16	169.0 (100.2)	19	778.4 (504.4)

Abbreviations: SD = standard deviation, MoM = Metal-on-Metal, CoC = Ceramic-on-Ceramic, C/P = central and peripheral, ppb = parts per billion. * mean ppb (SD)

Discussion

The present review shows that PHACT is mostly seen in primary MoM and after revision of a (fractured) CoC bearings for an MoP or MoM articulation. PHACT is a relevant and serious complication with severe systemic symptoms in the neurological, cardiovascular and thyroid system.

It was only after the recall of several MoM prostheses in 2010 that PHACT was increasingly associated with this type of bearing [6, 15]. Before that, only Jones et al. described several cases with cobalt-induced systemic issues in the McKee hip (first generation MoM). In this case series (seven cases), the most frequently mentioned symptom was hip pain and there was increased concentrations of cobalt ions in urine and joint fluid [25]. Three other reports before 2010 by Oldenburg et al., Rizzetti et al. and Steens et al. showed cobalt-related problems in revised ceramic bearings [26, 27, 28].

In primary MoM implants, the bearing surfaces can release metal particles through corrosion and adhesion (induced by wear). After revision of a (fractured) CoC bearing to a metal containing articulation (e.g. MoP or MoM), potentially remaining small ceramic particles in the soft tissue and joint space can cause massive abrasion on the metal surface through three-body wear. All mechanisms of particle release may contribute not only to local adverse reactions but also to potential systemic cobalt toxicity [8, 9, 29].

Limitations

There are some limitations that should be mentioned. Since there are no comparative studies, the present review consists mainly of case reports. Therefore, a publication bias is not ruled out and case reports are considered low- quality research. To minimize these limitations, we have assessed the articles on quality by two different methods as guidance for a systematic review methodology publication. As suggested by the Cochrane Handbook, we used the NOS to determine the RoB and assess the quality [22]. Since this questionnaire is not entirely consistent with the assessment of case reports, we also used the checklist suggested by Murad et al. [24]. A second major limitation is the lack of controlled comparison studies, no clear reported patient histories and a wide range of blood cobalt ion concentrations. Because of that, a direct relationship between the presented symptoms and elevated cobalt concentrations cannot be proven. Some of the reported symptoms can also occur independent of cobalt toxicity and might relate to common health issues or are associated with age. However, we were able to describe and present as adequately as possible the most reported symptoms associated with cobalt toxicity and high probability.

PHACT related to type of bearing

The present review showed PHACT in 38 patients with an MoM bearing; of which, 34 (89.5%) were detected within 2.1 (range: 0–13) years after the primary surgery. This is in contrast with the 32 described revised CoC bearings. In these bearings, only 1 (3.1%) patient had PHACT related complications after primary surgery, whereas 31 (96.9%) patients experienced PHACT within 2.4 (range: 0–9) years after revision surgery. In 29 (93.5%) of these revision cases, the indication was a fractured CoC-bearing plus, all the bearings used in the revision surgery contained at least one metal component (Table 3).

PHACT-related systemic symptoms

The three most affected systems in patients with cobalt toxicity are in the sensory, neurological and cardiovascular systems. The neurotoxic effects of cobalt have already been well established in multiple animal studies [12, 27, 30]. In addition, some case series describe the neurotoxicity in patients after the treatment with cobalt for anaemia. Not only tinnitus and deafness but also paraesthesia and ataxia seem to be associated with the use of cobalt [12].

All reviewed reports presume a direct relationship with increased blood cobalt concentrations. Within the sensory system, a total of 77 symptoms were described; of which, the most involved were hearing (n = 34; 44.2%) and visual impairment/loss. Most of these symptoms diminished after revision of the prosthesis and a decrease in blood cobalt concentrations was seen. The neurological problems contain mainly cognitive, memory and concentration dysfunction (n = 16; 25.8%), as well as paraesthesia/anaesthesia (n = 13; 21.0%). Patients with these symptoms also improved after explanting or revision of the hip prosthesis.

The second most reposted complaints were grouped in the cardiovascular origin (n = 71; 22.1%). Of these, dyspnoea/apnoea/orthopnoea (n = 25; 31.6%), cardiomyopathy (n = 12; 15.2%), heart failure (n = 10; 12.7%) and cardiogenic shock (n = 4; 5.6%) were most described. The four patients with a cardiogenic shock showed cobalt concentrations from 25 to 652 ppb; however, a clear dose–response effect of the cobalt in these cases could not be established. Of these four patients, one died due to the cardiogenic shock, one needed heart transplantation and two others clinically recovered after explanting the hip prosthesis.

Thyroid dysfunction in relation to cobalt toxicity is also well described in the literature [31] and proven in nine reported patients (11.4%). Another symptom, often mentioned in relation to thyroid dysfunction, is fatigue. A total of 17 patients reported fatigue; of which, only 3 had proven thyroid dysfunction. In all other cases, there was no thyroid dysfunction described. If we combine the 2 different groups, a total of 23 patients (29.11%) may have cobalt-related thyroid issues. This will make the thyroid dysfunction a third major affected systemic system; however, we could not prove this.

PHACT and blood cobalt concentrations

Most published reports provide a toxicity level of cobalt concentration in their cases; however, this concentration divers between all patients and different bearings. The cobalt levels associated with systemic toxicity were considerably higher in patients with revised CoC bearings when compared to patients with a primary MoM bearing (mean of 1078.2 and 123.7 ppb, respectively see Table 5). Our assumption is that corrosion- and adhesion-related metal exposition in MoM bearings is more gradual and slower than the massive release of cobalt-containing metal wear through three-body-related abrasion in fractured CoC bearings, which have been revised with metal-containing components. Another possible explanation is the awareness of local and systemic problems of the metal ions in MoM bearings. As a result, clinicians are more likely to link sudden or unexplained systemic issues to the hip prosthesis.

Unfortunately, we found no controlled studies to definitively link the systemic clinical findings with the elevated blood cobalt concentrations and we were unable to determine a safe upper limit threshold for cobalt toxicity.

Conclusion

Since many MoM bearings are still in situ, we can expect more PHACT cases. This systematic review showed that wide blood cobalt concentrations are observed in the onset of systemic symptoms linked to serum cobalt levels. It was not possible to provide a clear threshold level for cobalt-related toxicity from this analysis.

Nevertheless, clinicians should be aware that patients with an MoM or revised CoC bearing are at risk for developing systemic problems. Especially, new-onset systemic diseases related to neurological, both central/peripheral and sensory, and cardiovascular-related symptoms could be provoked by elevated cobalt concentrations. We also recommend not to use a metal-based articulation in the revision of a fractured ceramic bearing and suggest keeping a close follow-up with yearly blood cobalt concentration controls in patients with an MoM or revised fractured CoC bearing.

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CHAPTER 6

Safe Upper Limits of Serum Cobalt and Chromium Levels for the M2a-Magnum Metal-on-Metal Total Hip Bearing: A 10-Year Follow-Up Study.

M.C. Koper[1], Brechtje Hesseling[1], Wim E. Tuinebreijer[2]
Hans van der Linden[1], Nina M.C. Mathijssen[1]

[1] Department of Orthopedics, Reinier de Graaf Hospital, Delft, The Netherlands

[2] Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

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ABSTRACT

Background: Long-term survival of metal-on-metal (MoM) prostheses and the development of adverse reaction to metal debris (ARMD) around these bearings are still unclear. Serum levels of cobalt (Co) and chromium (Cr) are used as a screening tool to anticipate failure in MoM bearings and detect ARMD.

Materials and Methods: One hundred sixty primary large head MoM prostheses were followed up for 10 years. To estimate the revision risk, the cumulative incidence function (CIF) was used. Subdistribution hazard modeling was used to investigate the associations between cumulative incidence of revision for ARMD and Co levels, Cr levels, gender, age, head size, and cup inclination. Furthermore, the safe upper limits (SULs) for Co and Cr were determined.

Results: Univariate analyses showed an increased risk in revision for ARMD in females (subdistribution hazard ratio [sdHR] 3.43, 95% confidence interval [CI] 1.01-11.7, P = .049) and cup inclination angles over 45 (sdHR 4.70, 95% CI 1.63-13.58, P = .004). In addition, a higher last measured Co level (sdHR 1.05, 95% CI 1.03-1.07, P < .001) and last measured Cr level (sdHR 1.21, 95% CI 1.14-1.29, P < .001) were associated with a higher probability of revision for ARMD. We determined our bearing-specific SULs at 4.1 parts per billion (ppb) and 4.2 ppb for Co and Cr, respectively.

Conclusions: Guidelines regarding follow-up and surveillance should include a complete clinical assessment with bearing-specific SULs of serum metal ion levels. For the M2a-Magnum MoM bearing we advise an SUL for Co and Cr levels of 4.1 and 4.2 ppb, respectively.

Introduction

Patients with metal-on-metal (MoM) hip bearings are at high risk for early and late failure [1-3]. Due to the high revision rates and concerns of adverse reaction to metal debris (ARMD) there is a significant decline in use of MoM hip resurfacing arthroplasties and a prohibition in most countries for large head MoM total hip arthroplasties [4-7]. Because a large number of these bearings are still in situ, a frequent clinical surveillance is recommended to detect a possible ARMD or early failure.
ARMD represents an MoM specific mode of failure and includes a spectrum of different findings, such as metallosis, necrosis, osteolysis, and periprosthetic pseudotumors [2,8-10]. According to literature, symptomatic MoM bearings have higher serum metal ion levels and are more associated with failure and revision compared to asymptomatic bearings [11,12]. Within this group, ARMD is the most frequent cause of revision surgery in the large head total hip MoM bearings [13].
The prevalence of ARMD varies between the different MoM bearings and different manufacturers. Guidelines in most countries recommend a yearly outpatient control with physical examination and serum metal ion levels as a screening tool to predict a possible ARMD. However, there is no global consensus of the best follow-up protocol and no clear consensus over which safe upper limits (SULs) still in situ, a frequent clinical surveillance is recommended to detect a possible ARMD or early failure. ARMD represents an MoM specific mode of failure and includes a spectrum of different findings, such as metallosis, necrosis, osteolysis, and periprosthetic pseudotumors [2,8-10]. According to literature, symptomatic MoM bearings have higher serum metal ion levels and are more associated with failure and revision compared to asymptomatic bearings [11,12]. Within this group, ARMD is the most frequent cause of revision surgery in the large head total hip MoM bearings [13].

The prevalence of ARMD varies between the different MoM bearings and different manufacturers. Guidelines in most countries recommend a yearly outpatient control with physical examination and serum metal ion levels as a screening tool to predict a possible ARMD. However, there is no global consensus of the best follow-up protocol and no clear consensus over which safe upper limits (SULs) to use for long-term follow-up or to predict future failure. In a recent review from Pijls et al [14], they presented the different follow-up protocols and SULs for Co and Cr that are used within European countries. For example, the British, Italian, Norwegian, and Danish Registries all specified levels above the 7 ppb (parts per billion) for Co or Cr as too high, compared to the Dutch (1 ppb), Swiss (2 ppb), and Swedish (5pp) registries. In a recent statement from the United States, they advise to divide patients into low risk (<3 ppb), moderate risk (3-10 ppb), and high risk (>10 ppb) patients [15]. However, the reliability of SULs in long-term management and surveillance is yet unknown and most likely bearing and patient specific.
The aim of this study is to present a 10-year follow up of our large head MoM total hip bearing and calculate the risk of revision for ARMD in this specific type. We thereby specified new bearing-specific SULs for Co and Cr and advocate for an adjustment in follow-up management for this specific prosthesis.

Methods

Study Cohort

A prospectively collected database of 160 primary large head MoM THAs with a mean 10-year follow-up was retrospectively reviewed (Fig. 1). All prostheses were implanted in 153 patients between 2006 and 2010 in our clinic and all patients received the M2a-Magnum prostheses with ReCap cup and TaperLoc or Mallory stem (Biomet Inc, Warsaw, IN). Surgery was performed through either an anterior supine intermuscular) approach or through a straight lateral approach. During the first 24 hours postoperatively antibiotic prophylaxis was given. Postoperative rehabilitation with full weight bearing was allowed for all patients. Low-molecular- weight heparin was given 6 weeks postoperatively.

Clinical Follow-Up

All of our 160 MoM bearings were monitored yearly and outpatient controls and serum metal ion levels were obtained since the recall in 2011. Patients were followed up annually with clinical assessment, physical examination, anteroposterior pelvic radiographs, and serum metal ion samples. Anteroposterior pelvic and lateral hip radiographs were obtained and reviewed by a specialized radiologist. Radiographs were assessed for osteolysis, bone resorption, radiolucency, and component migration. The angle of inclination of the acetabular component was measured on the direct postoperative radiograph by 2 authors (MCK, NMCM) with high intra-observer and interobserver reliability as described in our earlier study [16]. Whole blood cobalt (Co) and chromium (Cr) ion levels (nmol/L) samples were obtained from all patients in trace-element free tubes and measured by mass spectrometry. To convert our measurements we used for 1 nmol/L = 0.059 ppb (mg/L or ng/mL) for Co and 1 nmol/L = 0.052 ppb (mg/L or ng/mL) for Cr. To assess a possible presence of ARMD, a metal artifact reduction sequence magnetic resonance imaging (MARS-MRI) was performed on patients with symptoms and/or with increased serum metal ion levels (determined by physician).

A total of 2 patients were revised before the recall and 8 patients died of unrelated causes to the prosthesis. One patient with bilateral MoM bearings died 2 months after the recall with serum metal ion measurements of Co 135.9ppb and Cr 86.4ppb. Because no additional examination was possible, the patient was excluded from further follow-up (Fig. 1).

Revision surgery was based on clinical history, physical examination, metal ion levels, pseudotumor on MARS-MRI, and/or patient request. The reason for revision, perioperative presence of ARMD, as well as the histopathological analysis of the tissue samples were all recorded. ARMD was defined according to recent literature as the presence of metallosis, tissue necrosis, osteolysis, and/or a pseudotumor [1,2,8]. Revision for ARMD was scored positive if seen during revision surgery or if proven histopathological. All revision operations were performed with informed consent.

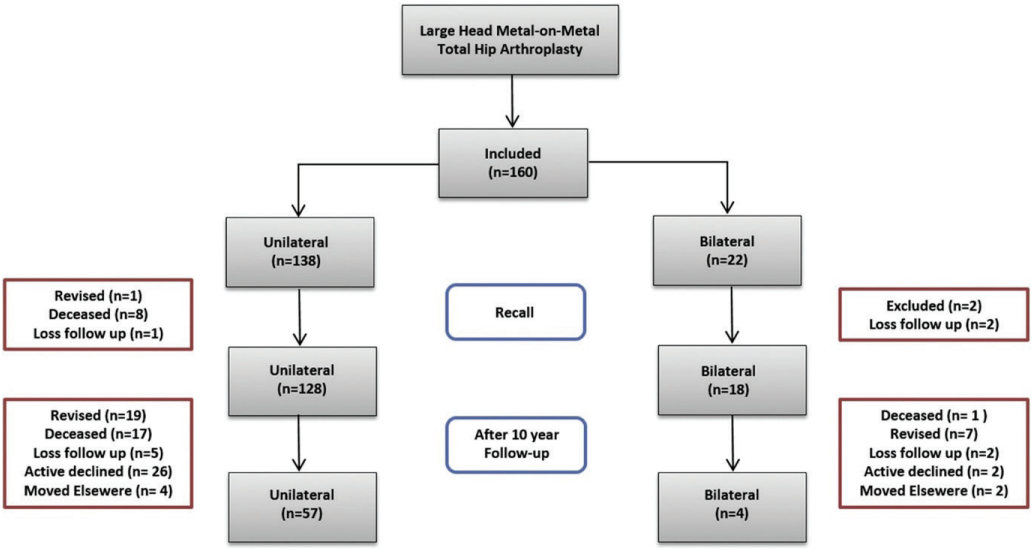

Fig. 1. Flowchart of the 10-year follow-up. Unilateral and bilateral patients were sub-analyzed. The excluded hips (n ¼ 2) in the bilateral group are from 1 patient who died 2 months after the recall and therefore received no further examinations and/or treatment.

Statistical Analysis

Demographic and surgical variables were investigated in each group by the Mann-Whitney U-test and the independent t-test. These analyses were performed using SPSS, Version 25 (IBM, Armonk, NY). All bilateral and revision patients were sub-analyzed. We also performed sub-analyses for the patients with ARMD and patients with no-ARMD in the revision group.

Cumulative Incidence Function

To account for the competing risk of death and revision for other reasons, both of which can occur before a patient experiences revision for ARMD, we calculated the cumulative incidence function (CIF) for each event. Revision of at least 1 component for any reason was set as endpoint of follow-up. The CIF was calculated with R software [17] according to the manual published by Scrucca et al with the package "cmprsk" [18,19].

Subdistribution Hazard Model

To determine which patients need to be followed up more closely (ie, identifying factors that increase the probability of revision for ARMD), we performed subdistribution hazard modeling (SDM). SDM can be used to study the association of factors with the cumulative incidence of revision for ARMD (thus accounting for competing risks), and is therefore suited for prognostic research [20,21]. To calculate the subdistribution hazard ratio (sdHR) we used the R-package "cmprsk" [19]. Factors of interest were age, gender, head size, inclination angle, and last measured Co/Cr levels. For the revised patients we used the levels measured prior to revision. We divided the head size and inclination angle into 3 different groups: for head size 40-44 mm, 46-50 mm, and 52-58 mm, and for inclination angle <35°, >35°-45°, and <45°.

To investigate whether different insights would emerge, we also performed cause-specific hazard modeling. This can be used to study the relationship between each factor and each risk, separately, and is thus more suited for etiological research [20,21]. We decided a priori that if the results from both types of analyses were very similar, we would only present those from the SDM [22].

Safe Upper Limits

To calculate the SULs of the Co and Cr levels we divided the group into ARMD positive and ARMD negative. A proven ARMD, perioperative or histopathological, was scored as positive. We used the R-package "pROC" to plot the receiver operator characteristic curve and to calculate Youden's cutoff to determine the SULs in our sample [23]. We used R-package "epiR" to calculate the sensitivity, specificity, and predictive values of our SUL [24].

Results

Clinical Follow-Up

A total number of 26 (17%) patients have died during the follow- up, all of unrelated causes to the prosthesis. In total, 27 patients (28 bearings) actively declined follow-up and 13 patients (16 bearings) were lost to follow-up or moved elsewhere (Fig. 1). We did not find any clinical important difference between the unilateral and bilateral patients. However, bilateral patients had a statistically significant higher last measured Co of 3.4 ppb and Cr of 3.1 ppb compared to the unilateral patients with 1.2 ppb and 1.8 ppb, respectively (Table 1). Figure 2 shows all Co and Cr measurements during the 10-year follow-up. Co and Cr levels are presented in parts per billion with the mean (standard deviation). An overall higher level of Co and Cr is seen in patients with bilateral MoM bearings (Fig. 2A and 2B) and the revised bearings (Fig. 2C).

Table 1. Patient demographic features and radiological parameters

Variables	Entire sample	Unilateral	Bilateral
Number of hips (patients)	158 (153)	138 (138)	20 (15)
Revised†	27 (17.1)	20 (12.9)	7 (4.5)
Deceased†	26 (16.5)	25 (15.8)	1 (0.6)
Age day of operation (years)*	61.7 (10)	61.7 (10.5)	61.5 (7.0)
Gender†			
Male	71(45)	64 (46)	7 (35)
Female	87 (55)	74 (54)	13 (65)
Side†			
Left	75 (47)	65 (47)	10 (50)
Right	83 (53)	73 (53)	10 (50)
Approach†			
Anterior Supine Intermuscular	94 (59)	83 (60)	11 (55)
Straight lateral	64 (41)	55 (40)	9 (45)
Head sizes (mm) †			
40-44	22 (14)	20 (14)	2 (10)
46-50	104 (66)	86 (63)	18 (90)
52-58	31 (20)	31 (23)	0 (0)
Inclination angle (degrees) †			
≤ 35 degrees	31 (20)	29 (21)	2 (10)
35-45 degrees	82 (53)	69 (51)	13 (65)
≥45 degrees	43 (27)	38 (28)	5 (25)
Last measured Cobalt (ppb) ‡	1.4 (0.8-2.9)	1.2 (0.8-2.2)	3.4 (1.8-13.6)
Last measured Chromium (ppb) ‡	2.0 (1.3-3.1)	1.8 (1.2-3.0)	3.1 (2.1-9.5)

Abbreviations: ppb = parts per billion
† Values given as n (%).
* Values given as mean (SD).
‡ Values given as median (IQR)

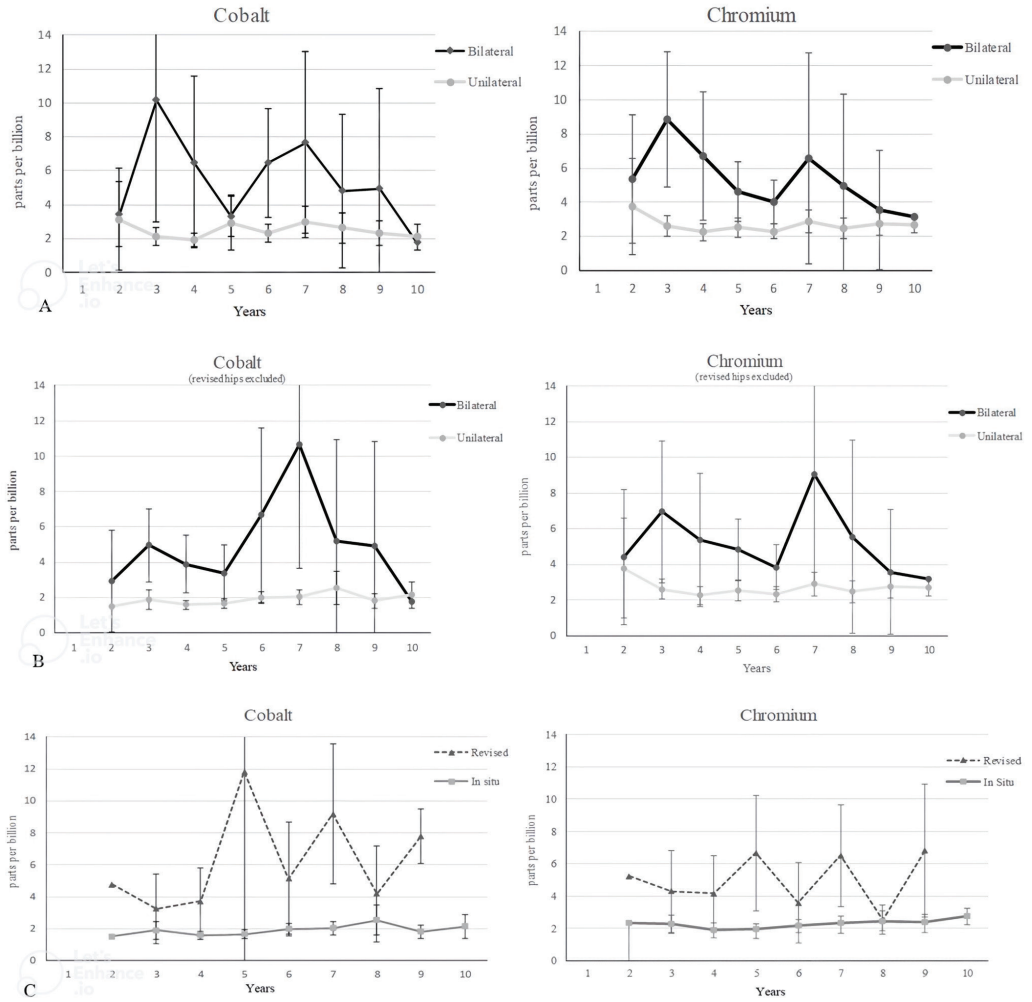

Fig. 2. All 10-year measurements of cobalt and chromium levels in our total cohort. (A) Unilateral and bilateral patients separated; (B) revised hips excluded; (C) only unilateral hips revised compared to the bearings still in situ. All graphs show the mean (standard deviation) values per year in parts per billion with a 95% confidence interval.

Revision Surgery

During the 10-year follow-up, a total of 27 (16.9%) bearings had been revised: 20 (12.5%) bearings from the unilateral group and 7 (4.4%) bearings from the bilateral group. A total of 22 patients received a MARS-MRI, 2 patients a computed tomography scan (due to claustrophobia), and 3 patients were revised due to loosening and no additional examination was necessary. A proven ARMD, perioperative or histopathological, was present in 16 revised bearings, 59% of all revisions, and in 10% of the total cohort. Table 2 presents the different reasons for revision between patients with ARMD and no-ARMD, whereas Table 3 shows the revision features of these groups. All performed revisions had multiple reasons and were not based on 1 single cause (Table 2).

Table 2. Reasons to Perform Revision Surgery.

Revision Reasons	ARMD (16)	No-ARMD (11)
Increased Co/Cr	16	0
Pain	12	9
Suspect pseudotumor (MARS-MRI)	9	3
Loosening	1	4
Infection	0	1
Other	1	0

All performed revisions (27) had multiple reasons and were not based on a single cause.
Abbreviations: ARMD, adverse reaction to metal debris; Co/Cr, cobalt/chromium; MARS-MRI, metal artifact reduction sequence magnetic resonance imaging. All values are given as n.

ARMD-proven patients had increased serum metal ion levels, either Co, Cr, or both. Table 3 shows that there was a higher last measured Co and Cr level in patients with proven AMRD; this result was statistically significant (P = .015 and P < .001, respectively). Table 4 illustrates the mean preoperative and postoperative Co and Cr levels between the revised patients with and without ARMD. The presence of ARMD in our revision patients was scored positive as this was seen as perioperative or histopathological proven. The mean (standard deviation) time (in weeks) of the postoperative collection of blood samples was 12 (7.1) and 5.2 (2.6) for patients with ARMD and no-ARMD, respectively. There was a statistically significant increased preoperative level of Co and Cr in the ARMD group compared to the no-ARMD group, with a Co level of 15.2 ppb and 1.9 ppb (P = .015) and a Cr level of 9.3 ppb and 1.7 ppb (P <.001), respectively. This difference continued after revision with a higher level of Co (P = .042) and Cr (P < .001) postoperative. After dividing the group into unilateral and bilateral, the Co and Cr levels generally remained higher in the ARMD group, with only - in the unilateral group - statistically significant higher level in preoperative Co and Cr levels and in postoperative Cr (Table 4).

Table 3. Revision Features and Radiological Parameters.

Variables	Revisions		P-value
	ARMD	No-ARMD	
Number of hips (patients)	16 (15)	11 (10)	
Deceased†	0 (0)	1 (3.7)	0.219
Bilateral†	4 (14.8)	3 (11.1)	0.895
Age day of operation (years)*	61.9 (4.4)	59.7 (15.0)	0.581
Gender†			
Male	3 (11.1)	6 (22.2)	0.053
Female	13 (48.1)	5 (18.5)	
Side†			
Left	8 (29.6)	6 (22.2)	0.816
Right	8 (29.6)	5 (18.5)	
Approach†			
Anterior Supine Intermuscular	9 (33.3)	6 (22.2)	0.930
Straight lateral	7 (25.9)	5 (18.5)	
Head sizes (in mm) †			
40-44	3 (19)	1 (9)	
46-50	11 (69)	9 (82)	0.827
52-58	2 (12)	1 (9)	
Inclination angle (degrees) †			
≤ 35 degrees	1 (7)	2 (18)	
35-45 degrees	5 (31)	6 (55)	0.110
≥45 degrees	10 (62)	3 (27)	
Last measured Cobalt (ppb) ‡	8.6 (6.3-16.3)	1.6 (1.1-2.8)	0.015
Last measured Chromium (ppb) ‡	8.1 (4.7-10.7)	1.9 (0.8-2.6)	<0.001

Abbreviations: ARMD = adverse reaction to metal debris, ppb = parts per billion, SD = standard deviation, IQR = interquartile range.
† Values are given as n (%).
* Values are given as mean (SD).
‡ Values are given as median (IQR).

Table 4. The mean Preoperative and Postoperative Cobalt and Chromium Levels in Revision Patients.

	ARMD		p-value
	YES (n=16)	NO (n=9)	
Preoperative Cobalt (ppb) *			
Total (n=25)	15.2 (19.3)	1.9 (1.0)	0.015
Unilateral (n =19)	15.7 (22.0)	1.5 (0.6)	0.046
Bilateral (n=6)	13.6 (9.5)	3.4 (0.0)	0.122
Postoperative Cobalt (ppb) *			
Total (n=20)	1.2 (0.8)	0.7 (0.3)	0.042
Unilateral (n=16)	1.0 (0.7)	0.7 (0.3)	0.157
Bilateral (n=4)	1.8 (1.2)	-	-
Preoperative Chromium (ppb) *			
Total (n=25)	9.3 (5.9)	1.7 (1.0)	<0.001
Unilateral (n =19)	9.7 (6.0)	1.5 (1.1)	<0.001
Bilateral (n=6)	8.0 (6.6)	2.5 (0.0)	0.190
Postoperative Chromium (ppb) *			
Total (n=20)	2.2 (1.5)	0.5 (0.5)	<0.001
Unilateral (n=16)	2.3 (1.7)	0.5 (0.5)	0.008
Bilateral (n=4)	2.1 (1.1)	-	-

Abbreviations: ARMD = adverse reaction to metal debris, ppb = parts per billion, SD = standard deviation.
* Values are given as mean (SD).

Statistical Analysis

Cumulative Incidence Function

During the follow-up period the CIF for death was higher at all times than the CIF for revision for ARMD and no-ARMD. Up to the 4- year marks the cumulative incidence of revision for a no-ARMD cause was higher compared to the ARMD group (Table 5). At 5 and 6 years, the cumulative incidence of revision linked to ARMD was equal to that of no-ARMD with 3.8% and 5.1%, respectively. From year 6 up, the CIF of revision for ARMD became higher compared to revision for no-ARMD with a 9.5% compared to 7.0% CIF respectively at 10 years.

Table 5. Cumulative Incidence Function with Death as Competing Factor.

	Months									
	12	24	36	48	60	72	84	96	108	120
ARMD*	0.0	0.0	0.6 (0.006-0.03)	1.3 (0.002-0.04)	3.8 (0.02-0.08)	5.1 (0.02-0.09)	7.0 (0.04-0.12)	8.9 (0.05-0.14)	9.5 (0.06-0.15)	9.5 (0.06-0.15)
No-ARMD*	1.2 (0.002-0.04)	1.9 (0.005-0.05)	2.5 (0.008-0.06)	3.2 (0.01-0.07)	3.8 (0.02-0.08)	5.1 (0.02-0.09)	5.7 (0.03-0.10)	5.7 (0.03-0.10)	6.2 (0.03-0.11)	7.0 (0.04-0.12)
Deceased*	0.0	1.3 (0.002-0.04)	3.8 (0.02-0.08)	6.3 (0.03-0.11)	7.0 (0.04-0.12)	8.2 (0.05-0.13)	8.9 (0.05-0.14)	8.9 (0.05-0.14)	9.5 (0.06-0.15)	11.1 (90.07-0.17)

Abbreviations: ARMD = Adverse Reaction to Metal Debris, CI = Confidence interval.
* Values are shown as percentage with a 95% CI given in parentheses.

Subdistribution Hazard Model

Based on our univariate analysis using the subdistribution hazard model, female patients had a higher probability of revision for ARMD (sdHR 3.4, 95% confidence interval [CI] 1.01-11.7, P = .049) as well as patients with an inclination angle >45 degrees (sdHR 4.7, 95% CI 1.6-13.6, P = .0043). There was no significant higher probability of revision depending on age or head size, even though the number of revisions almost doubled in the 40-mm to 44-mm head size group (Table 6). Higher last measured Co and Cr levels were associated with a higher probability of revision for ARMD (sdHR 1.05, 95% CI 1.03-1.07, P < .001 and sdHR 1.21, 95% CI 1.14-1.29, P < .001, respectively). No violation of the proportional hazards assumption was detected.

The results from the cause-specific analysis were very similar to those from the subdistribution hazard model.

Table 6. Univariable Analysis

Variables	sdHR*	p-value
Age	1.01 (0.98 – 1.04)	0.580
Gender (male vs female)	3.43 (1.01 – 11.7)	0.049
Head Size (mm)		
52 – 58 (reference)	1.0	-
46 – 50	1.44 (0.33 – 6.38)	0.630
40 – 44	1.99 (0.35 – 11.30)	0.440
Inclination angle		
35-45 degrees (reference)	1.0	-
< 35 degrees	0.54 (0.06 – 4.64)	0.580
> 45 degrees	4.70 (1.63 – 13.58)	0.004
Last measured Cobalt	1.05 (1.03 – 1.07)	<0.001
Last measured Chromium	1.21 (1.14 – 1.29)	<0.001

Abbreviations: sdHR = subdistribution hazard ratio

* The values are given as subdistribution Hazard, with the 95% Confidence Interval (CI) in parentheses.

Safe Upper Limits

The SUL for Co was calculated at 4.1 ppb (92% specificity, 100% sensitivity) whereas for Cr at 4.2 ppb (90% specificity, 88% sensitivity). Patients above these values are at higher risk of revision for ARMD. For these SULs, we calculated a negative predictive value (NPV) of 100% for Co and 98% for Cr with these SULs. The areas under the curves for Co and Cr did not differ statistically significantly from each other. A summary of the receiver operator characteristic analysis is presented in Table 7.

Table 7. Summary of Receiver Operator Characteristic Analysis

	Cobalt	Chromium
AUC*	96.8	93.3
Optimal threshold (SUL)	4.09 ppb	4.20 ppb
Specificity*	92 (85 –97)	90 (83 –95)
Sensitivity*	100 (79 – 100)	88 (62 –98)
Positive predictive value*	67 (45 – 84)	58 (37 –78)
Negative predictive value*	100 (96 – 100)	98 (93 – 100)
Positive likelihood ratio*	12.88 (6.62 – 25.05)	9.01 (4.86 – 16.71)
Negative likelihood ratio*	0.00 (0.00 – NaN)	0.14 (0.04 – 0.51)

Abbreviations: AUC = Area under the curve, SUL = Safe Upper Limit, ppb = parts per billion, CI = confidence interval, NaN = not a number.
* Values are shown as the mean percentage with a 95% CI given in parentheses

Discussion

Because many of the MoM bearings are still in situ, a valid surveillance protocol with regular measurements of serum Co and Cr levels is crucial. Changing metal ion levels are bearing and patient specific and should be measured on a regular basis. With this study, we show the 10-year survival of a large head MoM bearing and present different revision risks for ARMD. We also present bearing- specific SULs to use for future follow-up, with an SUL of 4.1 ppb and 4.2 ppb for Co and Cr, respectively.

There are several limitations in this study. First, this is a retrospective cohort study with a prospective follow-up. Unfortunately, not all patients have had yearly measured serum Co and Cr levels. In addition, there were 27 patients in our cohort who actively declined follow-up during the 10-year control. These are probably asymptomatic patients with a good functioning hip prosthesis since they actively canceled outpatient clinic appointments. Second, we also included bilateral patients in our study. To prevent overlapping data measurement we analyzed the serum Co and Cr levels separately for this group. Third, all performed revisions had multiple reasons. Increased Co/Cr levels were in all ARMD revisions one of the causes. This diagnostic reason could have influenced the hazard rations of Co and Cr for ARMD in a positive way. Fourth, the ARMD was only scored at perioperative or histopathology findings and therefore we could have missed asymptomatic ARMD patients. This could be the reason for our high sensitivity and NPV; mostly very clear cases of ARMD were detected. However, if asymptomatic patients would be included, we expect the SUL to even be lower. This potential bias would thus only strengthen the need to lower the currently used SULs.

Earlier studies of the ReCap M2a-Magnum MoM bearing showed a high incidence of ARMD [25,26] and a 10-year survival of 88% (95% CI 86-90) for the ReCap/Bimetric bearing and an 85% (95% CI 86-90) survival for the M2a38/Bimetric total hip prosthesis. These findings are similar to ours. In our study, the cumulative incidence of revision for ARMD was 9.5% in 10 years, compared to 7.0% for other reasons. As shown in Table 4, the risk for revision for ARMD slowly increases over time. This might be because the development of ARMD takes time.

To predict a possible ARMD, serum metal ion levels are regularly used as screening tool. Known factors that can contribute and influence high serum Co and Cr levels are female gender, malposition of the cup (high inclination), and implant design and size [1,27-30]. In our study, we found a statistically higher hazard of revision for ARMD in patients with an inclination angle above 45° ($P = .004$) and for female patients ($P = .049$).

Interestingly, there is still no consensus about the predictive value of Co and Cr in ARMD. Some studies demonstrate that Cr levels are associated with increased incidence of ARMD [31], while others state that Co is the most effective screening tool [29]. Most national authorities set the level of acceptance at 7 ppb for both Co and Cr. However, these levels are mainly based on research done with resurfacing hip arthroplasties [11]. Suggestions have arisen that all bearings should have their own specific SULs for follow-up because they all have their own running in phase and wear patterns [8,13,28,30,32]. In a recent consensus statement on management of MoM bearings from the EFORT, they advised the use of 2 different Co levels: levels <2 ppb (no clinical concern) and values between 2 and 7 ppb (clinical concern) [33]. Until now, only the Swedish Hip Arthroplasty Register has adjusted the levels to a threshold of 5 ppb [14]. Matharu et al. already

presented the importance of bearing-specific SULs. They showed almost 71% of the patients with ARMD are missed by using the 7 ppb SUL [29]. Even more, Matharu et al [32] suggest in a later study that significantly fewer patients with ARMD are missed by using implant-specific thresholds. Carlson et al [8] even demonstrated that both Co and Cr levels above the 5 ppb and 2.5 ppb respectively increased the risk of ARMD in patients with an ASR total hip bearing. These studies again demonstrate the importance of bearing-specific follow-up protocols.

For our M2a-Magnum MoM bearing, we calculated an SUL for Co of 4.1 ppb and for Cr of 4.2 ppb, with a sensitivity of 100% and 88%, respectively. Patients above these SULs have showed an increased chance of revision surgery for ARMD. Thereby, we had an NPV of 100% for Co and 98% for Cr. This means patients below these SULs have lower chance of being revised for ARMD. Our SULs are com- parable to the levels described by Van der Straeten et al [30]. They presented an SUL for Co of 4.0 ppb and Cr of 4.6 ppb, based on the findings with the MoM ASR (DePuy, Warsaw, IN) resurfacing bearing.

In conclusion, serum Co and Cr measurements should be a part of the complete long-term follow-up management and should be made bearing specific to miss fewer patients with ARMD. We must take into account that higher revision rates are the result of the recall of the ASR prosthesis and publicity worldwide about ARMD. This could have lowered the threshold for revision of the large head MoM bearings. Despite that, we still recommend a strict follow-up protocol over the entire time the prosthesis is in situ and the use of bearing-specific Co and Cr SULs for all commonly used MoM bearings. Patients with a large head M2a-Magnum MoM bearing and an SUL above our threshold of 4.1 ppb for Co and 4.2 ppb for Cr should have cross-sectional imaging and be closely monitored and followed over time.

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CHAPTER 7

Are serum cobalt and chromium levels predictors for patient-reported outcome measures in the ASR hip resurfacing arthroplasty? Insights from a 10-year Prospective Follow-up Study

M.C. Koper[1], R.W.A. Spek[2], M. Reijman[1], E.M. van Es[1]
S.J. Baart[3], J.A.N. Verhaar[1], P.K. Bos[1]

[1] Department of Orthopedics and Sports Medicine,
Erasmus MC, 3000 CA,Rotterdam, The Netherlands

[2] Department of Trauma and Orthopedic Surgery
Flinders Medical Center, Bedford Park SA 5042 Adelaide, Australia

[3] Department of Biostatistics,
Erasmus MC, 3000 CA, Rotterdam, The Netherlands

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ABSTRACT

Aims: The aims of this study were to determine if an increasing serum cobalt (Co) and/or chromium (Cr) concentration is correlated with a decreasing Harris Hip Score (HHS) and Hip disability and Osteoarthritis Outcome Score (HOOS) in patients who received the Articular Surface Replacement (ASR) hip resurfacing arthroplasty (HRA), and to evaluate the ten-year revision rate and show if sex, inclination angle, and Co level influenced the revision rate.

Methods: A total of 62 patients with an ASR-HRA were included and monitored yearly postoperatively. At follow-up, serum Co and Cr levels were measured and the HHS and the HOOS were scored. In addition, preoperative patient and implant variables and the need for revision surgery were recorded. We used a linear mixed model to relate the serum Co and Cr levels to different patient-reported outcome measures (PROMs). For the survival analyses we used the Kaplan-Meier and Cox regression model.

Results: We found that an increase of one part per billion (ppb) in serum Co and Cr levels correlated significantly with worsening of the HHS in the following year. This significant correlation was also true for the HOOS-Pain and HOOS-quality of life sub scores. The overall ten-year survival rate in our cohort was 65% (95% confidence interval (CI) 52.5 to 77.6). Cox regression analysis showed a significant hazard ratio (HR) of 1.08 (95% CI 1.01 to 1.15; $p = 0.028$) for serum Co level. No significance was found with sex or inclination angle.

Conclusion: This study shows that increasing serum Co and Cr levels measured in patients with an ASR-HRA are predictive for deterioration in HHS and HOOS subscales in the following year. Increasing serum Co and Cr should forewarn both surgeon and patient that there is a heightened risk of failure. Continued and regular review of patients with an ASR-HRA implant by measurement of serum Co/Cr levels and PROMs remains essential.

Introduction

Many younger patients with hip osteoarthritis received in the mid to late 2000s a metal-on-metal hip resurfacing arthroplasty (MoM-HRA) with the potential for bone preservation, lower wear rates, and early return to work and sport activities [1-3]. However, certain MoM-HRA designs, especially the Articular Surface Replacement (ASR; DePuy International, UK), reported early failure and high revision rates [4-8]. For that reason, this implant was withdrawn in 2010 [9,10] consequently, routine follow-up became the standard of care as advised by multiple orthopaedic societies [11-14]. By that time, an estimate of 93,000 patients worldwide had already received an ASR-HRA or ASR total hip prosthesis [15]. However, the problem was not only limited to the ASR bearing; many other implants with a MoM interface had similar clinical problems related to metal wear. Since many of these MoM bearings are still in situ, there is a need to optimize follow-up guidelines and protocols. Registry reports of the ASR-HRA showed high rates of revision in early- and late-stage follow-up with a ten-year revision rates ranging from 30% to 35% [16,17]. The design of the ASR-HRA acetabular component, in particular the rim design, arc of coverage, and small contact patch to rim distance, resulted in a higher revision rate compared to other HRAs [6,18,19]. Longevity is generally the best in males aged younger than 50 years with larger-diameter components [20,21]. Revision rates in females are higher compared to males, probably due to the use of smaller component sizes [6,22–27].

A well-recognized MoM bearing-specific complication, and one of the most frequent reasons for failure and revision surgery, is adverse reaction to metal debris (ARMD) or adverse local tissue reaction (ALTR). These adverse reactions are due to metal nanoparticles of cobalt (Co) and chromium (Cr) produced by wear, and includes findings such as bone and soft-tissue necrosis, osteolysis, metallosis, aseptic lymphocyte-dominant vasculitis-associated lesion (ALVAL), and periprosthetic pseudotumour formation [8,17,28,29]. Since the recall of the ASR, and the specific MoM problems, most hospitals undertake regular outpatient reviews to monitor symptoms, complaints, radiological abnormalities, patientreported outcome measures (PROMs), and serum Co and Cr levels. These serum levels are widely used as a clinical tool to predict ARMD and/or the need for revision surgery [13,17,30], however its potential predictive value in relation to PROMs is still unclear [15,31].

Predicting failure of the ASR-HRA by correlating serum Co and Cr levels to PROMs may help in preventing extensive soft-tissue damage and possibly more complex revision surgery. Over a period of ten years, we followed a cohort of patients, recruited in a previously conducted randomized controlled trial (RCT), with regular serum Co and Cr measurements and PROM assessments [32]. These unique long-term follow-up data enable us to evaluate the relationship between increasing serum metal ion levels and PROM outcomes. The primary aim of this study was to evaluate a increasing serum Co or Cr levels as a predictor of a deteriorating Harris Hip Score (HHS) [33] and Hip disability and Osteoarthritis Outcome Score (HOOS) [34] in patients with an ASR-HRA. The secondary aim was to investigate if sex, inclination angle, and Co levels were associated with the need for revision surgery.

Methods

Study design and protocol

This is a retrospective evaluation of data from a prospectively collected database of all patients from our hospital who participated in an earlier published multicenter RCT [32]. The trial compared computer-assisted surgery (CAS) to conventional surgery in patients who received an ASR-HRA, started in October 2006 and discontinued in January 2010 due to the worldwide ASR-HRA recall. Operations were performed using a standard posterolateral approach and the ASR-HRA were either placed according with the standard manual device or by using CAS. All patients received identical perioperative care as well as standardized postoperative management. After the clinical trial was ended, patients were prospectively followed with yearly serum metal ion levels (Co and Cr), and PROMs (HHS, HOOS) as advised by the Dutch Orthopaedic Association [35].

Variables

The following variables were extracted from the database: age, sex, BMI, side of procedure, and details of the ASR-HRA (femoral head size, CAS, or manual implanted femoral component) . Head size was divided into two groups: < 50 mm and ≥ 50 mm, according to Prosser et al. [36]. Postoperative anteroposterior pelvic radiographs were obtained and used to measure the acetabular inclination angle and postoperative stemshaft angle (SSA). Acetabular inclination was calculated by drawing a line between the ischial tuberosities and tangential to the face of the cup. The inclination angle was subdivided into three categories: < 35°, 35 to 45°, and > 45°. The SSA was defined as the angle between the stem of the femoral HR component and the axis of the femoral diaphysis, and measured accordingly. Two authors (MK, EvE) independently calculated these angles in a doubleblinded manner (duplicate measurements without patient details) using GeoGebra software (International GeoGebra Institute and GeoGebra, Austria) [32]. For the measurements of the inclination angle and SSA, the intra-observer and interobserver reliability were evaluated using the intraclass correlation coefficient (ICC). A two-way mixed model was used with absolute agreement and a confidence interval (CI) of 95%. ICC values range from 0 to 1 in which 1 indicates perfect reliability. An ICC > 0.75 is considered acceptable [37]. After the product recall in 2010, serum Co and Cr (nmol/l) samples were obtained from all patients in trace-element free tubes and measured by mass spectrometry. The levels in this study were presented as parts per billion (ppb). For converting our measurements, the following known values were used: Co 1 nmol/l = 0.059 ppb (µg/l or ng/ml) and Cr 1 nmol/l = 0.052 ppb (µg/l or ng/ml).

Clinical follow-up

Validated PROMs were collected pre- and postoperatively with a follow-up of ten years. The HHS was obtained by one attending orthopaedic surgeon (PKB), while the HOOS was filled out by the patient [33,38,39]. At each outpatient visit, the HHS was completed and used to score the hip function. The survey has ten questions and the score ranges from 0 to 100, with higher scores representing better function and outcome. The HOOS is subcategorized in five domains: pain, symptoms, sports, activity of daily living (ADL), and hip related quality of life (QoL). For this study we used only three domains: pain, ADL, and QoL. Scores on the HOOS range from 0 to 100, where 0 indicates the worst possible outcome and 100 the best possible.

Indications for revision and time to revision were collected from patients' files and predictive factors such as age at time of primary surgery, sex, BMI, and component size and position were defined as covariates. The decision for implant revision was based on clinical history, physical examination, serum metal ion levels, ARMD diagnosis or suspicion and/or patient concern regarding MoM-bearing, and subsequent request for revision. Reason for revision was noted and perioperative findings were scored to confirm the diagnosis (aseptic loosening, infection, fracture, or pseudotumour). ARMD was defined if the presence of this was seen during surgery or histo-pathological proven. ARMD includes findings, such as necrosis, osteolysis, metallosis, ALVAL, and periprosthetic pseudotumour. All revisions were performed with informed consent.

Table I. Baseline characteristics of the Articular Surface Replacement hip resurfacing arthroplasty patients.

Variable	All	Non-revisions	Revisions
Hips, n	63	41	22
Mean age, yrs (range)	48.1 (22.0 to 63.0)	48.2 (22.0 to 62.0)	48.0 (26.0 to 63.0)
Sex, n (%)			
Male	32 (51)	23 (56)	9 (41)
Female	31 (49)	18 (44)	13 (59)
Mean BMI, kg/m2 (range)	27.4 (18.9 to 39.6)	27.6 (20.3 to 35.6)	27.0 (18.9 to 39.6)
Side, n (%)			
Right	39 (62)	24 (59)	15 (68)
Left	24 (38)	17 (41)	7 (32)
Computer-assisted procedure, n (%)			
No	29 (46)	17 (41)	12 (55)
Yes	34 (54)	24 (58.5)	10 (45)
Mean head size, mm (range)	49 (43 to 57)	49 (43 to 57)	49 (43 to 55)
< 50 mm, n (%)	38 (60)	26 (63.4)	12 (55)
≥ 50 mm, n (%)	25 (40)	15 (36.6)	10 (45)
Mean inclination angle, ° (range)	42.5 (26.1 to 62.3)	40.9 (26.1 to 55.2)	45.5 (32.7 to 62.3)
< 35°, n (%)	8 (13)	6 (15)	2 (9)
35° to 45°, n (%)	33 (52)	24 (58)	9 (41)
> 45°, n (%)	22 (35)	11 (27)	11 (50)
Postoperative SSA, n (%)			
< 130°	9 (14)	5 (12)	4 (18)
130° to 140°	32 (51)	23 (56)	9 (41)
> 140°	22 (35)	13 (32)	9 (41)
Mean survival time, yrs (range)	8.4 (0.2 to 13.5)	9.2 (3 to 14)	5.7 (0.2 to 13.4)

*Two patients required bilateral hip resurfacing arthroplasty: one patient received both procedures within the study period, and one patient received only one hip within the study.
SSA, stem-shaft angle.

Patient characteristics and revision rate.

A total of 63 ASR HRAs (62 patients) with a mean age of 48.1 years (22.0 to 63.0) were evaluated. Two patients had bilateral MoM-bearings, of whom one patient received on both sides an ASR prosthesis via CAS. The other patient had an ASR bearing on one side (placed conventionally) and a MoM-total hip arthroplasty (THA) on the other side. Two patients (3.2%) were lost to follow-up, one patient (1.6%) moved elsewhere, and one patient died. A total of 22 MoM-bearings (35%) were revised, of which 11 were recorded as 'ARMD' and six 'non-ARMD'. Four patients were revised before the recall in 2010 (two for a acetabular fracture and two due to aseptic loosening) and for one patient no revision data were available. There was no significant difference in age, sex, or BMI between the revised and nonrevised patients (Table I).

Statistical analysis

All analyses were performed using SPSS v. 27 (IBM, USA). Baseline demographic details were reported as means and standard deviation (SD) or range (continuous variables) or as number with percentages (categorical variables) depending on their distribution. To assess whether Co and Cr levels were associated with PROMs, a linear multivariable regression analysis was performed. Two separate models were carried out: the first with the last known HHS (last outpatient visit measurement or last measured value before revision) as dependent variable, and the second with the last known HOOS subscale as dependent variable. In the model, the last measured serum metal ion levels were controlled for sex, inclination angle, and head size. Last measured Co and Cr level was defined as the last value before revision surgery, or the value measured during the last outpatient visit in patients who did not require a revision. β coefficients, the constant, as well as p-values, were reported.

A linear mixed model (LMM) was used to examine the inverse association between repeated Co or Cr levels in relation to repeated values of the HHS and HOOS. The inverse relation was used to relate increasing Co or Cr levels to worsening of the HHS and HOOS. The model was run with Co, Cr, sex, inclination angle, and head size as fixed factors while patients were entered as a random intercept. Co and Cr were also used as lagged variable in this model. This resulted in a total of four different LMMs for all the measured PROMs: Co level in the same year; Cr level in the same year; Co level one year before; and Cr level one year before the measured PROM.

To determine the cumulative survival rate, a Kaplan Meier estimate was calculated and presented with the 95% CI. Events were defined as revision of the femoral and/or acetabular component (independent of reason). To identify which variables would influence the revision rate, a Cox's regression model was performed. Nine cases were excluded due to missing values, hence the total number of patients included in this model was 54, with 17 events. Due to the relatively low number of events, and to prevent the model from overfitting, we ran the model with the known confounders: female sex and high inclination angle, and with the covariate 'last measured serum Co level'. Findings were presented with hazard ratios (HRs) and their 95% CI. pvalues ≤ 0.05 were considered significant.

Results

Radiological evaluation.

The calculated inter- and intra-observer reliability for the inclination angle and postoperative SSA between the two readers was excellent. The intra-observer reliability for the inclination angle was 0.99 (95% CI 0.98 to 0.99) for reader 1, and 0.99 (95% CI 0.99 to 0.99) for reader 2. The ICC for the interobserver reliability was 0.99 (95% CI 0.98 to 0.99). The same results were calculated for the intra-observer reliability for the SSA, with a 0.99 (95% CI 0.98 to 0.99) for reader 1, and 0.99 (95% CI 0.98 to 0.99) for reader 2. The ICC for the interobserver reliability was 0.99 (95% CI 0.98 to 0.99).

Trends of serum ion levels with PROMs.

As opposed to the non-revision group, the revision patients showed a trend of a greater increase in serum Co and Cr levels during the ten-year follow-up. Serum Co in the revision group increased from 1.68 ppb (SD 0.39) to 10.06 ppb (SD 10.31), whereas in the non-revision group this level increased from 0.88 ppb (SD 0.44) to 2.56 (SD 2.66). For both groups, the Cr levels showed the same trend (Supplementary Material). Within the two groups (non-revision and revision patients) the yearly serum metal ion levels were depicted with corresponding PROMs (Figures 1 and 2). The non-revision group showed a slow increase in Co and Cr levels and a relatively steady state in PROMs over the ten years. Conversely, the revision group showed an overall steeper increase in Co and Cr levels with lower PROMs with time.

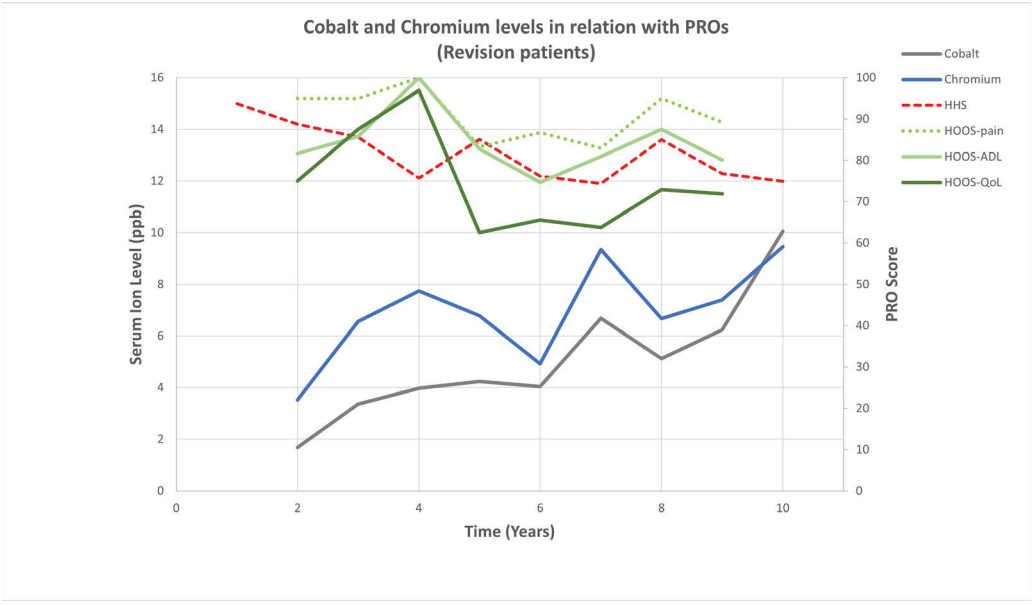

Figure 1: Mean serum level of cobalt and chromium and the means of Harris Hip Score (HHS) and Hip disability and Osteoarthritis Outcome Score (HOOS) over time among revised patients. ADL, activities of daily living; ppb, parts per billion; PRO, patient-reported outcome; QoL, quality of life.

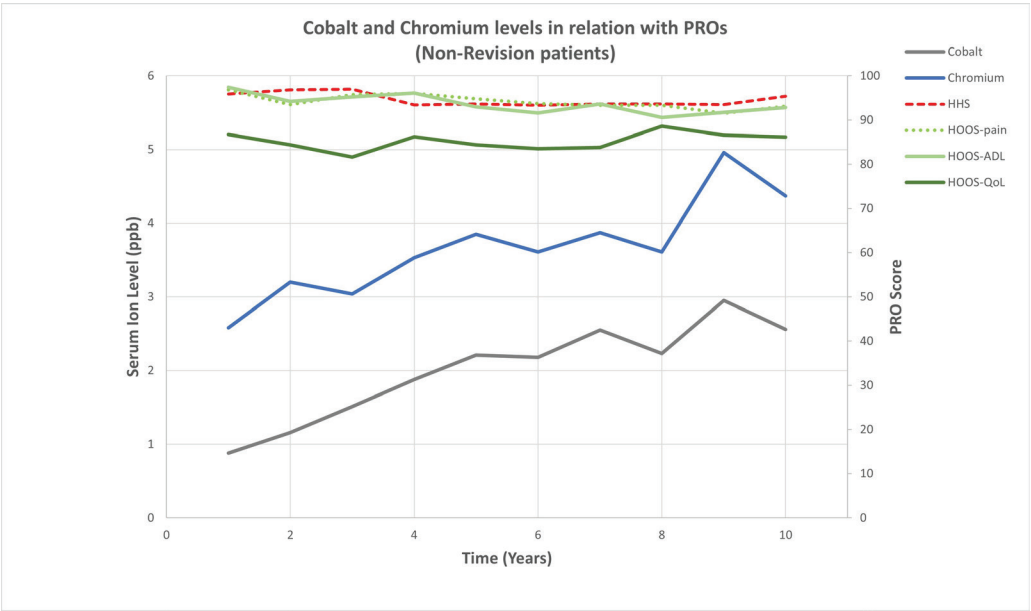

Figure 2: Mean serum level of cobalt and chromium and means of Harris Hip Score (HHS) and Hip disability and Osteoarthritis Outcome Score (HOOS) over time among all non-revised patients. ADL, activities of daily living; ppb, parts per billion; PRO, patient-reported outcome; QoL, quality of life.

As revealed by the linear regression model, the negative coefficient value implies decreasing HHS and HOOS subscale scores with increasing serum cobalt and chromium levels. However, this association between Cr and the PROMs did not reach statistical significance. This was also true for all measurements in relation to Cr levels (Table 2).

The results of the LMM examining the inverse association between repeated Co/Cr and HSS or HOOS measurements are presented in Table 3. Co and Cr measurements in relation to the HHS and HOOS in the same year did not show any significant correlation (Table 3). However, the measured Co values one year prior to the measured PROMs showed a significant correlation with the HHS and the HOOS subscales Pain and QoL. An increase in Co of 1 ppb predicts a decline of 0.9 points (95% CI 0.5 to 1.3; $p < 0.001$) in HHS the next year. This association for increase of Co of 1 ppb was also found for the subscale HOOS-Pain, with a decrease of 0.43 points (95% CI 0.00 to 0.86; $p = 0.050$) and HOOS-QoL, with a decrease of 0.92 points (95% CI 0.25 to 1.59; $p = 0.008$). For the measured Cr levels, we found only an association within the HHS; a 1 ppb increase is predictive of a decrease of 0.33 points (95% CI 0.02 to 0.64; $p = 0.036$) in the following year's HHS.

Table 2. Linear regression with HHS and HOOS as dependent variables

	HHS (n = 54)		HOOS-ADL (n = 39)		HOOS-pain (n = 42)		HOOS-QoL (n = 41)	
	B (95%CI)	p-value	B (95%CI)	p-value	B (95%CI)	p-value	B (95%CI)	p-value
Cobalt	-0.25 (-2.10 – 1.60)	0.785	-0.70 (-3.72– 5.11)	0.751	-0.46 (-4.03 – 3.12)	0.797	-0.77 (-6.45 – 4.91)	0.784
Chromium	-0.69 (-2.37 – 1.00)	0.416	-0.84 (-4.52 – 2.84)	0.645	-0.12 (-3.09 – 2.85)	0.936	-0.26 (-4.98 – 4.47)	0.913
Female gender	-5.53 (-15.14 – 4.07)	0.252	-4.44 (-17.41 – 8.54)	0.491	-2.89 (-13.34 – 7.57)	0.579	-1.91 (-18.49 – 14.68)	0.817
Inclination angle*								
<35°	4.19 (-6.49 – 14.87)	0.434	-4.78 (-19.85 – 10.29)	0.523	3.16 (-9.08 – 15.40)	0.603	-0.27 (-19.96 – 19.16)	0.978
>45°	-7.43 (-15.54 – 0.68)	0.071	-4.30 (-16.93 – 8.33)	0.493	-5.60 (-15.15 – 3.94)	0.241	-5.56 (-21.34 – 10.22)	0.479
Head size ≥ 50	-6.70 (-16.44 – 3.15)	0.178	2.60 (-11.20 – 16.41)	0.704	-0.23 (-11.11 – 10.65)	0.966	-1.07 (-18.66 – 16.51)	0.902
Constant	100.9		93.49		96.76		90.47	

B = coefficient
* The 35 - 45° inclination angle was used as reference
Abbreviations: HHS = Harris Hip Score; HOOS = Hip disability and Osteoarthritis Outcome Score; ADL = Activity of Daily Living; QoL = Quality of Life, CI = Confidence Interval.

Table 3. Linear mixed model parameters estimates: Reversed HHS and HOOS in relation with cobalt and chromium (54 patients).

Parameter	HHS (n=306)		HOOS-ADL (n=226)		HOOS-pain (n=246)		HOOS-QoL (n=248)	
	Estimate (95%CI)*	P-value	Estimate (95%CI)*	P-value	Estimate (95%CI)*	P-value	Estimate (95%CI)*	P-value
Cobalt (n=286)	0.40 (-0.05 – 0.86)	0.083	-0,21 (-0,77 - 0,35)	0.453	0,13 (-0.25 - 0.52)	0.494	0,16 (-0.44 - 0.77)	0.592
Chromium (n=291)	0.19 (-0.11 – 0.50)	0.212	-0.20 (-0.58 - 0.18)	0.304	-0.10 (-0.38 - 0.18)	0.474	0.13 (-0.30 - 0.56)	0.547
Cobalt 1 year before (n=282)	0.90 (0.49 – 1.32)	<0.001	0.37 (-0.22 - 0.95)	0.215	0.43 (0.00 - 0.86)	0.05	0.92 (0.25 - 1.59)	0.008
Chromium 1 year before (n=287)	0.33 (0.02 – 0.64)	0.036	0.20 (-0.23 - 0.62)	0.36	0.23 (-0.07 - 0.54)	0.129	0.22 (-0.25 - 0.69)	0.355

* A positive (±) value in front of the estimates shows the direction of the relationship with the dependent variable, which in this case is the reversed HHS or HOOS subgroup.
For example; the positive estimate of 0.40 means that increasing cobalt with 1 part per billion the HHS decreased with 0.40 points.
For each patient reported outcome and parameter separate models were used (4 models).

Survival analysis and Cox regression analysis.

The adjusted ten-year survival rate was 74.2%, whereas the unadjusted implant survival analysis showed an overall ten-year survival of 64.9% (95% CI 52.5 to 77.6). For females and patients with an acetabular inclination angle ≥ 45°, this survival rate was even lower at 52.8% and 51.9%, respectively. Figure 3 shows the curve and Table 4 shows the cumulative survival for all years. The Cox's regression model indicated that a higher last measured serum Co level was associated with a higher likelihood for revision surgery (HR 1.08 (95% CI 1.01 to 1.15); p = 0.028). Table 5 shows detailed information of all 17 wear-related revisions. Nine (52.9%) patients had an inclination angle above 45° and two (11.8%) patients below 35°. Nine revised patients had pathological proven ARMD, of whom seven had an inclination angle above 45° (Table 5). With the smaller head sizes and coverage angles, the effective inclination angle would be even greater in theory. The mean pre-revision Co and Cr levels were 6.85 (0.63 to 24.73) and 8.97 (0.9 to 32.9), respectively. Females were not significantly more susceptible for revision compared to males (HR 1.37 (95% CI 0.51 to 3.67); p = 0.538). This was also true for patients with an inclination angle > 45°; they were not more likely to undergo a revision procedure (Table 6).

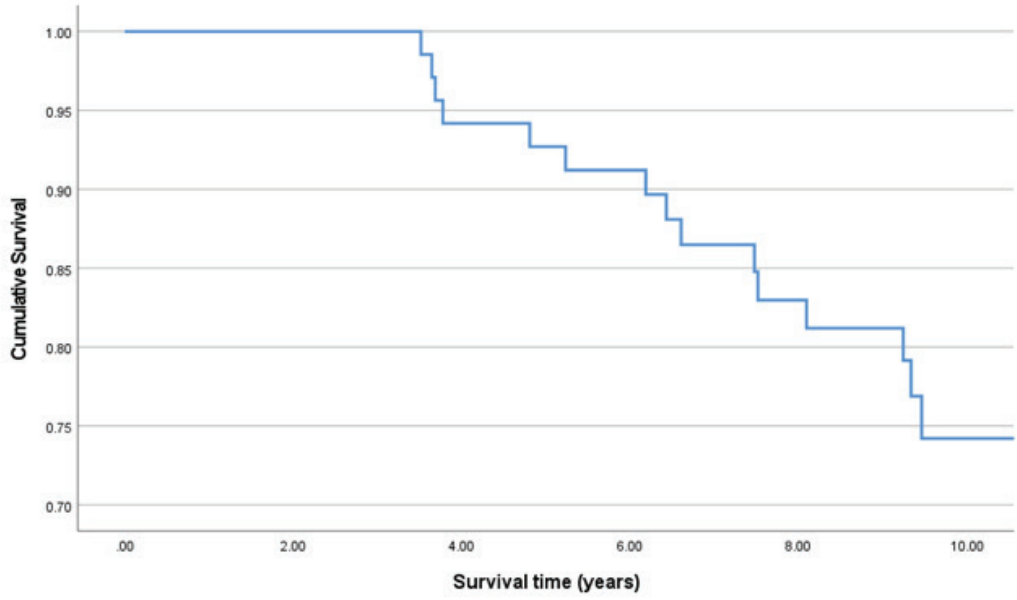

Figure 3: Adjusted cumulative survival curve.

Table 4. Cumulative Survival Analysis

	Adjusted	Unadjusted	95% CI
1-year	100%	95%	(89.9 - 100)
2-year	100%	94%	(87.6 - 99.8)
3-year	100%	94%	(87.6 - 99.8)
4-year	94%	86%	(77.0 - 94.2)
5-year	93%	84%	(75.0 - 93.0)
6-year	91%	82%	(72.9 - 91.7)
7-year	87%	77%	(66.6 - 87.8)
8-year	83%	74%	(62.8 - 84.8)
9-year	81%	72%	(60.7 - 83.5)
10-year	74%	65%	(52.5 - 77.6)

Abbreviations: CI = Confidence Interval.

Table 5. Details of all wear-related revised Articular Surface Replacement hip resurfacing arthroplasties (n = 17).

Head size, mm	Coverage angle, degrees	Gender	Inclination angle, degrees	Survival, years	Cobalt, ppb*	Chromium, ppb*	ARMD
43	150	F	50.37	3.69	1.13	3.5	yes
45	151	F	47.7	4.81	5.96	13	yes
47	153	F	42.05	3.64	2.53	3.2	no
		F	40.57	11.36	17.35	16.22	no
		F	44.89	9.46	24.32	18.6	unknown
		F	46	6.18	7.61	14.4	yes
49	151	F	56.08	6.43	1.91	2.1	no
		M	50.82	7.47	24.73	32.9	yes
51	152	M	32.72	3.78	2.93	7.7	no
		F	32.81	9.24	5.17	9.1	no
		F	38.3	8.09	1.65	4.6	yes
		M	39.94	3.52	3.46	5.3	no
		M	47.85	5.23	2.83	1.6	no
		M	62.29	6.6	5.37	9.88	yes
		M	45.97	13.41	7.35	6.66	yes
53	153	M	38.65	7.52	0.63	0.9	yes
		M	53.61	9.33	1.45	2.8	yes

*Pre-revision measured value.
Abbreviations: ppb = parts per billion; ARMD = Adverse Reaction to Metal Debris

Table 6. Cox's regression model with revision surgery as outcome

	HR	95% CI	p-value
Female gender	1.37	(0.51 - 3.67)	0.538
Inclination angle			
35 - 45°	Reference		
<35°	1.56	(0.30 - 8.21)	0.597
>45°	2.55	(0.87 - 7.5)	0.088
Cobalt*	1.08	(1.01 - 1.15)	0.028

*Last measured cobalt used.
Abbreviations: HR= hazard ratio; CI = Confidence Interval.

Discussion

Our ten-year follow-up data of the ASR-HRA, has shown that an increase in serum level of Co and Cr can predict a deterioration in HHS and HOOS outcome scores in the following year. We also found that a high last-measured Co level was associated with a greater likelihood for revision surgery with an adjusted ten-year survival of 74.2%.

Due to the high failure rates in MoM bearings, defined follow-up protocols and decision-making guidelines are needed for surgeons to effectively follow up their patients, especially since many surgeons may experience uncertainty with managing patients with MoM bearings in relation to when to recommend revision arthroplasty and diagnosing ARMD. As such, patients are currently subjected to continuous PROM evaluation with serum Co and Cr level measurement, but the relationship between these two entities is unclear. This study shows that increasing serum metal Co and Cr levels can predict deterioration in PROMs, and therefore can be used as a clinical tool to manage patients' and surgeons' expectations. Most national and professional bodies advise regular outpatient review and monitoring of patients with a MoM bearing. Yearly outpatient review with PROMs and serum Co and Cr level measurements are obtained and used as a predictive tool for ARMD and revision [30]. Galea et al. [15] performed a three year follow-up study with a mean time of 7.4 years after the primary surgery of patients with an ASR hip arthroplasty. They found that serum metal ions Co and Cr tended to increase over time, while the PROMs did not change. Males in particular with an ASR-HRA maintained a good performance over time with high general health indicators. The increasing Co and Cr levels and steady PROMs suggests that patient symptoms may not completely reflect the implant performance; however, no significance was shown. Another recently published study examined the HOOS in HRA patients with or without ALTR or metallosis on MRI [31]. The authors showed a significant elevation of Co and Cr serum levels in patients who had an ALTR or metallosis on the MRI, compared to non-ALTR after one year of follow-up. A serum Co level of 4.7 ppb (SD 3.5) and Cr level of 4.7 ppb (SD 2.6) was reported for the ALTR group compared to a serum level of 1.8 ppb (SD 1.0) and 2.3 ppb (SD 0.5), respectively, in the non-ALTR group. However, there were no differences in other years of follow-up and no differences among the HOOS subscales between the two groups. In our study, we also found an overall increase in Co and Cr levels in the entire cohort, while the different PROMs remained largely unchanged. However, when we analyzed patients who underwent revision, we observed a more rapid increase in metal ion levels and lower PROMs over time compared to the non-revision group. The HHS and HOOS subscales also showed a more consistent value during the ten-year follow-up in patients not requiring revision compared to the revision group. With our linear regression model we showed that an increase of 1 ppb in serum Co and/or Cr levels leads to a decrease in the HHS and all HOOS subscales. These results did not reach statistical significance. As shown by our LMM, we found that an increase in serum Co levels in the preceding year before the PROMs correlated positively with a decrease in HHS and the HOOS subscales 'Pain' and 'QoL'. An increase in Co of 1 ppb predicts a drop of 0.9 points (95% CI 0.5 to 1.3) in HHS the next year. This positive association is also true for the subscale HOOS-Pain and HOOS-QoL with a decrease of 0.43 points (95% CI 0.00 to 0.86) and 0.92 points (95% CI 0.25 to 1.59), respectively. For the measured Cr levels, we found only a positive correlation within the HHS. This once more shows the importance of regular serum ion level control, especially for Co levels. The explanation as to why there was no correlation within the same year might be explained by the fact

that we correlated the difference between two different ion level measurements and the PROMs. If the increase in ppb was already significantly large one year before the PROM is taken, it might result in a smaller difference or steady state level of ppb the following year. In order to use these results in daily practice, we evaluated whether the increase in Co level met a minimal clinically important difference (MCID) in HHS and HOOS scores. For the HHS, Singh et al. [40] reported a MCID ranged from 15.9 to 18 points. This means that the Co level one year prior to the measured HHS should demonstrate a difference of at least 20 ppb to result in a clinically important change in HHS (MCID = 18 points). For the HOOS, the results reported by Ayers et al. [41] showed a MCID for HOOS-Pain of 10.42 and for HOOS-QoL of 12.66. With these data, we are able to state that a difference in Co level, one year prior to the HOOS measurement, of 24 ppb and 14 ppb will lead to a MCID in HOOS-Pain and HOOS-QoL, respectively.

Some of the known risk factors for failure in MoM bearings are design, female sex, and acetabular component position. Due to the specific design of the acetabular component in the ASR-HRA, perfect implant positioning is essential. The initial design concept of the sub-hemispherical ASR acetabular component design was to preserve acetabular bone stock and reduce metal wear due to a low clearance. However, studies showed that this design in particular, with a reduced arc of coverage and a contact patch to rim (CPR) distance < 10 mm, results in more edge loading and wear [6,42,43]. The CPR distance is dependent on the diameter of the acetabular component, the arc of coverage, and the inclination and anteversion angles [44]. Since the inclination and anteversion angles contribute to the CPR distance, a low CPR distance (< 10 mm) allows less margin for errors [18]. Depending on the acetabular component size, an ASR-HRA in 45° inclination can have an effective inclination of 60° or more. This shows that the Lewinnek's safe zone of acetabular component position (40° (± 10°) inclination and 15° (± 10°) anteversion) is narrower in the ASR-HRA compared to other designs [45,46]. The above-mentioned factors contributed to the high failure rate of the ASR-HRA. In our study, we found a mean unadjusted ten year survival rate for the ASR-HRA of 65%, which is consistent with earlier studies reporting values between 65% and 70% [16,17]. We also showed that a higher last-measured serum Co level was associated with a higher likelihood of revision surgery (HR 1.08 (95% CI 1.01 to 1.15)). There was no association with sex or inclination angle in our cohort. However, we did not calculate the effective inclination angles per different cup size.

Our study has some limitations. There was some missing data. We did not have constant yearly collections of PROMs and Co/Cr samples from our patient group. In some cases, the follow-up interval could be extended to two or three years, as recommended by the Dutch Orthopaedic Association, if the patient had no complications or signs failure at that stage. Another limitation is the small group of patients. Due to the product recall in 2010, we were unable to include the planned number of patients in our RCT, resulting in a relatively small cohort. This had consequences for our variables in the Cox regression analysis. We could not use more than three variables to protect the model for overfitting. However, patients and orthopaedic surgeons were both motivated to maintain a close follow-up, resulting in a valuable yearly prospective cohort with excellent data of Co and Cr values and PROMs over a mean time of ten years.

In conclusion, this study demonstrated a predictive effect of serum Co and Cr levels with deteriorating HHS and HOOS values for patients with a ASR-HRA. An increase in Co levels of at least 14 to 24 ppb can predict a clinical important decrease in HHS and HOOS one year later. A high serum level of Co is also predictive for revision surgery. Since there are still many ASR-HRAs in situ, and no clear long-term follow-up protocols are available, we believe regular review for patients with this type of bearing remains essential. For clinical practice, our findings show the importance of regular serum Co level measurement and clinical evaluation with PROMs. We believe the Cr levels are less predictive of failure in patients with an ASR-HRA. Surgeons must continue to be vigilant of future problems and keep patients properly informed. For patients with normal serum Co and Cr levels it might be safe to extend their outpatient review period up to two years to avoid unnecessary visits and costs.

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THA
MoM
ASR
PHACT
M2a
MAGNUM
Cr
Co
Cu

PART 4

General Discussion and
Future perspectives

CHAPTER 8

General discussion and conclusion

GENERAL DISCUSSION

This thesis documents a comprehensive analysis of two well-known Metal-on-Metal (MoM) hip bearings, specifically the Articular Surface Replacement (ASR, DePuy Orthopedics, Warsaw, Indiana, USA) Hip Resurfacing Arthroplasty (HRA) and the large head M2a-Magnum (Biomet Inc. in Warsaw, Indiana, USA) Total Hip Arthroplasty (THA). Our research aimed to contribute to the continuous quest for enhancing total hip prosthesis outcomes through investigating various factors, including component positioning optimization, mid- and long-term survival, specific wear analysis, wear-related issues, and their correlation with Patient-Reported Outcome Measures (PROMs).
We observed no significant improvement in direct postoperative positioning with the implementation of computer-assisted surgery (CAS) compared to conventional placement. Furthermore, our findings showed notably inferior survival rates compared to conventional THAs for the two MoM bearings. Our results also underscore the importance of regular follow-up assessments in hip implants with a MoM bearing, as we demonstrated a significant association between cobalt levels and long-term clinical outcomes.

The **first** part of the discussion focuses on evaluating the use of Computer-Assisted Surgery (CAS) to optimize implant positioning in the ASR HRA. The effectiveness of CAS and Robotic Hip Surgery (RHS) in achieving optimal component placement was examined in detail. In the **second** part, the survival and wear analysis of the large head M2a-Magnum THA were explored. This section examines the mid-term outcomes and the potential for wear-related complications associated with this particular bearing design. The **third** and final part of the thesis investigates the importance of regular serum cobalt (Co) and chromium (Cr) control in patients with MoM bearings. The significance of monitoring and managing serum metal ion levels, specifically Co and Cr, is thoroughly examined.

Part 1 – Optimizing component positioning in Metal-on-Metal Hip Arthroplasty

- Evaluate the effects of Computer-Assisted Surgery on component positioning in Metal-on-Metal Hip Resurfacing Arthroplasty.

Optimal placement of hip arthroplasties is crucial for their long-term success, particularly for Metal-on-Metal (MoM) bearings. Early studies on Hip Resurfacing Arthroplasty (HRA) have shown that non-optimal component positioning can lead to early failures such as femoral neck fractures, notching, loosening and impingement [1–4]. To improve accuracy in component placement, Computer-Assisted Surgery (CAS) was introduced for both HRAs and Total Hip Arthroplasties (THAs) [5–11]. **Chapter 2** described a multi-center randomized controlled trial (RCT) to evaluate the use of CAS on the placement of the femoral component in the Articular Surface Replacement (ASR) HRA (DePuy Orthopedics, Warsaw, Indiana, USA) . The RCT showed no benefit for the use of CAS in accuracy of placement of the femoral component in HRA compared to manual implantation. We examined the planned stem-shaft angle (SSA) and the final placement of the femoral component with a 3-degree accuracy, and in both groups no difference was observed. Unfortunately, the study was prematurely terminated because of the global recall of the ASR-HRA in 2010, leading to

a smaller patient population than initially calculated. This limited sample size may have hampered our statistical analysis and potentially led to a false negative outcome (Type 2 error). Nevertheless, considering the p-value of 0.592 for the mean degree difference between postoperative SSA and preplanned SSA, it is unlikely that a significant difference would emerge. Consequently, no other RCT has demonstrated the advantages of this CAS system in the context of HRA procedures.

The recall of ASR-HRA and ASR-THA marked the beginning of the decline for most MoM bearings. Unfortunately for the ASR-bearings, it was the 'new and improved' design that proved to be the cause of the high revision rates compared to other HRAs [12–14]. Wear analysis of the ASR-bearing design showed important flaws due to the sub-hemispherical shape, low clearance, reduced arc of coverage, and a small contact patch to rim (CPR) distance (≤10mm).
The CPR-distance represents the distance between the center of the contact patch, which is the specific area on the surface of the femoral head that comes into contact with the acetabular component, and the acetabular rim (figure 1). This distance is influenced by several factors, including the arc of coverage, the diameter of the cup, and the inclination/anteversion angles of the cup. The CPR-distance plays a crucial role in determining how susceptible the bearing is to edge loading, which refers to excessive stress placed on the outer edges of the bearing surfaces [15,16].

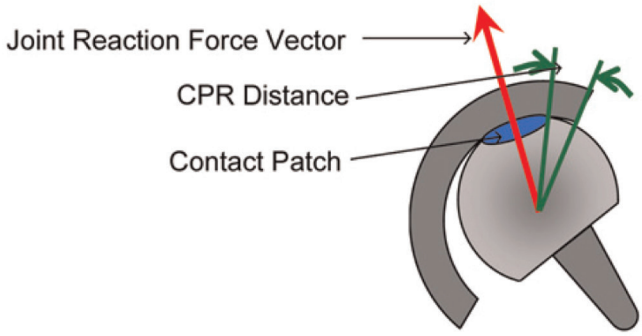

Figure 1. Schematic diagram of the CPR-distance [17].

Research has indicated that patients with a CPR-distance of 10 mm or less may face a substantially higher risk, up to 37 times, of elevated serum cobalt (Co) levels and up to an 11-fold increased risk of elevated serum chromium (Cr) levels when compared to patients with a CPR-distance greater than 10 mm [16]. As previously mentioned, the inclination and anteversion angles of the acetabular component also contribute to the CPR distance. It has been observed that bearings with a lower CPR distance have a narrower range of safe cup inclination and anteversion compared to other types of bearings [12.] In the case of ASR-HRA (with a CPR of ≤10mm), this means that the expected Lewinnek's safe zone for the position of its acetabular component is much narrower compared to other bearings. The presumed, and industry-advised, Lewinnek's safe inclination angle of 40 degrees (±10 degrees) and anteversion angle of 15 degrees (±10 degrees) do not apply to ASR-bearings [18,19]. All above-mentioned factors, including small acetabulum or female gender, can contribute to increased edge loading, excessive wear, and high failure rates [13,20].

These findings highlight the importance of optimal component positioning and emphasize the use of all available tools to improve it. Since the recall and understanding of various failure mechanisms, there has been a growing utilization of computer-assisted surgery (CAS) and Robotic Hip Surgery (RHS). Especially systems utilizing CT-guided navigation have promising perspectives. This technique has the potential to improve component positioning, resulting in fewer deviations from the pre-operative plan and, consequently, a reduction in postoperative malposition. Malposition, in this context, denotes the incorrect orientation of the femoral stem or acetabular cup concerning the patient's anatomy. Accurate component positioning is paramount for achieving good functional outcomes, reducing the risk of complications (impingement, leg length discrepancy or instability), and extending the lifespan of the hip prosthesis. Numerous studies have demonstrated that even experienced orthopedic surgeons and high-volume arthroplasty centers frequently encounter malpositioned components, particularly cups, when compared to surgeons utilizing navigation systems [21,22].

There are various types of navigation or robotic surgery systems available, including passive, active, and semi-active systems [22] .

- Passive robots, such as the da Vinci® Robotic Surgery System (Intuitive Surgical, Sunnyvale, CA), are utilized for tasks that remain under the continuous control of the surgeon, without any feedback loops. However, these robots are not used in orthopedic surgery.
- Active robots, like the ROBODOC (THINK Surgical Inc., Fremont, CA, USA), are designed to perform all the necessary bony preparation for the implantation of different arthroplasty components. These actions are preplanned, based on calculations of preplanned implant positioning.
- Semi-active robots, such as the MAKO system (Stryker Corporation, Kalamazoo, MI, USA), do require the involvement of the surgeon and utilize haptic feedback loops. These systems are characterized as robotic arm-assisted systems.

Although RHS systems are increasingly advocated by the industry and certain orthopedic hip surgeons, there remains a lack of conclusive evidence regarding their clinical benefits in terms of Patient-Reported Outcome Measures (PROMs) and overall survival rates [23]. A recent review by Sweet et al. showed that postoperative PROMs for patients with RHS THA are comparable to those of patients who received a manually implanted THA [23]. In a meta-analysis conducted by NG et al., it was found that RHS THA resulted in a moderate three-point improvement in Harris Hip Score (HHS), which did not exceed the threshold for minimal clinically important difference (MCID) and therefore lacks clinical relevance [24,25]. Furthermore, no significant difference was observed in short- and mid-term follow-up survival rates between the two groups [26].
The only demonstrated evidence in RHS lies in the improvement of implant position accuracy [23]. The previously mentioned Lewinnek safe zone is commonly used as a parameter for successful acetabular component implantation [18]. Several studies have demonstrated that the MAKO system achieves significantly more accurate cup placement within the safe zone, potentially resulting in lower dislocation rates compared to manual placement [27–29]. However, it should be noted that the presumed safe zones for acetabular component positioning may not be optimal for all bearing

types, as observed in the ASR-bearing design and individual patient variations. The increased focus on and insights into the dynamics of the spinopelvic plane have shifted the perspective on the importance of the Lewinnek safe zone concept. The spinopelvic mobility of each individual patient seems to be crucial in determining the optimal cup position, and its implications must be considered when aiming for the ideal safe cup position. None of the mentioned RHS systems address these dynamics concerning optimal cup anteversion and inclination. We could only find one study that investigated enhanced preoperative planning, taking spinopelvic tilt into consideration, which enhance the postoperative acetabular component placement but did not yield clinical benefits [30]. Robotic surgery in hip arthroplasty holds promising prospects according to manufacturers, despite the lack of high-quality evidence comparing RHS with manually implanted bearings. Nowadays, THA is already one of the most successful surgeries with long-term implant survival and low complication rates, making it challenging to further improve outcome with regards to PROMs or clinical outcome. Postoperative PROMs following manually placed THA are already excellent and 10 year implant survival exceeds 95% in national joint registries. Moreover, current reviews indicate an increase in operative time and significant cost implications associated with the use of these RHS surgical systems [21,22].

The CAS system used in the RCT presented in chapter 2 is now considered outdated and no longer utilized in hip surgery. While our RCT did not reveal any enhancements in femoral component positioning or PROMs, the ongoing technological advancements suggest the possibility of substantial advancements in RHS systems, which have the potential to significantly improve surgical outcomes. The integration of information regarding static and dynamic spinopelvic tilt, along with RHS systems, has the potential to align with the pre-planned position and thus optimize the postoperative component placement. This, in turn, helps reduce the risk of instability and dislocation and reduce the need for intraoperative adaptation ultimately resulting in enhanced outcomes and long-term survival. Coupled with intraoperative feedback during surgery, it facilitates a more personalized and ideal implant positioning for each individual patient. However, it is essential to maintain a critical perspective when evaluating new technologies. Prior to their adoption, it is crucial to test innovative treatment in a setting of informed consent and ensure that their clinical use is based on solid, evidence-based research.

Part 2 – Survival and Failure Analysis of a Metal-on-Metal Hip Arthroplasty

- Determine the early clinical outcome and survival of a large head Metal-on-Metal Total Hip Arthroplasty.

After the global recall of the ASR-HRA and ASR-THA implants, many orthopedic associations recommended a comprehensive evaluation and follow-up of patients with MoM bearings. In 2011, the Dutch Orthopedic Association advised an active review and monitoring of all patients with MoM-HRA and large-head MoM-THA. At that time, reports had already emerged concerning the high rates of revision in large-head MoM-THAs. In that same year, the British Medical Journal published a study highlighting a revision rate of 13.6% at seven years for various MoM-THAs, which varied among different manufacturers [31]. In contrast, revision rates for hip implants made from other bearings ranged from 3.3% to 4.9%. Bosker et al. reported a revision rate of 12% at 3.6 years

for the large-head M2a-Magnum implant (Biomet Inc., Warsaw, Indiana, USA) in their cohort of 108 patients. They also observed a significantly higher incidence of Adverse Reaction to Metal Debris (ARMD) formation (39%) compared to other large-head MoM bearings [32]. Similarly, Mokka et al. examined a cohort of 80 hips, with 54% demonstrating definite, probable, or possible ARMD. However, only three patients underwent revision due to ARMD [33].

In our study, conducted at the Reinier de Graaf Hospital, we examined 160 large-head M2a-Magnum bearings and observed a 5-year survival rate of 93%, with a ARMD prevalence of 8.75% [34]. It is important to note that we did not conduct ultrasound or MRI scans on all patients, which might have resulted in a lower overall prevalence of ARMD compared to other studies. As outlined in Chapter 3, the main reasons for revision within the initial 5-years were loosening, pain, infection, and pseudotumor formation.

When compared to 5-year survival data from the Australian register in 2015, all other bearing types (excluding the MoM bearings) exhibited a 5-year revision percentage ranging from 3.0% to 3.2% in patients with osteoarthritis. Furthermore, the 10-year survival of MoM bearings was still notably lower with a mean of 5.2% [35]. These findings clearly indicate the increased rate of revision in all the MoM bearings. However, we must also consider the impact of the worldwide news regarding the complications and risks associated with MoM bearings. In response to this information, some orthopedic surgeons promptly initiated revisions on all their MoM bearings, thereby inevitably contributing to higher revision rates compared to other types of bearing.

Other mid-term survival studies investigating the large-head M2a-Magnum implant have reported similar outcomes to our study. Mokka et al., conducted a review of 1188 patients (1329 hips) with the M2a-Magnum bearing. The mean follow-up time was 5.2 years, and they observed a 5-year survival rate of 93.3% (95% CI: 91.9% - 94.8%). Among the patients, 104 (106 hips) required revision surgery, with 33 patients (2.5%) undergoing revision due to ARMD [36]. Another study of 47 M2a-Magnum implants reported only 2 revisions during a 7-year follow-up period, resulting in a 7-year survival rate of 95.4% (95% CI: 89.1% - 100%) [37]. There was one study that reported a high mid-term revision rate of 11.5% at a mean follow-up of 5.4 years. However, this study had a small sample size of only 26 male patients, with two revisions performed for aseptic loosening and one for ARMD [38]. The same research group from Bosker recently published their findings on the 10-year survival rate of the large-head M2a-Magnum bearing. A revision percentage of 17.6% was reported, primarily attributed to pseudotumor formation (68%), followed by pain, infection, loosening, and osteolysis [39]. In our own study, which included data from a 10-year follow-up (see chapter 6), we observed a comparable revision percentage of 16.9%, resulting in the revision of 27 bearings. Among the revised bearings, 16 (59%) were confirmed to have ARMD [40]. These revision percentages are considerably higher compared to the 10-year survival data of other THA bearings, cemented and uncemented. In the 2022 annual report from the Dutch implant database, the 10-year revision percentages for all age groups were reported as 3.7% for cemented THAs and 4.7% for uncemented THAs [41]. Furthermore, a recent study by Pietiläinen et al. presented the 14-year survival of 1450 patients with an M2a-Magnum bearing, reporting a survival rate of 85% for hip revision due to any cause, and a 69% survival rate for revision specifically related to adverse events associated with ARMD event [42]. These findings highlight the unacceptably high failure rate associated with these MoM bearings.

- Study the causes of early failure and perform wear analysis on revised Metal-on-Metal bearings

As briefly discussed in Part 1, wear analysis, also referred to as "tribology," plays a crucial role in understanding the reasons behind the failure rates observed in certain bearing designs. Tribology is a scientific field that investigates the behavior of artificial surfaces in relative motion, employing wear simulators to measure wear, friction, and lubrication characteristics. In simulation research, the wear pattern of MoM bearings demonstrated a distinct "running-in phase" characterized by high initial wear, followed by a transition to a lower-wear steady-state phase. However, the duration and nature of this running-in phase varies among different MoM bearings, making precise wear prediction challenging. Some studies suggest a running-in period of approximately 500,000 to 1 million cycles, while others argue that this estimation may be inaccurate [43–45]. Moreover, there is also a debate regarding the wear rates during the running-in phase versus the steady-state phase, with some studies suggesting lower wear rates during running-in and higher wear rates during steady-state conditions [45,46]. Wear analysis of the ASR design revealed that the sub-hemispherical cup design, in particular, contributed to edge loading and increased wear [13,14,20]. Other critical factors influencing wear characteristics in all MoM bearings include clearance, coverage angle and CPR-distance [47].
Clearance refers to the difference in radius (radial clearance) or diameter (diametrical clearance) between the acetabular and femoral bearing surfaces, which significantly impacts lubrication (figure 2).

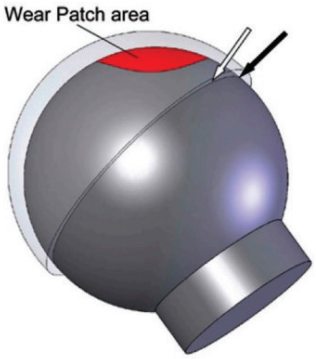

Figure 2: The clearance is difference in radius (radial clearance) or in diameter (diametrical clearance) between the acetabular (white arrow) and the femoral (black arrow) bearing surfaces. Lubrication of the articulation is achieved by fluid being entrapped in that inter-bearing space [49].

Excessive clearance (polar loading) leads to a small contact area during loading, resulting in high contact stresses and increased wear (figure 3A). Conversely, insufficient clearance (equatorial loading) causes the components to become jammed together during loading, also leading to increased wear (figure 3C). Ideally, a fluid film should form between the acetabular and femoral components, facilitated by a small wedge, to minimize wear [47]. The typical radial clearance for an ASR HRA was approximately 50µm (too little, figure 3C), compared with approximately 110µm for the Birmingham HRA (optimum, figure 3B) [12,48].

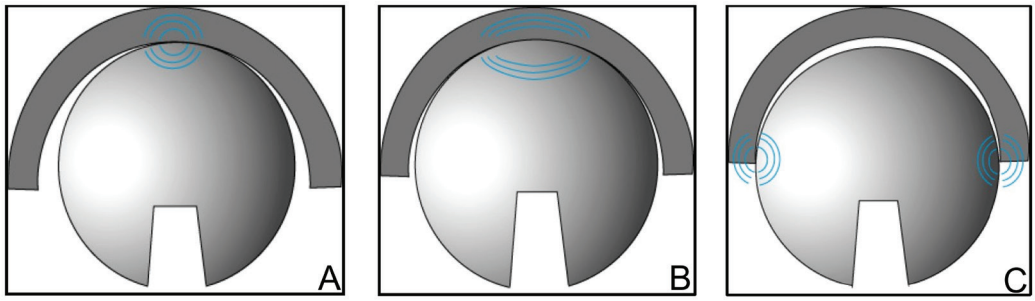

Figure 3: Schematic view of (A) too much (polar loading) clearance, (B) optimum clearance and (C) too little (equatorial) clearance [50].

The coverage angle is another significant contributing factor to the failure of MoM bearings due to its impact on the contact patch to rim (CPR) distance. As mentioned earlier in part 1, a smaller coverage angle results in a reduced CPR distance, and a CPR distance of less than 10 mm leads to edge loading, resulting in increased wear. Wear analysis showed that the ASR design had low coverage angles, which were identified as a major problem contributing to the failure of this particular bearing. However, even small-sized successful bearings like the Birmingham Hip Resurfacing (BHR, Smith&Nephew, London, UK) exhibited smaller coverage angles, making them more susceptible to edge loading and wear. Additionally, factors such as the diameter of the head and/or acetabular shell, higher inclination angles, or inaccurate anteversion angles also influenced the CPR, making these bearings also susceptible for failure [15,16,47]. All of the aforementioned findings underscore the necessity of conducting thorough research and possessing adequate knowledge regarding the diverse characteristics of new implants before introducing them safely to the market.

For large-head MoM bearings, wear can occur at two different locations: (1) the articulating surfaces of the head-cup and (2) the taper-trunnion junction. The phenomenon occurring at the taper-trunnion junction (crevice corrosion) is also known as "trunnionosis" or “cold welding”, and it is primarily observed in large head MoM bearings [49,50]. The taper-trunnion junction refers to the proximal conal extremity of the femoral stem (trunnion; male component) and the area inside the femoral head that receives the trunnion (taper; female component). The space between the taper and trunnion, called crevices, can create an environment that significantly affects the local chemistry. This includes the entrapment of fluid, leading to oxygen exclusion and pH reduction, as well as the entrapment of particles and corrosion products. The combined effect of a low pH environment

and the presence of these particles and corrosion products can induce cell death, necrosis, and tissue destruction, even at relatively low concentrations of Co and Cr ions. Crevice corrosion occurring at the taper-trunnion junction is regarded as one of the primary mechanisms underlying failure in large-head MoM total hip arthroplasties (THAs), contributing to the development of adverse reaction to metal debris (ARMD) [47,51,52]. Some researchers believe that corrosion at this connection may even be the main contributing factor to the development of ARMD [47,51]. Explant analyses conducted by Scholes et al. on five large-head M2a-Magnum bearings reported a mean wear rate of the articulating surfaces at 6.1 mm^3/year (ranging from 4.1 to 7.6 mm^3/year) [53]. The authors concluded that taper wear was relatively low compared to the wear observed on the head-cup surfaces, which appeared significant enough to be the primary cause of failure. This is in contrast to the taper wear observed in the ASR XL (mean 2.6 mm^3/year) and Pinnacle Articuleze (mean 2.8 mm^3/year) implants, both manufactured by DePuy Orthopedics [54]. However, as described by Scholes and discussed in **Chapter 4**, conducting a complete taper-trunnion wear analysis is often challenging as the stem (trunnion) often remains in situ after revision surgery [53,55]. Another important distinction among large-head MoM bearings is the type of taper used. To the best of our knowledge, all large-head bearings, except the M2a-Magnum, feature a Co/Cr taper, whereas the M2a-Magnum utilizes a titanium-titanium (Ti/Ti) taper. This difference may explain the significantly higher serum metal ion levels observed in other large-head MoM bearings such as the Zimmer Durom, Wright Medical Conserve Total, DePuy ASR XL, and Smith and Nephew Birmingham implants compared to the M2a-Magnum [56–58]. However, this does not account for the higher incidence of adverse reaction to metal debris (ARMD) reported in multiple studies specifically associated with the M2a-Magnum bearing compared to others [32,33,36,39]. We hypothesize that the observed correlation between the M2a-Magnum bearing and lower levels of serum metal ions, as well as the higher incidence of ARMD can potentially be attributed to the Ti/Ti taper. Our tissue analyses of the M2a-Magnum revealed remarkably elevated titanium levels, indicating significant wear in the taper-trunnion junction [55]. This finding highlights the importance of comprehensive wear analyses that encompass not only the taper connection but also the trunnion. It emphasizes that examining the taper connection alone is insufficient. Furthermore, while most studies on MoM bearings primarily examine Co and Cr levels in relation to ARMD, our research demonstrates that Ti can induce a similar tissue response and contribute to the development of ARMD. Taper-trunnion wear in the large-head M2a-Magnum bearing is considerably underappreciated but serves as a significant factor in bearing failure. This junction, coupled with the wear issues affecting both the head and cup components, has been the root cause of elevated serum metal ion levels observed in all large head MoM bearings. Consequently, these concerns have prompted their discontinuation in hip surgeries worldwide.

We observe a similar concern emerging in recent literature regarding other bearings, such as metal-on-polyethylene (MoP) or (modular) dual mobility (DM) implants. This phenomenon is referred to as "mechanically assisted crevice corrosion" (MACC) occurring at the taper-trunnion junction or between the metal liner and metal shell in modular DM implants [59–61]. These modular junctions have been implicated as potential sources of unexplained hip pain, elevated levels of Co and Cr, and the development of ARMD. Due to the prevalence of stems and trunnions

remaining in situ during revision surgery, verifying wear analyses related to this interaction is challenging. Nevertheless, with advancements in bearing technology and tribology research, it is crucial to consider all different wear sites and comprehend the impact of any modifications in the design of new implants.

Part 3 – Significance of Serum Cobalt and Chromium in Metal-on-Metal Hip Arthroplasty

- Investigate the differences in serum metal ion levels during long-term follow-up.
- Evaluate the utility and predictive significance of routine monitoring of serum metal ion levels.

Due to wear and corrosion in MoM bearings, Co and Cr particles are released, which can lead to local and systemic adverse effects. The released Cr ions typically exist in the form of trivalent Cr^{3+} ions, which have limited availability for binding with biomolecules (such as proteins, RNA, and DNA) both intra- and extracellularly. The unbound free Co^{2+} ions, on the other hand, remain soluble for a longer duration and have the potential to bind with biomolecules, potentially leading to systemic toxic effects [47].
The systemic toxicity caused by Co release from hip bearings is known as Prosthetic Hip-Associated Cobalt Toxicity (PHACT) [62,63]. Patients with PHACT demonstrate a wide range of symptoms, including neuro-ocular toxicity (e.g., ototoxicity, tinnitus, vertigo, blindness), cardiotoxicity, and thyroid toxicity [62,64]. Chapter 5 provides a detailed description of the most commonly reported symptoms in patients with PHACT and the types of bearings associated with these symptoms [64]. Co toxicity is frequently observed in primary MoM bearings or revised fractured Ceramic-on-Ceramic (CoC) bearings.
The most frequently reported symptoms are related to the sensory system (24%) and involve hearing and visual impairment or loss. Other commonly reported symptoms are of a neurological nature (19%), including cognitive deficits, memory impairment, and concentration difficulties, as well as cardiovascular nature (22%), such as dyspnea, heart failure, and cardiomyopathy. Unfortunately, the literature does not provide a clear threshold level for Co concentration due to the substantial variability in reported serum Co concentrations in the literature.
In MoM bearings, the design, size and the positioning of the bearing components are the three major factors that contribute to excessive wear. The formation of ARMD, resulting from wear debris, is more prevalent in smaller-sized bearings and patients with developmental dysplasia of the hip (DDH) and/or post-traumatic osteoarthritis [47,65]. This can be attributed to the challenges associated with surgical approaches and exposure in such cases, particularly after previous reconstructions. These findings also provide support for the higher risk of excessive wear and ARMD in MoM bearings among females. Females are more frequently diagnosed with DDH, exhibit higher anatomical hip anteversion, and need smaller-sized bearings [47,66].

In order to identify patients with potential failure of their MoM bearings and the development of ARMD, specific follow-up protocols have been recommended by various countries and orthopedic societies. These protocols typically include PROMs, serum Co and Cr levels controls, and additional imaging such as ultrasound or MARS-MRI/CT. Increased levels of Co and Cr are primarily attributed

to edge loading, excessive wear or crevice corrosion at the taper-trunnion junction (large-head MoM-THA). Therefore, elevated levels indicate a possible failure of the implant. Within the literature, Co and Cr measurements are expressed using different units. These measurements can be found in various studies in both nmol/L and µg/L. To provide clarity, the following conversion table is presented below.

	Cobalt	Chromium
Molar mass (g/mol)	58.993	51.996
Molar mass (nmol/L)	0.059	0.052
nmol/L	= 1 µg/L / 0.059	= 1 µg/L / 0.052
µg/L (parts per billion)	= 1nmol/L x 0.059	= 1nmol/L x 0.052

Unit conversion table.
Abbreviations: g = gram; nmol = nano mol; L = liter; µg = microgram

In a recent review by Pijls et al., 11 registries from the Network of Orthopaedic Registries (NORE) were surveyed to describe their national follow-up guidelines for patients with MoM bearings. Minor variations were observed among the different national registries regarding follow-up time/frequency and the use of a safe upper limit (SUL) for serum Co and Cr. Most commonly, the advised assessments included serum Co and Cr level measurements and additional MARS-MRI imaging [67]. However, the differences in SULs for serum metal ions may account for variations in revision rates reported in the literature. For instance, the guidelines of the Medicines and Healthcare product Regulatory Agency (MHRA) from the United Kingdom suggest a SUL of 7 parts per billion (ppb) for both Co and Cr, which is higher than the recommendations in other guidelines [67,68].
In 2013, van der Straeten et al. established SULs for serum Co and Cr in HRAs. These levels were calculated based on a cohort of patients with unilateral ASR-HRA (Cr < 4.6 µg/L; Co < 4.0 µg/L) or bilateral ASR-HRA (Cr < 7.4 µg/L; Co < 5 µg/L) [68]. However, since these SULs were derived from the worst-performing MoM bearing, a direct comparison to other bearings may be inaccurate. Given that each MoM bearing has its own running-in and steady-state phases, unique designs, and wear patterns, it is essential to define bearing-specific SULs. For instance, the Birmingham Hip Resurfacing (BHR) has demonstrated superior outcomes compared to other HRAs and remains the sole HRA currently in use. Consequently, different SULs might be applicable for this prosthesis as an indication of potential issues. The recent review by Pijls et al. recommended the use of two different levels: levels below 2 ppb (no clinical concern) and levels between 2 and 7 ppb (clinical concern). Nevertheless, only a few registries have implemented changes to their protocols accordingly. In addition to these existing recommendations, we propose the implementation of bearing-specific SULs for monitoring serum Co and Cr levels. This is particularly relevant for large head MoM-THA, where some studies have reported higher serum metal ion levels compared to HRAs [69,70]. The elevated levels in large head MoM-THA are likely attributed to trunnionosis/crevice corrosion in the taper-trunnion (Co/Cr or Ti/Ti) connection. However, differences among various large head MoM-THA designs also indicate the need for specific SULs tailored to each bearing. In **Chapter 6**, we presented the bearing-specific SULs for the large head M2a-Magnum THA, which were determined as 4.1 ppb for Co and 4.2 ppb for Cr [40]. Other studies also support the adoption of bearing-specific SULs to enhance the detection of ARMD and improve revision outcomes [71–73].

However, it is important to note that elevated serum Co and Cr levels are only relative indications for revision, and other factors should be considered as well. Notably, elevated Co and Cr levels appear to be correlated with PROMs. As discussed in **Chapter 7**, an increase in serum Co and/or Cr levels predict a decline in the Harris Hip Score (HHS) and Hip Disability and Osteoarthritis Outcome Score (HOOS) in the following year. In our research, Co levels were shown to be the most important predictor for early failure detection and potentially the formation of ARMD.

As the long-term effects of prolonged exposure to elevated Co and Cr levels remain uncertain, ongoing research and follow-up are essential. Therefore, we recommend regular follow-up for all patients with a MoM bearing still in situ. We also emphasize the need for standardized international guidelines, ideally bearing-specific, for the follow-up of MoM patients. Follow-up protocols and acceptable levels of Co and Cr can vary internationally, which can have an impact on the outcomes of bearing survival and, ultimately, patient outcomes. Standardized international guidelines should recommend lifelong follow-up for MoM patients. Regular outpatient visits should be scheduled at intervals of 2-3 years for asymptomatic patients with Co and Cr levels below the SUL. For this specific type, the large head M2a-Magnum THA, SULs can be adhered to as proposed: 4.1 ppb for cobalt and 4.2 ppb for chromium. If a deviation is detected in any of these suggested assessments, further investigation, possibly involving MARS-MRI, should be considered to determine whether the prosthesis can be retained, and follow-up intervals should be intensified accordingly. It is of utmost importance to provide patients and surgeons with bearing-specific data that can be used in bearing-specific guidelines and assist in determining the optimal timing for potential revision surgery. Patient complaints/symptoms, PROMs, and additional imaging play all crucial roles in the decision-making process. All these factors should be incorporated into a patient- and bearing-specific follow-up protocol and thoroughly documented. Together with the patient, the surgeon can decide whether or not to proceed with revision after obtaining informed consent and discussing potential risks and complications.

Conclusion

Overall, this thesis contributes valuable insights into the outcomes and control measures related to MoM bearings, aiming to improve patient care and to inform orthopedic surgeons. Failure in hip arthroplasty surgery is a complex process influenced by multiple factors. It depends on three main elements: the patient, the implant, and the surgeon. This holds true not only for the failure of hip bearings in general but also for the development of Adverse Reaction to Metal Debris (ARMD). As demonstrated in this thesis, the failure of a MoM-HRA or large head MoM-THA or development of ARMD is dependent on:

1. Patient factors: Certain patient characteristics, such as female gender, young age, and hip dysplasia, have been associated with an increased risk of failure and adverse reactions in MoM bearings.
2. Implant factors: Tribology (the study of friction, lubrication, and wear) showed that implant features (CPR, clearance and coverage angle) play a significant role in the failure of hip bearings.
3. Surgical factors: The surgical technique, choice of implant and decisions made by the surgeon (e.g. inclination and anteversion angles of the cup) can influence survival.

Orthopedic surgeons play an essential role in the success or failure of hip arthroplasty. Their decisions regarding patient selection and implant choice have a direct impact on outcomes. The accuracy of component positioning is essential, and advancements such as robot-assisted surgery hold promise for improving surgical precision, although further research is needed to validate its benefits in hip arthroplasty. Tribology research, RSA studies and wear analysis are also essential aspects of our orthopedic practice. These areas of study should receive greater attention and be factored into our decision-making processes. While new implants and innovations can lead to improved outcome, caution should be exercised when implementing changes. Thorough knowledge on above mentioned factors and intelligent introduction on the market is important.

For patients with MoM bearings still in situ, the development of a clear algorithm for monitoring and follow-up is crucial. Each patient and bearing exhibit unique wear patterns and failure rates, underscoring the importance of bearing-specific protocols. Early detection of failure of the MoM bearing may be associated with improved outcome. Serum metal ion levels have been shown to be reliable markers for indicating wear and failure, making them an essential component of follow-up protocols. There is even be a correlation between elevated serum metal ion levels and different PROMs. Therefore, patient characteristics, PROMs, pain and function, implant positioning (especially the acetabular shell), and serum Co and Cr levels are all essential parameters to monitor during follow-up. In light of the uncertain long-term effects and anticipated wear, it is advisable to maintain lifelong follow-up as long as the MoM bearing is in situ. Regular monitoring is crucial to avoid delays in detecting bearing failure. For ASR-HRA and the large head M2a-Magnum THA, a recommended follow-up interval of at least every two to three years remains effective in predicting prosthesis failure in a timely manner. Our data have shown that even after 10 years, some prostheses still exhibit elevated levels of cobalt and chromium. Furthermore, we do not have information on how the wear of these prostheses increases over the years

The decision to revise a MoM bearing should be made through a shared decision-making process between the surgeon and the patient. Revision surgery should be considered in patients with a painful hip and/or elevated levels of Co and/or Cr, along with local or systemic complaints. Revision surgery can stop local progression, but it cannot reverse soft tissue damage. Systemically, it can reduce Co and Cr levels and alleviate most neurological, thyroid, and cardiac symptoms associated with systemic toxicity. However, some damage caused by high Co and Cr levels may be irreversible.

CHAPTER 9

Future perspectives

FUTURE PERSPECTIVES

Looking ahead to the future, what insights have we gained from the challenges encountered with Metal-on-Metal (MoM) bearings?

The utmost lesson that emerges from all the issues associated with MoM bearings is the importance of a careful and thorough approach to introduce new implants. It is essential to exercise caution in adopting new advancements as long as their superiority over existing methods has not been unequivocally demonstrated. Although the utilization of MoM-HRAs has significantly declined, continued research in this area remains necessary, as some bearings are still in use. Currently, the Birmingham Hip Resurfacing remains the most used MoM-HRA. Data from the Australian registry indicate a comparable 5-year cumulative percentage of revision for primary HRA (3.1%; 2.8 – 3.4) and THA (2.9%; 2.8-2.9) in patients with osteoarthritis. However, for all other primary diagnosis (e.g., osteonecrosis or developmental dysplasia), the revision percentage is notably higher. Additionally, at 10-years, the revision percentage in HRA compared to THA is 6.1% versus 4.4%, and at 15 years, it is 9.0% versus 6.3% for patients with a primary diagnosis of osteoarthritis. Furthermore, other HRA-bearings, such as Ceramic-on-Ceramic HRAs, are being promoted by some surgeons, particularly for female patients and smaller sizes. However, the use of these new bearings should be limited to well-designed research settings with full patient consent. Close follow-up and meticulous documentation of possible complications and implant survival are imperative.

Based on our studies there seems to be no place for the use of any HRA at this stage due to their narrow indications, high risk of complications and limited benefits. In my opinion, the potential benefits for younger patients do not outweigh the associated risks. As described in this thesis, both MoM HRA and large head MoM bearings have a higher risk of revision in the early-, mid- and late-terms. Moreover, they do not demonstrate superior PROMs, and patients with these implants face an increased likelihood of local and systemic complications due to elevated serum Co and Cr levels. Other lessons learned from our research underscore the essential significance of prosthesis design and the potential for wear to occur at any point where motion is present. Notably, even minor movements, such as that observed in the taper-trunnion junction of large head MoM bearings, can lead to substantial wear-related issues.

It seems justified to assert that, at this moment, HRA (MoM or CoC) should exclusively occur within the context of scientific research, enabling the acquisition of robust data that either supports or refutes the beliefs of orthopedic surgeons who advocate for this bearing. Additionally, the use of robotic surgery may offer significant improvements in the precise placement of HRA components. However, the utilization of RHS in the implantation of various types of bearings still requires additional validation. There is a lack of studies investigating better survival outcomes, and it is necessary to demonstrate that longer operation time and higher costs justify its use. Radiostereometric analysis (RSA) offer a solution for this purpose and complement the research to justify the use of Robotic Hip Surgery (RHS). RSA is currently considered the gold standard for evaluating the fixation of new implants.

In addition to ensure precise component positioning and stability with RHS, RSA can offer a reliable assessment of implant fixation and survival in cases involving robotic techniques. Hence, investigating RHS through a randomized controlled trial is warranted. Regarding the large head MoM bearings our research suggests that they currently offer no added value compared to the existing highly crosslinked polyethylene liners and, as a result, should no longer be implanted, even in the young patient population.

National Joint Registers and Orthopedic societies may play an important role in providing guidance and advice to orthopedic surgeons. With use of registry data, well-founded research can be carried out utilizing all data provided by the national orthopedic surgeons. The significance of their contribution is exemplified by the Australian register (AOANJRR), which was the first to raise concerns regarding all large-head MoM bearings in their Annual Report of 2009 [74]. The documentation of long-term clinical follow-up, implant characteristics, implantation techniques and fixation methods, are important tools to select the best product for each individual patient.
Good documentation of new products and implants has shown to be of great importance. As shown with the Metal-on-Metal bearings, the product worked well in laboratory tests and in preliminary research done by the inventors. This made all medical authorities approve the use of these bearings. Unfortunately, it emerged as one of the largest failures in the field of orthopedics, leading to widespread use, followed by discontinuation, recall and patient harm. As we learned our lessons, since 2021 all orthopedic implant manufactures need to do post-market surveillance of their new products and demonstrate the clinical safety of their products on a yearly basis. This regulation has been made mandatory by the Medical Device Regulation (MDR) [75]. This specific implant monitoring can identify underperforming bearings and take immediate action.

In conclusion, as orthopedic surgeons, we have a responsibility of informing patients about the potential treatment options, expected clinical improvement as well as the associated risks and complications. Furthermore, it is essential that we continually monitor and critically assess our own actions and treatments. As our oath state; we should abstain from all intentional wrong-doing and harm, and therefore, we must always prioritize the health of the patient.

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CHAPTER 10

Summary (also in Dutch)

SUMMARY

The number of total hip arthroplasties (THAs) continues to increase worldwide. This is primarily due to its established success as a treatment for patients suffering from hip joint osteoarthritis. Especially for younger patients with severe hip osteoarthritis, a long prosthesis lifespan is of great importance. With heightened expectations for the longevity of prostheses, these patients are more likely to undergo additional surgical interventions during their lifetimes. Consequently, there is a continuous pursuit of solutions tailored to this cohort, including the introduction of Metal-on-Metal (MoM) articulations into the market.
This thesis is centered around diverse MoM bearing configurations, encompassing hip resurfacing- and large head THA articulations. Various aspects are examined, ranging from the optimal positioning of these prostheses, to their long-term survival and outcomes assessed through Patient Reported Outcome Measures (PROMs), as well as the importance of follow-up evaluations involving serum cobalt (Co) and chromium (Cr) measurements.

Part 1. Optimizing component positioning in Metal-on-Metal Hip Arthroplasty

- Evaluate the effects of Computer-Assisted Surgery on component positioning in Metal-on-Metal Hip Resurfacing Arthroplasty.

Chapter 2: No added value for Computer-Assisted Surgery to improve femoral component positioning and Patient Reported Outcomes in Hip Resurfacing Arthroplasty. A multi-center randomized controlled trail.

This chapter introduces one of the early instances in which Computer-Assisted Surgery (CAS) was utilized to achieve precise positioning of the femoral component in ASR Hip Resurfacing Arthroplasty. In this multicenter, single-blinded, randomized controlled trial, we investigate the potential improvement in femoral component placement through CAS, comparing it with manual placement. The primary outcome measure is defined as a deviation of up to 3 degrees between the postoperative Stem Shaft Angle (SSA) and the preplanned SSA. Additionally, we present Patient-Reported Outcome Measures (PROMs), which include the Hip disability and Osteoarthritis Outcome Scale (HOOS), Harris Hip Score (HHS), and Visual Analogue Scale (VAS) pain score.

Conclusion and Recommendations: Our cohort analysis revealed no significant differences between the two groups, indicating that there are no advantages to using CAS for femoral component placement in HRA. Consequently, there remains insufficient justification for integrating CAS to enhance component placement or enhance PROMs in hip arthroplasty surgery.

Part 2. Survival and Failure Analysis of Metal-on-Metal Hip Arthroplasty

- Determine the early clinical outcome and survival of a large head Metal-on-Metal Total Hip Arthroplasty.
- Study the causes of early failure and perform wear analysis on revised Metal-on-Metal bearings.

Chapter 3: A 5-year survival analysis of 160 Biomet Magnum metal-on-metal total hip prostheses.

Between 2006 and 2010, we implanted 160 large-head Magnum M2a (Biomet Inc., Warsaw, Indiana, USA) MoM THAs in 150 patients in the Reinier de Graaf Hospital. Given the established high failure rates and the prevalence of adverse reactions to metal debris (ARMD) in all large-head MoM bearings, we conducted comprehensive patient reviews in response to an advisory from the Dutch Orthopaedic Association (NOV). This chapter elucidates the survival analyses of this first review, extending over a mean follow-up duration of 6.1 years (range: 4.8-8.4 years). Our evaluation enclosed clinical and radiographic assessments of the bearings, serum cobalt (Co) and chromium (Cr) level determinations, as well as hip ultrasounds. Additionally, when indicated, supplementary Metal Artifact Reduction Sequence (MARS)-MRI or CT scans were performed. Upon assessment, a total of 13 bearings (8.1%) qualified for revision. Pseudotumor formation constituted the predominant reason for revision. The cumulative survival rate after 5 years was 93.1% (95% CI: 88.3-98%). Reasons for revision included loosening, pain, infection, and pseudotumor formation.

Conclusion and recommendations: In patients with a large head M2a Magnum MoM bearing, pseudotumor formation is a significant risk. A total of 8.75% of the patients were diagnosed with pseudotumor formation after the first review. Our findings underscore the importance of a comprehensive follow-up protocol for large-head MoM bearings to identify and manage early complications.

Chapter 4: Clinical and Wear Analyses of 9 Large Metal-on-Metal Total Hip Prostheses.

This prospective study presents the analysis of 9 revised large-head M2a Magnum bearings from the preceding chapter. An enhanced understanding of failure, wear rate and clinical presentation is relevant to understand and predict the outcome of hip bearings. Our wear analyses were conducted at the Biomechanics Section of Hamburg University of Technology, Germany. The bearings had a median survival of 41 months. Most bearings showed signs of wear, however with a great diversity in clinical analysis. A clear correlation between the serum Co and Cr levels and wear rates did not emerge. Patients exhibiting high inclination angles exhibited the most pronounced cup wear area ratios. Moreover, cases of high head wear ratios coincided with elevated serum Co and Cr levels. One remarkable discovery was the notable presence of titanium in both fluid and tissue analyses. These elevated titanium levels suggest a substantial degree of wear occurring at the taper-stem junction (trunnionosis). This phenomenon can be attributed specifically to the fact that the junction in this specific bearing is composed of titanium alloys.

Conclusion and recommendations: Our revised bearings exhibited diverse wear patterns, which correlated with clinical variations, cup inclination angles, and serum levels of Co and Cr. Notably, high cup inclination angles were associated with the most significant cup wear area ratios. Wear analyses are of great importance for a comprehensive understanding of the complex mechanisms contributing to failure, particularly in patients with MoM bearings.

Part 3. Significance of Serum Cobalt and Chromium in Metal-on-Metal Hip Arthroplasty

- Investigate the differences in serum metal ion levels during long-term follow-up.
- Evaluate the utility and predictive significance of routine monitoring of serum metal ion levels.

Chapter 5: Prosthetic hip-associated cobalt toxicity: a systematic review of case series and case reports.

This chapter presents a review of prosthetic hip-associated cobalt toxicity (PHACT) in patients after hip arthroplasty. The systematic review was conducted adhering to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The most frequently implicated bearing types for PHACT were MoM (38 cases) and revised (fractured) ceramic-on-ceramic (CoC) bearings (32 cases). In the latter type, the fractured ceramic head was substituted with a metal head, leading to excessive wear due to small particles from the fractured ceramic head. The mean Co concentration in MoM bearings was 127.7 ppb, while for the revised fractured CoC bearings it was 1078.2 ppb. Unfortunately no clear safe Co threshold could be determined for either type of bearings. PHACT primarily causes symptoms in the neurological system, with 24% affecting the sensory system and 19.3% impacting the central/peripheral system. Cardiovascular symptoms ranked as the second most frequently reported systemic manifestation, at 22.1%.

Conclusion and recommendations: We strongly advise against employing a metal-based articulation following the revision of a fractured CoC bearing. For patients with a MoM articulation or those who have undergone a revision involving metal components after a fractured CoC bearing, consistent follow-up with annual serum Co level monitoring is recommended.

Chapter 6: Safe Upper Limits of Serum Cobalt and Chromium Levels for the M2a-Magnum Metal-on-Metal Total Hip Bearing: A 10-year Follow up study.

In this chapter, we present the long-term survival of our large head MoM cohort, as previously introduced in chapter 3. With our 10-year follow up data, with regular serum metal ion level controls, our aim was to establish a safe upper limit (SUL) for the Co and Cr levels in patients with this bearing. For this specific type of bearing, we identified bearing-specific SULs of 4.1 ppb for Co and 4.2 ppb for Cr. Our analyses additionally showed an elevated risk of revision surgery for ARMD among female patients and those with a cup inclination exceeding 45 degrees. Furthermore, a high last measured Co and Cr level is correlated with an increased likelihood of adverse reaction to metal debris (ARMD) related revisions.

Conclusion and recommendations: We recommend and advocate for a consistent follow-up and surveillance of patients with M2a-Magnum MoM bearings. This includes comprehensive clinical assessments with PROMs and monitoring of serum Co and Cr levels, while adhering to the proposed SULs of 4.1 and 4.2 ppb for Co and Cr levels, respectively.

Chapter 7: Are Serum Levels Cobalt and Chromium Predictors for Patient-Reported Outcomes Measures in the ASR™ Hip Resurfacing Arthroplasty? A 10-year Prospective Follow-up Study.

This chapter aims to describe the predictive value of increased Co and Cr levels in patients with an ASR-HRA for deterioration in HHS and HOOS subscales in the following year. Patients from the cohort introduced in chapter 2 underwent annual monitoring involving serum Co and Cr level control as well as PROMs. We found that an increase of 1 ppb in serum Co and Cr level correlated significantly with deterioration in the HHS within the subsequent year. This correlation was similarly evident in the sub-scores HOOS-pain and HOOS-quality of life. In addition, we also presented a comprehensive 10-year survival analysis, yielding a survival rate of 65% (95% CI: 52.5 to 77.6).

Conclusion and recommendations: The observed elevation of serum Co and Cr levels among patients with ASR-HRA serves as a predictive marker for the subsequent decline in both HHS and HOOS subscales over the following year. In light of these findings, we advocate for the sustained monitoring of patients with this particular bearing through the periodic assessment of serum Co and Cr levels alongside PROMs.

SAMENVATTING

Wereldwijd neemt het aantal geplaatste totale heupprotheses (THPs) bij patiënten met artrose van het heupgewricht toe. Dit is voornamelijk te danken aan het feit dat de THP operatie een van de meest succesvolle chirurgische interventies betreft. Met name voor de jongere patiënten met ernstige artrose van de heup is een lange levensduur van de prothese van groot belang. Zij hebben vaak hoge verwachtingen van de prothese en zullen in hun leven met grote waarschijnlijkheid nog een of meerdere operaties moeten ondergaan. Hierdoor wordt er voortdurend gezocht verbeteringen van deze behandeling voor deze specifieke groep, en zo werd ook de Metaal-op-Metaal (MoM) prothese ontwikkeld en op de markt gebracht. Bij deze prothese is zowel de heupkop als de heupkom van een metaallegering en wrijven deze twee metalen oppervlakken bij elke beweging over elkaar

Dit proefschrift richt zich op verschillende MoM protheses; de Heup Resurfacing Articulatie (Hip Resurfacing Arhtroplasty; HRA) en de grote kop THP. Diverse aspecten worden onderzocht, variërend van de optimale positionering van de prothese tot de lange termijn overleving daarvan. Bovendien worden de prothese-resultaten beoordeeld aan de hand van door de patiënt gerapporteerde uitkomstmetingen (Patient Reported Outcome Measures: PROM's), en wordt het belang van vervolgonderzoeken, waarbij het bloedserum kobalt (Co) en chroom (Cr) worden gemeten, benadrukt.

Deel 1. Optimalisatie van component positie bij Metaal-op-Metaal Heup Protheses

- Evaluatie van het effect van Computer Ondersteunende Chirurgie op component positionering bij Metaal-op-Metaal protheses

Hoofdstuk 2: Geen toegevoegde waarde van Computer Navigatie Chirurgie om de positionering van de femorale component en patiënt gerapporteerde uitkomstmetingen te verbeteren bij de Heup Resurfacing Articulatie. Een multicenter gerandomiseerde studie.

Dit hoofdstuk beschrijft een van de eerste voorbeelden waarbij Computer-ondersteunde Chirurgie (Computer-Assisted Surgery; CAS) werd ingezet voor het plaatsen van het femorale component bij de ASR HRA. Binnen dit multicenter, enkel geblindeerd en gerandomiseerd onderzoek werd gekeken naar de mogelijke optimalisatie van plaatsing van het femorale component van de ASR via CAS, waarbij we dit vergeleken met handmatige plaatsing. De primaire uitkomstmaat bestond uit een drempelwaarde van maximaal 3 graden afwijking tussen de postoperatieve Steel-Schacht Hoek (Stem-Shaft Angle: SSA) en de vooraf geplande SSA. Bovendien presenteren we PROMs, waaronder de Hip Disability and Osteoarthritis Outcome Scale (HOOS), Harris Hip Score (HHS), en de Visual Analogue Scale (VAS) pijnscore.

Conclusie en Aanbevelingen: Bij onze analyse vonden wij geen verschillen tussen de twee groepen en daardoor geen voordelen van het gebruik van CAS bij de plaatsing van het femorale component bij de ASR HRA werd vastgesteld. Er is onvoldoende bewijs om het gebruik van CAS

te rechtvaardigen bij de optimalisatie van plaatsing van de femorale component of om de PROMs te verbeteren.

Deel 2. Overlevings- en Faal-analyses bij Metaal-op-Metaal Heup Protheses

- Bepalen van de vroege klinische uitkomst en overleving van een grote kop Metaal-op-Metaal totale heup prothese.
- Onderzoek van de oorzaken van vroegtijdig falen en slijtage analyses op gereviseerde grote kop Metaal-op-Metaal protheses.

Hoofdstuk 3: De 5-jaars overlevingsanalyse van 160 Biomet Magnum Metaal-op-Metaal Totale Heup Protheses.

Tussen 2006 en 2010 hebben we in het Reinier de Graaf Gasthuis 160 grote koppen M2a Magnum (Biomet Inc., Warsaw, Indiana, VS) MoM THP's geïmplanteerd bij 150 patiënten. Gezien het hoge revisie percentages en de prevalentie van nadelige reacties op metaaldeeltjes (ARMD) bij grote koppen MoM protheses, hebben we alle patiënten opgeroepen voor poliklinische beoordeling als reactie op het advies van de Nederlandse Orthopedische Vereniging (NOV). Dit hoofdstuk bespreekt de overlevingsanalyse van de prothese na de eerste beoordeling met een gemiddelde follow-up periode van 6,1 jaar (bereik: 4,8-8,4 jaar). Onze evaluatie bevat de klinische en radiografische beoordelingen van de protheses, bepalingen van het serum Co en Cr, evenals een echografie van de heup. Bovendien werd, indien nodig, nog een aanvullende Metal Artifact Reduction Sequence (MARS)-MRI of CT-scan uitgevoerd. Na de eerste beoordeling kwamen in totaal 13 protheses (8,1%) in aanmerking voor revisie. Pseudotumorvorming was de belangrijkste reden voor revisie. Het cumulatieve overlevingspercentage na 5 jaar was 93,1% (95% betrouwbaarheidsinterval: 88,3-98%). Redenen voor revisie betroffen loslating, pijn, infectie en pseudotumorvorming.

Conclusie en aanbevelingen: Patiënten met een grote kop M2a Magnum MoM THP lopen een aanzienlijk risico op pseudotumorvorming . Na de eerste beoordeling werd bij 8,75% van de patiënten pseudotumorvorming vastgesteld. Onze bevindingen benadrukken het belang van een uitgebreid follow-up protocol voor alle grote kop MoM protheses om vroege complicaties te identificeren en te behandelen.

Hoofdstuk 4: Klinische en Slijtage-analyses van 9 grote koppen Metaal-op-Metaal Totale Heup Protheses.

Deze prospectieve studie presenteert de slijtage-analyse van 9 gereviseerde M2a Magnum protheses uit het vorige hoofdstuk. Een goed begrip van falen, slijtage en klinische presentatie is relevant om de uitkomst van heupprotheses te voorspellen. Slijtage analyses werden uitgevoerd aan de Biomechanica Sectie van de Technische Universiteit Hamburg, Duitsland. De protheses hadden een mediane overleving van 41 maanden. De meeste vertoonden tekenen van slijtage, zij het met een grote diversiteit in klinische analyse. Er kwam geen duidelijke correlatie naar voren tussen de serum Co en Cr niveaus en mate van slijtage. Patiënten met hoge inclinatiehoeken

vertoonden de meest uitgesproken slijtage in de cup. Bovendien werd gezien dat hoge slijtage verhoudingen van de kop samen vielen met verhoogde serum Co en Cr levels. Een opmerkelijke ontdekking was ook de hoge aanwezigheid van titanium in zowel vloeistof- als weefselanalyses bij deze prothese. Deze verhoogde levels van titanium suggereren een aanzienlijke mate van slijtage op de taper-steel koppeling (trunnionosis). Dit fenomeen kan specifiek worden toegeschreven aan het feit dat de koppeling in deze M2a Magnum prothese is samengesteld uit titanium legeringen.

Conclusie en aanbevelingen: Onze gereviseerde protheses vertoonden een grote diversiteit in slijtage patronen, die correleerden met klinische variaties, inclinatiehoeken van de cup en serum levels van kobalt en chroom. Opmerkelijk is dat een hoge inclinatie hoek van de cup geassocieerd is met de meest uitgesproken slijtage in de cup. Slijtage-analyses zijn van groot belang om een beter begrip te krijgen van de complexe mechanismen die kunnen leiden tot falen. Dit is vooral nog relevant voor patiënten met een MoM prothese.

Deel 3. Belang van Serum Kobalt en Chroom in Metaal-op-Metaal Heup Protheses

- Onderzoek de verschillen in het niveau van serum metaal ionen tijdens lange follow-up.
- Evalueren van de toepasbaarheid en voorspellende waarde van routinematige controle van serum metaal ion levels.

Hoofdstuk 5: Heupprothese geassocieerde kobalt toxiciteit: een Systematische Review van Case Series en Case Reports.

Dit hoofdstuk presenteert een overzicht van de literatuur die heupprothese geassocieerde kobalt toxiciteit (prosthetic hip-associated cobalt toxicity: PHACT) bij patiënten na een heupprothese onderzoekt. Deze systematische review werd uitgevoerd volgens de richtlijnen van de Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). De protheses waarbij PHACT het meeste voorkwam waren MoM protheses (38 gevallen) en gereviseerde (gebroken) keramisch-op-keramisch (CoC) protheses (32 gevallen). Bij dit laatste type werd de gebroken keramische kop vervangen door een metalen kop, wat leidde tot verhoogde slijtage als gevolg van het achterblijven van kleine deeltjes van de gebroken keramische kop.
De gemiddelde Co concentratie in MoM protheses was 127,7 parts per billion (ppb), terwijl het voor de gereviseerde CoC protheses 1078,2 ppb was. Helaas kon er geen duidelijke veilige drempel-waarde voor Co worden bepaald voor de beide typen protheses. PHACT veroorzaakt voornamelijk symptomen in het neurologische systeem, waarbij 24% invloed heeft op het sensorische systeem en 19,3% op het centrale/perifere systeem. Cardiovasculaire symptomen werden gescoord als de op een na meest gemelde systemische klachten, met 22,1%.

Conclusie en aanbevelingen: We raden sterk af om een op metaal gebaseerde articulatie te gebruiken na de revisie van een gebroken CoC prothese. Voor patiënten met een MoM prothese, of degenen die een revisie hebben ondergaan met metalen componenten na een gebroken CoC prothese, wordt aanbevolen om regelmatige follow-up uit te voeren met jaarlijkse monitoring van het serum Co.

Hoofdstuk 6: Veilige bovengrens van serum Kobalt en Chroom levels bij patiënten met een M2a-Magnum Metaal-op-Metaal prothese: een follow-up studie van 10 jaar.

In dit hoofdstuk presenteren we de lange termijn overleving van ons grote kop M2a Magnum MoM THP cohort, eerder geïntroduceerd in hoofdstuk 3. Met onze 10-jaar follow-up gegevens, inclusief de regelmatige controles van serum metaal ionen, is ons doel om een veilige bovengrens (Safe Upper Limit: SUL) vast te stellen voor de Co en Cr waardes bij patiënten met deze prothese. Voor deze specifieke prothese hebben we een SUL van 4.1 ppb voor Co en 4.2 ppb voor Cr geïdentificeerd. Onze analyses toonden bovendien een verhoogd risico op revisiechirurgie voor ARMD bij vrouwelijke patiënten en patiënten met een cup inclinatie van meer dan 45 graden. Daarnaast vertoonden recent gemeten hogere Co en Cr levels een correlatie met een verhoogde kans op revisies gerelateerd aan ARMD.

Conclusie en aanbevelingen: Wij adviseren en pleiten voor een consequente follow-up en monitoring van patiënten met de M2a-Magnum MoM THP. Dit omvat klinische beoordelingen met PROMs en monitoring van de serum Co en Cr waardes, waarbij de voorgestelde SULs van respectievelijk 4.1 en 4.2 ppb voor Co en Cr in gebruik worden genomen.

Hoofdstuk 7: Zijn serum Kobalt en Chroom levels voorspellers voor Patiënt gerapporteerde uitkomstmetingen (PROMs) bij de ASR Heup Resurfacing Articulatie: een prospectieve follow-up studie van 10 jaar.

Dit hoofdstuk heeft als doel de voorspellende waarde te beschrijven van verhoogde Co en Cr levels bij patiënten met een ASR-HRA voor verslechtering van de HHS en HOOS sub-schalen in het daaropvolgende jaar. Patiënten uit de cohort geïntroduceerd in hoofdstuk 2 werden jaarlijks gemonitord in combinatie met het controleren van het serum Co en Cr en PROMs.

Wij hebben vastgesteld dat een toename van 1 ppb in het serum Co en Cr level significant correleert met verslechtering van de HHS in het jaar daaropvolgend. Deze correlatie was eveneens duidelijk zichtbaar in de sub-scores HOOS-pijn en HOOS-kwaliteit van leven. Als aanvulling presenteren we ook de uitgebreide overlevingsanalyse van 10 jaar, met een overlevingspercentage van 65% (95% betrouwbaarheidsinterval: 52,5 tot 77,6).

Conclusie en aanbevelingen: Een verhoging van het serum kobalt en chroom bij patiënten met ASR-HRA dient als een voorspellende waarde voor de latere afname van zowel de HHS als HOOS sub-schalen gedurende het volgende jaar. In het licht van deze bevindingen pleiten we voor een regelmatige monitoring van patiënten met deze specifieke prothese met periodieke beoordeling van serum kobalt en chroom waardes naast het afnemen van de PROMs.

ADDENDUM

Acknowledgements
List of Publications
Curriculum Vitae / Portfolio

Acknowledgements

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List of Publications

LIST OF PUBLICATIONS

Koper MC, Mathijssen NMC, van Ravenswaay Claasen HH, Witt F, Morlock MM, Vehmeijer SBW. Pseudotumor After Bilateral Ceramic-on-Metal Total Hip Arthroplasty: A Case Report. JBJS Case Connect. 2014, Mar 12.

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Koper M, Verdijk R, Bos K. Asymptomatic intraprosthetic dual mobility cup dislocation with increased metal ion levels. Arthroplast Today. 2019 Jan 22:38-42.

Koper MC, Reijman M, van Es EM, Waarsing JH, Koot HWJ, Keizer SB, Jansen I, van Biezen FC, Verhaar JAN, Bos PK. No added value for Computer-Assisted surgery to improve femoral component positioning and Patient Reported Outcomes in Hip Resurfacing Arthroplasty; a multi-center randomized controlled trial. BMC Musculoskelet Disord. 2019 Oct 25:473.

Koper MC, Bos K. Response to letter to the editor on "Asymptomatic intraprosthetic dual mobility cup dislocation with increased metal ion levels". Arthroplast Today. 2020 Feb 16:134-5.

van Rijn J, **Koper MC,** Bos PK. Routine Fracture Fixation for a Periprosthetic Hip Fracture Below Birmingham Hip Resurfacing: A Case Report. JBJS Case Connect. 2020, Sep 10.

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Curriculum Vitae / Portfolio

MAARTEN CORNELIS KOPER

01-01-1984
Admiraliteitskade 228, 3011 TT Rotterdam
+31 06 43 05 77 36
maartenkoper@outlook.com

Education

2006 - 2012	Medical Doctor, Study of Medicine, Erasmus MC, Rotterdam, the Netherlands
2002 - 2005	Bachelor in Biomedical Sciences, University of Amsterdam, the Netherlands
1996 - 2002	High School Gymnasium, Sancta Maria Lyceum, Haarlem, the Netherlands

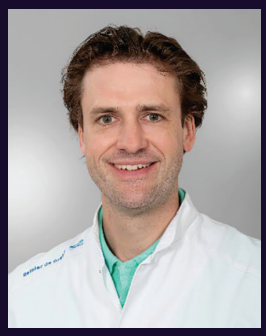
Medical Experience

06/2023 - now	Consultant Orthopaedic & Trauma Surgeon, Reinier Haga Orthopedic Center, Zoetermeer and Reinier de Graaf Hospital, Delft
07/2022 - 05-2023	Fellowship Hip Arthroplasty and Orthopedic Trauma, Reinier Haga Orthopedic Center, Zoetermeer and Reinier de Graaf Hospital, Delft
12/2020 - 03-2022	Fellowship Arthroplasty and Orthopedic Trauma, Flinders Medical Center, Adelaide, Australia
2012 - 2020	Residency Orthopedic Surgery, ROGO Rotterdam, the Netherlands

Training and Teaching activities

		Year	ECTS
Courses			
	Laboratory animal science (art 9), Leiden, the Netherlands	2009	1.0
	Wetenschappelijk schrijven in het Engels	2012	2.0
	Scientific Integrity	2016	0.3
	Stralingscursus	2019	1.0
	Hip Revision Surgery, London, United Kingdom	2019	2.0
	Residents Educational Pathway, Tampere, Finland	2019	5.0
	Hospital Major Incident Management and Support (HMIMS), Tilburg, the Netherlands	2020	2.0
	Emergency Management of the Severe Burn Course, Adelaide, Australia	2021	5.0
	Definitive Surgical Trauma Care (DSTC): Surgical Trauma Course, Melbourne, Australia	2021	10
	Osteosynthesis & Trauma Care (OTC) III, Uden, the Netherlands	2022	10
	Good Clinical Practice, Delft, the Netherlands	2022	1.5
	Teach the Teacher, Leiden, the Netherlands	2023	1.0
Oral Presentations			
	Metal-on-Metal Total Hip Follow-up Delft - ROGO dag, Rotterdam, the Netherlands	2016	1.0
	Metal-on-Metal Hip Arthroplasty: update - ROGO dag, Delft, the Netherlands	2019	1.0
	Annual Trauma Audit - Flinders Medical Center, Adelaide, Australia	2021	1.0
	Safe Upper Limits of Serum Cobalt and Chromium Levels for the M2a-Magnum Metal-on-Metal Total Hip Bearing -Science Day Reinier de Graaf Gasthuis, Delft, the Netherlands	2021	1.0
	What's new in Trauma - Limerick, Ireland	2022	1.0
Poster Presentation			
	Asymptomatic intra-prosthetic dual mobility cup dislocation with increased metal ion levels: a case report and review of current literature - European Hip Society, Den Haag, the Netherlands	2018	1.0
Lecturing			
	Surgical anatomy Masterclasses - Erasmus Anatomy Research Project (EARP), Rotterdam, the Netherlands	2009 - 2012	1.0
	Physiological Response to Trauma (DCO, Second hit, Early appropriate care etc.) - Limerick, Ireland	2022	1.0
Other			
	Editorial Board Member Magazine "Zorg voor Beweging"	2018 - now	2.0

About the Author



Maarten Koper was born on January 1, 1984, in Haarlem, and spent his childhood in Zandvoort. In 2002, he successfully completed his Gymnasium education at the Sancta Maria Lyceum in Haarlem, setting the stage for his subsequent academic years.

At the University of Amsterdam, he pursued Biomedical Sciences for three years after his graduation. Following his bachelor's degree, he commenced his Medicine studies at the Erasmus University in Rotterdam.

During his Medicine studies, Maarten developed a keen interest in Orthopedics and Trauma surgery, undertaking two internships in South Africa. After completing his studies in 2012, he joined the Orthopedic department at the Reinier de Graaf Hospital. After one year, he started his orthopedic training while simultaneously initiating his PhD project.

His training involved rotations at different medical institutions, including the Albert Schweitzer Hospital, Reinier de Graaf Hospital, Erasmus Medical Center and Reinier Haga Orthopedic Center. In 2015, he married Tanja, whom he had met several years earlier as a neighbor in the student residence. The following year, they welcomed their daughter Mabel, followed by their son Floris in 2017. During the final year of his training in 2020, their son Olivier was born.

After completing his training in 2020, the family commenced on an international adventure, living in Adelaide, Australia, for nearly 1.5 years. Maarten utilized this time to undertake a fellowship in "Orthopedic Trauma surgery and Arthroplasty" at the Flinders Medical Center. Before returning to the Netherlands, they explored Australia for two months and continued their journey across Thailand for an additional two months.

In June 2022, upon returning to the Netherlands, Maarten began at the Reinier Haga Orthopedic Center and Reinier de Graaf Hospital, initially as a Hip Arthroplasty fellow and Orthopedic Trauma surgeon. Within a year, he secured a position on the staff as an Orthopedic consultant. Outside of medicine, Maarten takes pleasure in running and cycling. However, his greatest happiness originates from the precious moments shared with his family and exploring the world with his beloved wife and wonderful children by his side.