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Evaluation of a metal-on-metal total hip arthroplasty

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Karolinska Institutet, Stockholm, Sweden

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Henrik Dahlstrand, MD

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Till Hanna

-vad vore jag, utan dina andetag?

ABSTRACT

Background

After the introduction of the Metasul system by Weber in 1988, total hip arthroplasty (THA) with metal-on-metal (MoM) bearings became increasingly popular in the 1990s. MoM bearings aimed to reduce the problem of aseptic loosening associated with polyethylene wear particles from conventional polyethylene cups. The following introduction of hip resurfacing added positive factors as bone sparing and large caliber heads, reducing the risk of dislocations. After almost two decades of increasing use of MoM prostheses, reports of implant failure and adverse reactions to metal became numerous. Starting in 2009, a dramatic decrease in the use of MoM bearings has been seen.

Patients and methods

Paper I was an experimental in vitro study measuring the amount of metal worn off from a MoM prosthesis with a 28-mm diameter head, using a hip simulator. Papers II-IV were all based on a prospective, randomized, controlled clinical trial including 85 patients allocated into two groups. One group was operated with a MoM prosthesis while the other group received a similar prosthesis with a conventional metal-on-polyethylene (MoP) bearing. All components were cemented and 28-mm heads were used. Clinical outcome and serum metal ion concentrations were evaluated at short-term (three, six, 12 and 24 months, paper II), medium-term (7 years, paper III) and long-term (16 years, paper IV) follow-up. Overall long-term survival of the implants was estimated after a mean of 16 years (paper IV).

Results

A so-called run-in phase with higher initial wear from MoM implants was seen in the joint simulator testing within the equivalent of the first year of use. As expected, patients with MoM bearings showed higher cobalt (Co) and chromium (Cr) ion concentrations compared to patients in the MoP group at all time-points from 3 months to 16 years postoperatively. The percentage of circulating HLA DR^+ $CD8^+$ T-cells was higher in the MoM compared to MoP group (10.6 vs. 6.7 %; $p = 0.03$) and was positively correlated to systemic concentrations of Co and Cr. At the last follow-up 16 years after the index surgery, radiographic result and clinical performance was similar in both groups (Harris hip score: MoM=91, MoP=95, p=0.28) and no difference between groups was seen regarding implant survival (MoM: 93 % [95% CI: 83-100%]; MoP: 95 % [95% CI: 87-100%], p=0.99).

Conclusions

This thesis evaluated a 28-mm head THA, comparing a MoM bearing with a conventional MoP articulation. Both articulations performed equally well in regard to long-term implant survival and clinical outcome. Due to the absence of clinical superiority of the MoM bearing and concerns about biological effects of the MoM articulation, the use of MoP articulations is recommended.

LIST OF SCIENTIFIC PAPERS

I. **The wear pattern in metal-on-metal hip prostheses**

Anissian L, Stark A, Good V, Dahlstrand H, Clarke I
J Biomed Mater Res (Appl Biomater), 2001, 58: 673–678

II. **Elevated serum concentrations of cobalt, chromium, nickel and manganese after metal-on-metal alloarthroplasty of the hip:**
A prospective randomized study

Dahlstrand H, Stark A, Anissian L, Hailer N
J of Arthroplasty, 2009, Sep;24(6): 837-45

III. **Elevation of circulating HLA DR^+ $CD8^+$ T-cells and correlation with chromium and cobalt concentrations 6 years after metal-on-metal hip arthroplasty**

Hailer N, Blaheta R, Dahlstrand H, Stark A
Acta Orthop, 2011, 82:1, 6-12

IV. **Comparison of metal ion concentrations of total hip arthroplasty with metal-on-metal versus metal-on-polyethylene 28-mm articulations:**
Long-term follow-up of a prospective randomized study

Dahlstrand H, Hailer N, Stark A, Wick M, Weiss RJ
Manuscript, 2017

CONTENTS

LIST OF ABBREVIATIONS

ALVAL	Aseptic Lymphocytic Vasculitis-Associated Lesion
ARMD	Adverse Reaction to Metal Debris
ASR	Articular Surface Replacement
CI	Confidence Interval
Co	Cobalt
Cr	Chromium
CoCr	Cobalt-Chromium
DDIW	Distilled De-Ionized Water
FDA	Food and Drug Administration
HHS	Harris Hip Score
OA	Osteoarthritis
MHRA	Medicine and Healthcare products Regulatory Agency
MoC	Metal-on-Ceramic
MoM	Metal-on-Metal
MoP	Metal-on-Polyethylene
PE	Polyethylene
SF-36	Medical Outcome Study Short Form 36
THA	Total Hip Arthroplasty
UHMWPE	Ultra-High Molecular Weight PolyEthylene

1 BACKGROUND

1.1 THE HISTORY OF TOTAL HIP ARTHROPLASTY

Ever since surgeons in the 1920s and -30s started experimenting with the implantation of different materials covering the femoral head, the orthopaedic community has strived for perfection when it comes to materials, designs and techniques of hip arthroplasty. The first hip arthroplasty is considered to be an implanted stainless steel cup covering the femoral head, described by Smith-Petersen in 1938.[1] The first total hip arthroplasty (THA) replacing the entire joint by mechanical parts was described only some years later by Wiles.[2]

The implant design evolved in several directions, including for example the McKee-Farrar metal-on-metal (MoM) THA made from a cobalt-chromium (CoCr) alloy, introduced in 1956 and used, with some modifications, for decades.[3] When Charnley introduced the low friction arthroplasty, THA became even more successful over time.[4, 5] Charnley's superior results led however to the discontinuation of the McKee-Farrar prosthesis and similar designs on the market. The concept of a metal femoral component articulating against a polyethylene cup would however inevitably lead to attrition of the cup component, especially in the younger, more active patient. A fraction of implants failed due to so-called aseptic loosening of the components, which was later, in part, attributed to tissue reactions to polyethylene wear particles from the cup.[6] In 1998, Weber developed and started using a second generation MoM arthroplasty, the Weber-Metasul, which was supposed to solve the problem of polyethylene wear particles with no apparent side effects.[7]

1.2 SECOND GENERATION METAL-ON-METAL TOTAL HIP ARTHROPLASTY AND RESURFACING

When the second-generation MoM THAs and resurfacing implants were released onto the market in the 1990's, it was expected that aseptic loosening due to polyethylene particles would be drastically reduced. Many surgeons in the orthopaedic community promptly embraced the hip resurfacing design as they were appealed by the idea of bone preservation of the proximal femur, combined with a large femoral head which reduced the risk of dislocation. The reduced risk of dislocation was one of the reasons for implant manufacturers to develop THA systems with traditional stems and all-metal bearings with large-diameter heads and cups. This made it possible to revise only the femoral component of a resurfacing system while keeping the acetabular component. Revision of the cup would otherwise often prove to be a challenge because of its big size. By 2006, 35 % of the implanted hip arthroplasties (including hip resurfacing) in the U.S. were MoM, increasing to a peak of 40 % in 2008 and declining numbers ever since.[8, 9] Most all-metal implant systems are made from high carbon CoCr alloys because of their properties, making them well suited for use in hard, low-friction surfaces.[10]

1.3 COMPLICATIONS RELATED TO METAL-ON-METAL IMPLANTS

The re-introduction of the MoM concept did not however improve the results after THA. Over the years it became more apparent that aseptic loosening was associated with MoM bearings as well. Another important cause of implant failure and subsequent revision was, and still is, localized pain around the prosthesis, often associated with tumour-like tissue reactions. Lymphocytes and giant cells were found in tissues surrounding failed MoM prostheses in several studies and case reports.[11] Suspicions arose of an association between the reactions and metal nanoparticles in the soft tissue surrounding the implant.[12] The histology of the tissue was shown to be rather different from the granulocyte mediated loosening that polyethylene particles were believed to cause in MoP implants.[6, 11, 13]

An increasing number of publications raised the issue of soft tissue complications emerging in patients presenting with local pain within months or years after surgery with a resurfacing implant, and to some extent after stemmed MoM THA.[14] Several studies have since then investigated this phenomenon and described it in greater detail. The following terminology has been taken into general use:

- Metallosis – meaning the dark discoloration of soft tissue surrounding the implant related to trace metals worn off and released from it.[15]
- Pseudotumours – a solid or cystic mass of soft tissue adjacent to the prosthesis sometimes presenting with local symptoms of pain or swelling, often with a histological appearance of ALVAL, giant cells and necrosis.[14]
- ALVAL – Aseptic Lymphocytic Vasculitis-Associated Lesions, a histological diagnosis of soft tissue that can be present with or without metallosis and pseudotumours.[11]
- ARMD – Adverse Reaction to Metal Debris, which all of the three previous conditions are examples of.[16]

It is yet unknown whether these conditions are a result of cellular toxicity of metals or of hypersensitivity to them.[12] It is now clear that the conditions are associated with high levels of metal ions in local tissues and elevated levels in serum, but far from always correlating to complications in a dose-dependent manner.[17-19]

Several MoM prosthesis systems using large caliber heads have shown high failure rates and the use of these systems has therefore diminished considerably.[20, 21] Studies have shown major variations in survival rates for different hip resurfacing implants. Some systems performed very poorly and were retracted from the market due to high rates of early failure, whereas other systems continue to perform well over time.[22] A large register study on hip resurfacing implants, found evidence that the general survival rate of these prostheses was only at acceptable levels in male patients with large caliber head implants, even when a resurfacing system well-known to be of inferior design, was excluded from the analysis.[23] For men requiring smaller head sizes and for all women, hip resurfacing is strongly discouraged based on the outcome of that and many other studies.

In contrast, MoM systems using small heads, like the 28-mm bearing studied in this thesis, have performed over-all well, with implant survival rates at, or close to, the level of traditional MoP systems.[15, 24]

1.4 WEAR FROM METAL-ON-METAL IMPLANTS

The origin of metal particles in the surrounding tissue and ions in blood and serum are primarily worn off from the bearing surfaces in resurfacing implants. However, in MoM THA, the source can also be the metallic interface between the trunnion of the neck and the head in modular prostheses, as a result of corrosion or mechanical wear. This can explain the discrete but measurable elevation of metals in serum that can be seen after implanting modular MoP THAs.[13]

All MoM implants produce wear debris of metallic nanoparticles and ions through both mechanics and corrosion. Particles are two orders smaller than polyethylene (PE) particles, which may explain the different immune response in vivo, where PE has been shown to evoke response from granulocytes while lymphocytes seem to respond more to metals[12, 13, 15].

Risk factors associated with higher wear rates are:[25-28]

- small resurfacing heads
- equatorial design, where the components apply friction around the diameter of the head, as apposed to polar design where friction is primarily applied to the central head
- cup implantation at a high inclination angle, leading to edge loading of the bearing
- low carbon content in the alloy composition leading to a rougher surface

Implants with these characteristics have a higher risk of early failure and need of revision. It is not concluded whether this is because of the higher local load of metal wear debris or if the reason is mainly mechanical.[15]

1.5 FACTS ON COBALT AND CHROMIUM

Cobalt (Co, atomic number 27) is a ferro-magnetic transition metal of silvery gray appearance. Like iron and chromium, it's a hard metal with a high melting and boiling point. The Swedish chemist Georg Brandt discovered it in 1739. It is the 33rd most common element on earth and usually only found in small amounts, hardly worth unearthing on its own. Co is never found in pure form, only in minerals where it is combined with other elements. In many places Co is mined together with silver, copper or nickel. The mixed ore usually also contains arsenic and thus becomes poisonous when heated, which led to unwanted effects when extracting the precious metals. Co was blamed for these adverse effects and was named from the German word "Kobold" that translates to "mean goblin".

Co has been used by humans for thousands of years and even the ancient Egyptians made blue colored glass and pottery from Co salt.[29]

There is only one known use for Co in the human body, which is in the form of cobalamin (vitamin B12), an essential co-factor in different enzyme reactions in vivo where methyl groups are transferred between biologically active compounds. The reactions take place in every cell in the human body and most important is the transformation of homocysteine to methionine. Cobalamin deficiency leads to neuropathy and anemia.[30]

Negative biological effects of Co administered to humans was first described in 1966 in Quebec after a brewery started adding Co to its beer to improve foaming performance. Investigations were initiated because of a sudden onset of a minor local epidemic of acute cardiomyopathy in alcoholics. At first, the health care authorities were taken by surprise by the spread of a new type of cardiomyopathy and the clinical findings were different from the known form of cardiomyopathy caused by alcohol alone.[31] Even with considerable beer intake the amount of ingested Co was not more than 20-25 % of the doses used therapeutically at the time to treat anemia. It was later concluded that the combination of malnutrition, excess alcohol and added Co became cardiotoxic, leading to cardiomyopathy.

There have been case reports of cardiomyopathy in patients following MoM THA, mainly after resurfacing. No causality has been established between the condition and the implant, even though reports state improvement in cardiac function after hip revision where the MoM implant has been removed.[32]

There is no conclusive evidence of genetic toxicity of Co to human DNA, but it is marked as "possibly carcinogenic to humans" by the International Agency for Research on Cancer, IARC, an agency under the World Health Organization.[33, 34]

Chromium (Cr, atomic number 24) is a silvery shining transition metal. It was discovered in 1761 by the German prospector JG Lehmann, but it was not until 1797 that the French chemist LN Vaquelin first isolated it in metallic form. As a transition metal, Cr has the potential of creating alloys with similar metals, like Co. It does not react readily with other substances and is therefore resistant to corrosion, a trait used when coating metal details ("chrome") in cars for example. In various alloys, including the ones used in orthopaedic implants and so-called stainless steel, Cr has the role of reducing corrosion.[35]

The systemic toxicity of Cr (III) derived from hip implants has been debated, but to most extent been ruled out. The role of Cr in local tissue reactions around hip implants is yet unclear and Co is believed to play a more important role.[36] The major concern for Cr as a health hazard, is the shown relation between inhaled Cr (VI) and carcinogenesis in the respiratory tract.[37] This is however the case only with hexavalent Cr and not with the trivalent form present in the alloy of implants. It is unlikely for trivalent Cr to be physiologically oxidized to the hexavalent form at neutral pH in vivo. The trivalent form cannot move freely across lipid membranes.[36]

1.6 PRESENT USE OF METAL-ON-METAL IMPLANTS

It is estimated that 755,000 MoM hip bearings were implanted in the U.S. alone between the years 2000 and 2010, of which 2008 was the year with the highest incidence. 84 % of the implants were primary THAs, 12 % revision THAs and 5 % hip resurfacing THAs.[9] A similar development was seen in Great Britain.[38] Many of the questions mentioned above, about safety and reliability of MoM bearings together with poor implant survival results, caused severe concern for clinicians, orthopaedic organizations and authorities. Even though there are MoM implant systems that are performing well in long-term follow-ups, several systems were recalled between 2008 and 2011 due to poor results.[39] In 2011 and 2012 the Food and Drug Administration (FDA) in the U.S. and the Medicine and Healthcare products Regulatory Agency (MHRA) in Great Britain issued recommendations to surgeons on stricter patient selection (FDA) and even advising against all use of MoM bearings (MHRA), suggesting protocols for life long clinical follow-up of patients with regular measurements of systemic Co and Cr concentrations.[40-43]

Since these concerns were raised, THA surgery with MoM bearings have been drastically diminished. According to data from the Swedish Hip Arthroplasty Register, only 0.2 % of the THAs implanted in 2014 had MoM bearings, hip resurfacing included.[44] However, it is estimated that over one million patients world-wide, presently are living with an implanted MoM device.[8] One may speculate that more than a few of them (and their orthopaedic surgeons) are wondering, even with a well-functioning implant, what the long-term effects may be of the metals being continuously released by their bearings.

2 AIMS OF THE THESIS

The overall aim of this thesis was to evaluate a MoM THA with a 28-mm head by testing it both in vitro with a joint simulator and in vivo in patients.

The specific aims of this thesis were to investigate:

1. the presence of a run-in phase of metal wear from a MoM hip device in vitro, during the equivalent of the first four years of use in vivo (paper I).
2. the systemic load of metal ions over time in THA patients with a MoM compared with a MoP bearing (papers II-IV).
3. if systemic metal ion concentrations in patients after THA correlate with immunological reactions (paper III).
4. the clinical performance and long-term survival of a MoM THA compared to a conventional MoP THA (paper IV).

3 PATIENTS AND METHODS

3.1 STUDIED IMPLANTS AND SURGICAL TECHNIQUES IN PAPERS I-IV

In paper I, six hip simulators were equipped with 28-mm Metasul heads articulating against cups consisting of a Metasul liner in a polyethylene (PE) backing (Sulzer; Winterthur, Switzerland).

In papers II-IV, in the setting of a randomized, controlled study, the intervention group received THAs with the same MoM 28-mm Metasul bearing as investigated in paper I, while the control group received a MoP bearing with a 28-mm metal head (Protasul, Sulzer) and an all-polyethylene cup (Müller, Sulene, Sulzer). The PE was made of ultra-high molecular weight polyethylene (UHMWPE), but not highly cross-linked.

In both groups, the same cemented stem was used: the MS-30 (Sulzer) with a matte surface finish. Both stem and cup were cemented with high pressure technique using Palacos bone cement (Heraeus; Hanau, Germany). All surgeries were performed using a posterior approach, and most were performed by one senior surgeon. The MS-30 stem and Metasul bearing are shown to the right.

Both Metasul and Protasul implants are made from similar wrought, high carbon, CoCr alloy. The alloy consists of a minimum of 50 % Co, 26-30 % Cr, 7 % molybdenum and 1 % manganese and nickel, respectively. The only difference between the two alloys, is that Metasul has a higher amount of carbon (0.2-0.25 %) compared to Protasul (0.05-0.08 %), which allows for the surfaces of the Metasul implants to be polished into a slightly harder and smoother surface compared to Protasul.

3.2 SIMULATOR STUDY, PAPER I

In this tribological study, the six Metasul implant pairs were mounted in servo-hydraulic hip simulators of orbital type and run at one Hz for a total of 4.2 million cycles, which is estimated to be the equivalent of four years of moderate activity in vivo. Alpha calf serum diluted to 50 % concentration was filtered and used as a synovial fluid substitute between the head and the cup. Temperature and humidity of the simulator laboratory was maintained at narrow intervals and loss of lubricant from evaporation was replaced by distilled water. Wear from the metal components was measured at regular intervals: every 50,000 cycles up to 300,000, every 100,000 cycles up to 700,000 and above that every 250,000 cycles. Wear was calculated by measuring weight-loss of components using Sartorius-type scales. Weight-loss was then converted to volumetric wear expressed as cubic millimeter per million cycles.

3.3 PATIENTS IN THE CLINICAL STUDY, PAPERS II-IV

166 patients referred to the Orthopaedic Department at the Karolinska Hospital during 1998 and 1999 were assessed for participation in the study. Inclusion criteria were age between 40 and 75 years and need for THA because of pain due to primary osteoarthritis of the hip. Exclusion criteria were: declining to participate in the study, previous joint replacement or surgery with metal osteosynthesis, weight over 105 kg, previous infection or surgery in the affected hip, local or general osteoporosis, intake of steroids during more than three months during the last year, alcohol or drug abuse and mental disorders including dementia. After application of these criteria a cohort of 85 patients were included in the study. They were randomized into two groups by a computer application using the minimization method,[45] allocating 41 patients into an intervention group receiving the MoM articulation and 44 patients into a control group receiving the MoP bearing (Figure 1). The algorithm in the application is designed to use information about body weight, smoking habits, sex and age to ensure equal size and composition of cohorts. Statistical analysis of the two groups was performed and did not show any significant differences regarding these variables. Patient characteristics are shown in Table 1.

Table 1. *Patient characteristics preoperatively. Total numbers or mean values (± standard deviation) and significance (p) of the difference (Independent t-test).*

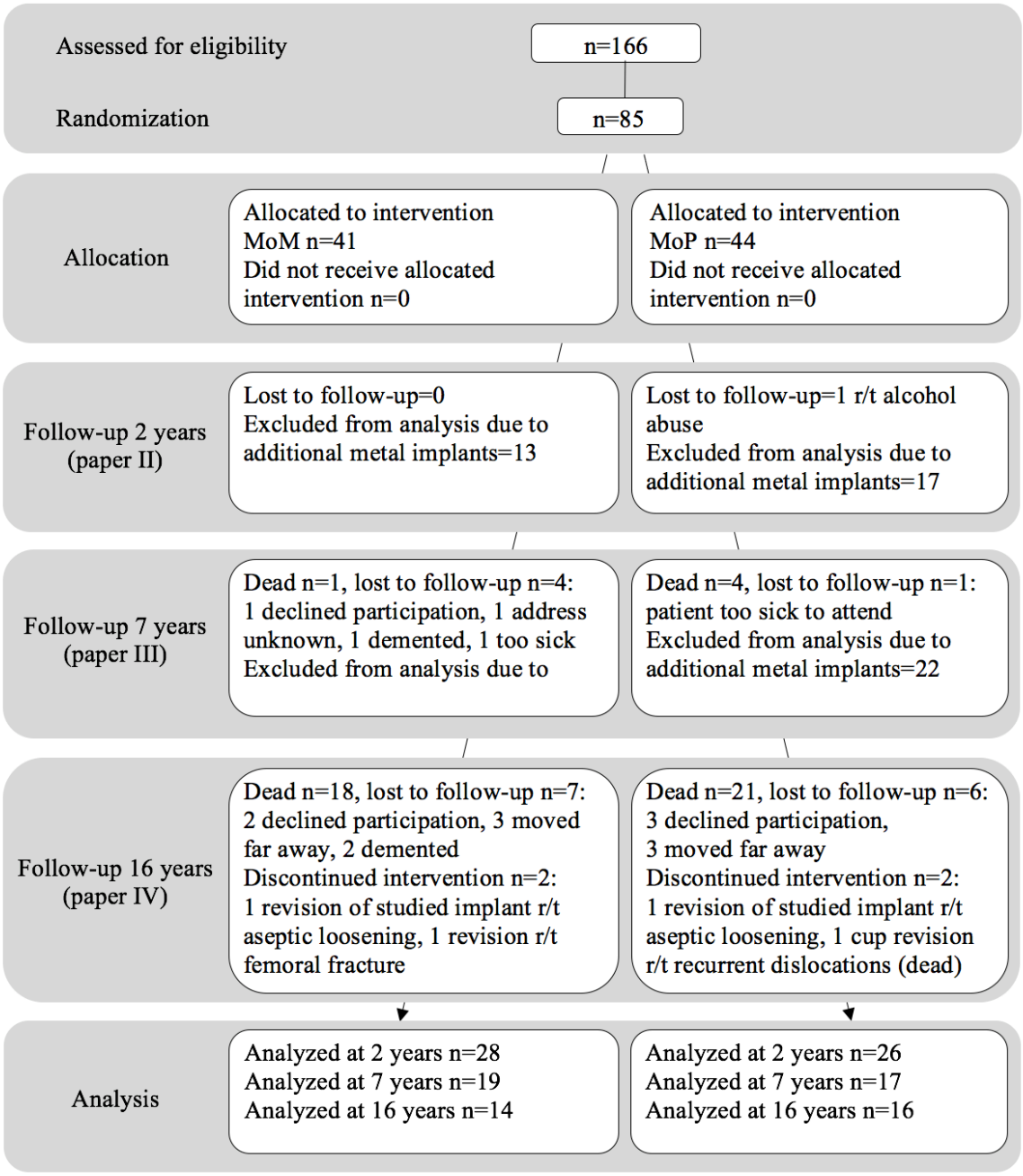
Parameter	MoM (n=41)	MoP (n=44)	p value
Age at surgery, years	64.8 ± 6.6	66.6 ± 7.2	0.23
Male sex, n	20	19	0.67[I]
Smokers, n	7	6	0.77[I]
Body mass index, kg/m^2	26.8 ± 3.5	26.5 ± 3.7	0.72
Harris hip score	38.0 ± 12.5	37.3 ± 12.5	0.80

MoM=metal-on-metal, MoP=metal-on-polyethylene, [I] Fisher's exact test

Follow-up visits were performed at three, six, 12 and 24 months (paper II), at a mean of seven years (mean 82 months, range 72-97 months; paper III) and finally at a mean of 16 years (range 15-17 years; paper IV). Patients who had additional joint replacement surgery after the index operation were excluded from follow-up until seven years. The reason for this

exclusion was to minimize the risk that additional metal exposure would confound the results of the metal ion concentrations. At 16 years, patients with additional implants were not excluded from the analysis because of the small number of patients still available for follow-up. The proportion of patients with additional implants in each group was similar at 16 years (MoM=nine out of 14 patients, MoP=10 out of 16 patients; p=0.61). None of the patients in the study cohort had an additional MoM hip implant at any time. At the final follow-up (16 years, paper IV), the frequency of revision and other re-operations in the patient cohort since the index operation was confirmed in the Swedish Hip Arthroplasty Register.

Figure 1. CONSORT flow chart paper II-IV.



3.4 ANALYSES OF METAL ION CONCENTRATIONS, PAPERS II-IV

All concentrations of metal ions reported in papers II-IV were analyzed by an accredited external laboratory specialized in trace metal analyses, ALS Scandinavia AB (formerly SGAB Analytica AB, Lulea, Sweden).

Internal standards and calibration solutions used were prepared by diluting one mg/ml single-element standard solutions (SPEX Plasma Standards, Edison, NJ, USA), taking inter-element compatibility into account.

Quality control samples were made by diluting 10 mg/L multi-element standard solutions (PE Pure Plus Atomic Spectroscopy Standard, Norwalk, USA) to check the concentrations of the calibration standards. Nitric acid (Merck, Darmstadt, Germany) was used after additional purification by sub-boiling distillation. Dilution of samples, blanks and standards was made with distilled de-ionized water (DDIW). The analysis of samples was performed after dilution (1+9) with 0.14 M HNO_3 in DDIW. This dilution factor provides a compromise between the necessity to decrease matrix effects and the requirement for lowest possible detection limits for trace elements.

Samples were collected preoperatively and at three, six, 12 and 24 months postoperatively (paper II), at seven years (paper III) and at the 16-year follow-up (paper IV). They were drawn using an intravenous cannula with the stainless-steel needle removed and the first five mL of blood discarded. The containers used were 10 mL polypropylene tubes with sodium heparin (Teklab Ltd, Durham, United Kingdom) from the same batch, except from at 16 years when five mL glass containers without additive were used (Vacutainer, BD, New Jersey, USA). This means that plasma was separated up until the seven-year follow-up and serum was used at the later follow-up at 16 years.

Blood samples were then centrifuged at 2000 G for 10 minutes, after which plasma (or serum at the 16-year follow-up) was transferred to acid-washed polypropylene test tubes and stored at - 20°C until analysis.

Metal ion concentrations were measured by high-resolution inductively coupled plasma mass spectrometry using commercially available devices. For all samples except the ones collected at 16 years, the same device was used (Element, Finnigan-MAT, Bremen, Germany). The detection limit was 0.2 μg/L (4 nmol/L) for Cr and 0.05 μg/L (0.8 nmol/L) for Co. At the 16-year follow-up, another device was used (Element 2, Therma Scientific, Waltham, USA). The detection levels were 0.05 μg/L for Co and 0.5 μg/L for Cr.

To facilitate comparison with other studies, ion concentrations were presented in micrograms per liter, μg/L, sometimes referred to as ppb in the literature.

3.5 RADIOLOGICAL ASSESSMENT

Follow-ups at two, seven and 16 years included anteroposterior and lateral radiographs of the investigated hips as well as anteroposterior pelvic radiographs. All radiographs were

compared to those taken in the first two days after surgery. The radiographs taken at two and seven years were examined by a radiologist for periprosthetic osteolysis around implants and liner wear. At 16 years, the radiographs were analyzed for radiolucent lines in the three acetabular zones described by DeLee and Charnley and in the seven femoral zones described by Gruen et al.[46, 47] Femoral stem subsidence was measured by the distance between the lateral part of the stem in relation to the greater trochanter. Subsidence exceeding five mm was considered as migration. The cup inclination angle was also determined.

3.6 IMMUNOLOGICAL ANALYSES

In paper III, subpopulations of leukocytes were measured by flow cytometry on a Coulter EPICS-XL-MCL, using commercially available antibodies (CD3, CD8, CD45, CD4: Tetracrome Beckman Coulter, Bromma, Sweden cat. no. 6607013; CD3, CD16/56, CD45, CD19: Tetracrome cat. no. 6607073 and Becton-Dickinson cat. no. 332779; HLA DR: Becton-Dickinson cat. no. 6604366; CD4: Becton-Dickinson cat. no. 345768; CD8: Dako cat. no. C7079). Results were reported as numbers/nL or as percentages. Immunoglobulins and IgG subclasses were analyzed by nephelometry (Dade-Behring BN II, Siemens). A commercially available kit (The Binding Site Group Ltd., Birmingham, UK) was used to determine subclasses. The results were expressed in g/L.

3.7 HARRIS HIP SCORE

Clinical function of the operated hips was reported in papers II-IV, using the Harris hip score (HHS).[48] The Harris hip score is calculated from range of motion and absence of deformity, combined with the answers to questions in two dimensions: pain and function. Since the study started, there have been discussions about the use of the HHS in orthopaedic research, including criticism concerning a “ceiling effect” of the result.[49] All patients in papers II-IV were evaluated clinically with the subsequent calculation of HHS preoperatively and at all follow-up visits. The investigator carrying out the examination was blinded as to the type of bearing the patient had received.

3.8 SHORT FORM 36

The Short Form 36 collected by a physiotherapist preoperatively and follow-ups at 12 and 24 months were reported in paper II. SF-36 consists of 36 items divided into eight domains that can be aggregated into summaries based on physical and mental health.[50] The domains are:

- Bodily pain
- Physical functioning
- Role limitations due to physical health
- General health
- Mental health
- Vitality
- Social functioning
- Role limitations due to emotional health.

3.9 ETHICS

Paper I did not include patients, animals or human tissue and did not require ethical permits. The study protocols of the clinical study reported in papers II-IV were reviewed and approved by the Ethics committee of the Karolinska Hospital and the Regional ethical review board of Stockholm at Karolinska Institutet, respectively. Informed consent was given by all participants and the study was conducted in accordance with the Helsinki Declaration.[51]

3.10 STATISTICAL METHODS

Variables were summarized using standard descriptive statistics such as frequencies, means, medians, standard deviations and 95 % confidence intervals. The level of significance (two-tailed) was 0.05 in all analyses. Fisher's exact test was used for analysis of categorical variables when expected counts were five or less, when higher frequencies were expected the Chi square test was used.

A power analysis preceded the planning of the clinical study in papers II-IV, indicating that 20 patients per group would be sufficient to detect differences in metal ion concentrations (our primary endpoint) of one standard deviation with a power of 80 %, given a two-tailed p-value of 0.05.

The distributions of metal ion concentrations were positively skewed which suggested the use of nonparametric methods when comparing groups. Except for a few outliers with higher ion concentrations, most subjects were found at the lower ends of concentrations just above the detection limit. Metal ion concentrations were transformed to near-normal distributions by calculating natural logarithms. This allowed for the use of parametric comparisons between means and 95% confidence intervals using independent t-test.

The investigation of immunological parameters in paper III was not intended at the beginning of the study, but became relevant at a later stage. Thus, the power estimation was not based on this secondary endpoint. Most immunological parameters were normally distributed. The absence of baseline data demanded that inter-group comparisons of immunological parameters were performed using the independent t-test. Pearson's correlation coefficient was used in performing correlation analysis of logarithmically transformed metal ion concentrations with immunological parameters.

Group comparisons of means and 95 % confidence intervals in papers II-IV were made using an independent t-test.

Implant survival in paper IV was estimated by the Kaplan-Meier method. The Mantel-Cox log rank test was used to investigate whether survival estimates differed between groups

Statistical analyses for this thesis were performed using the SPSS software version 23 (SPSS inc., Chicago, Illinois, USA).

4 RESULTS

4.1 WEAR RATE IN JOINT SIMULATOR, PAPER I

Wear from the investigated components showed a similar wear rate pattern with an accelerated initial phase of high wear followed by a lower steady state wear rate. This initial so called "run-in" phase ended between 0.670 and 0.925 million cycles (Mc).

The average wear from the liners in the run-in phase was 0.72 mm^3/Mc (R^2 >0.94) which was reduced to 0.28 mm^3/Mc (R^2 >0.96) in the subsequent steady-state. One liner (L6) deviated from this pattern and continued to have a high wear rate throughout the study.

The heads exhibited similar wear phases with a high wear run-in phase, averaging 1.50 mm^3/Mc (R^2 >0.98) and a reduced average wear steady-state of 0.69 mm^3/Mc (R^2 >0.99). Two of the heads (H4 and H6) did not seem to reach the lower steady-state and continued to show a high wear rate throughout the study.

When comparing the total wear rate from the combined head-liner pairs, three noticeable groups were seen related to their respective wear rate: a low, an intermediate and a high wear rate group (Table 2).

Table 2. *Summary of volumetric wear rates in run-in and steady-state phases.*

Implant pair	Wear rate RI H+L, mm^3/Mc	Wear rate SS H+L, mm^3/Mc	Total wear head, mm^3	Total wear liner, mm^3	Wear rate group
H3/L3	1.31	0.53	1.4	0.6	Low
H2/L2	3.06	0.48	1.8	0.9	Low
H1/L1	1.61	0.20	2.9	1.0	Medium
H5/L5	3.03	1.36	3.3	0.8	Medium
H4/L4	2.15	0.87	5.3	1.7	High
H6/L6	2.17	2.44	6.2	4.6	High

H=Head, L=Liner, RI=Run In, SS=Steady State, Mc=Million Cycles.

During the writing of this thesis, an error was discovered in the result section of paper I published in J Biomed Mater Res. In the paper's result table corresponding to Table 2 above, rows are designated the wrong pairs of heads and liners in column one. In Table 2 above, this unfortunate error has been corrected.

4.2 CONCENTRATION OF COBALT AND CHROMIUM, PAPERS II-IV

Mean concentrations of Co and Cr in plasma and serum were low in both groups pre-operatively. No difference was shown between groups. From the first postoperative control at three months and at all subsequent measurements to the last control at 16 years, patients in the MoM group showed higher levels of both Co (Table 3 and Figure 2) and Cr (Table 4 and Figure 3). The difference between groups was statistically significant at all time-points.

Figure 2. *Concentration of cobalt over time, mean and 95 % CI.*

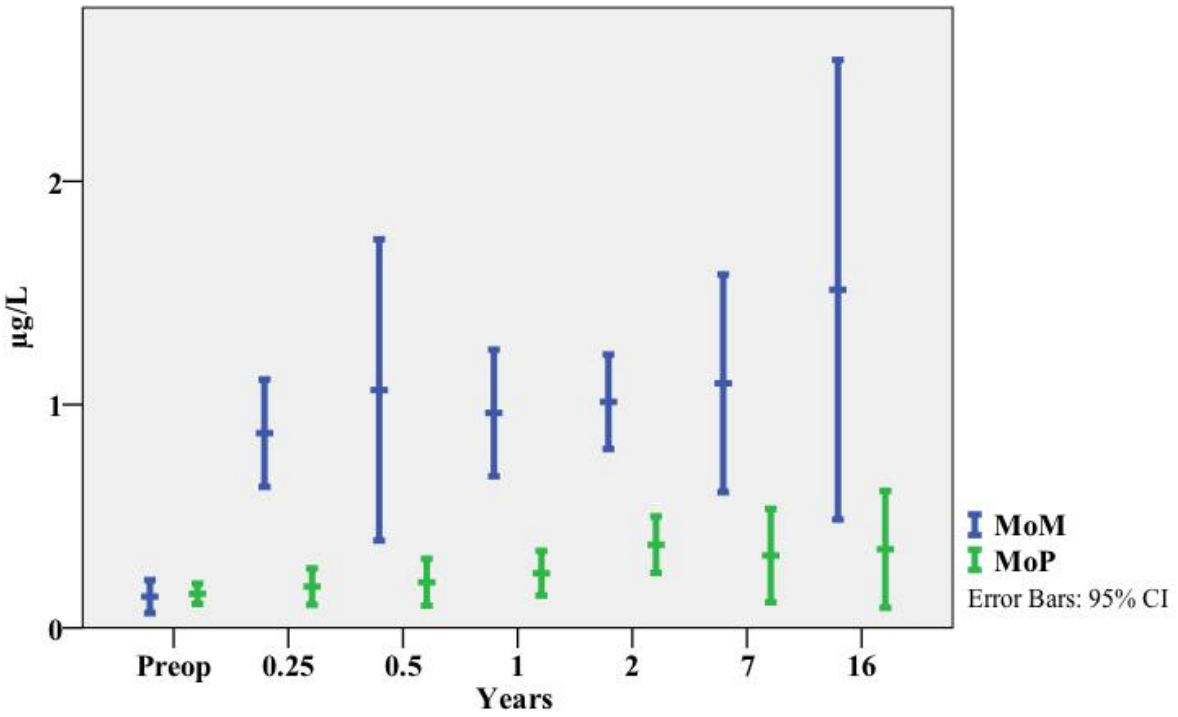


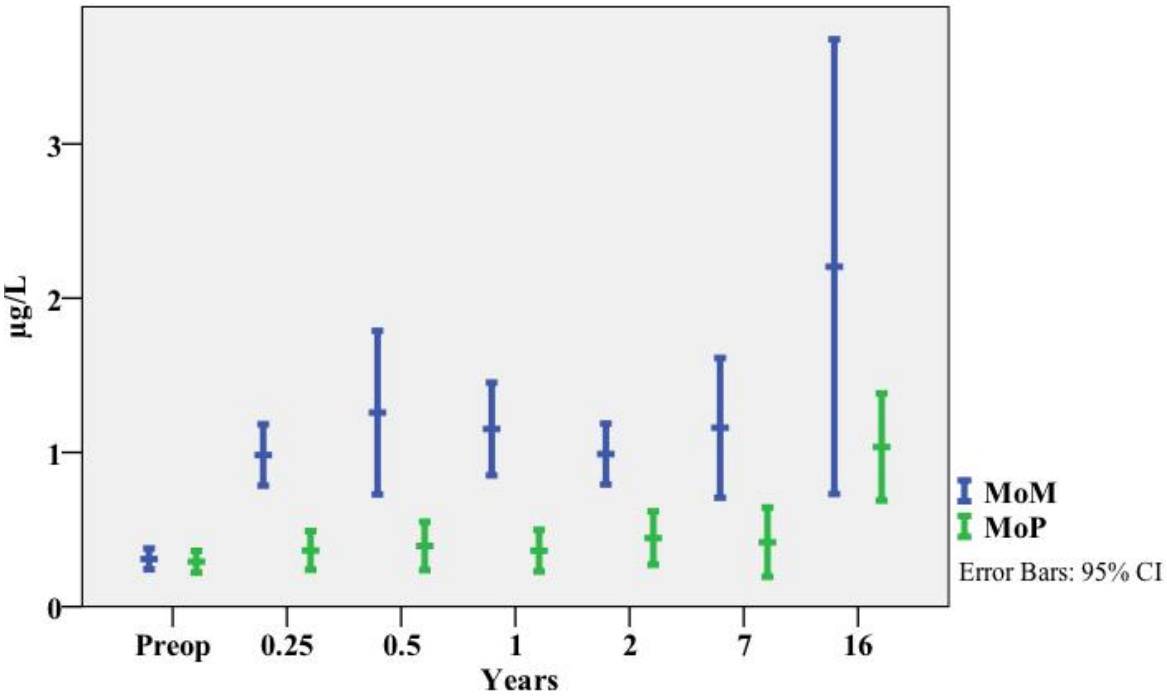
Table 3. *Mean cobalt concentration, µg/L and p-value (independent sample T-test on log transformed values)*

	MoM	MoP	p
Preop	0.14	0.15	0.264
0.25 year	0.87	0.19	<0.001
0.5 year	1.07	0.20	0.03
1 year	0.96	0.24	<0.001
2 years	1.01	0.37	<0.001
7 years	1.10	0.32	0.008
16 years	1.51	0.35	<0.001

Table 4. *Mean chromium concentration, µg/L and p-value (independent sample T-test on log transformed values)*

	MoM	MoP	p
Preop	0.31	0.29	0.644
0.25 year	0.98	0.36	<0.001
0.5 year	1.26	0.39	0.007
1 year	1.15	0.36	<0.001
2 years	0.99	0.44	<0.001
7 years	1.16	0.42	0.007
16 years	2.20	1.04	0.047

Figure 3. *Concentration of chromium over time, mean and 95 % CI.*



The increased mean concentration of Cr seen at 16 years was statistically significant in the MoP group compared to the mean concentration seen at seven years (p=0.021), but not in the MoM group (p=0.174). This increase, however, did not correlate with an increase in mean cobalt concentration. There was no statistically significant increase of Co in any group at sixteen years compared to seven years (MoP p=0.355; MoM p=0.197).

4.3 IMMUNOLOGICAL ANALYSIS, PAPER III

Immunological analysis of the clinical cohorts was performed at a mean of seven years after the index operation. The mean concentrations of immunoglobulins and the number of leukocytes and lymphocytes were within the reference intervals for both groups and no significant differences were seen between groups (Table 5). Most tested subsets of lymphocytes were similar in the two groups except for the population of $CD8^+$ T-cells positive for the HLA DR-antigen: 6.7 % in the MoP compared to 10.6 % in the MoM group (p=0.03). B-cells were found in a lower proportion of the total number of lymphocytes in the MoM group (9.3 % versus 12.9 % in the MoP group, p=0.01). There was no difference between groups regarding the total B-cell count.

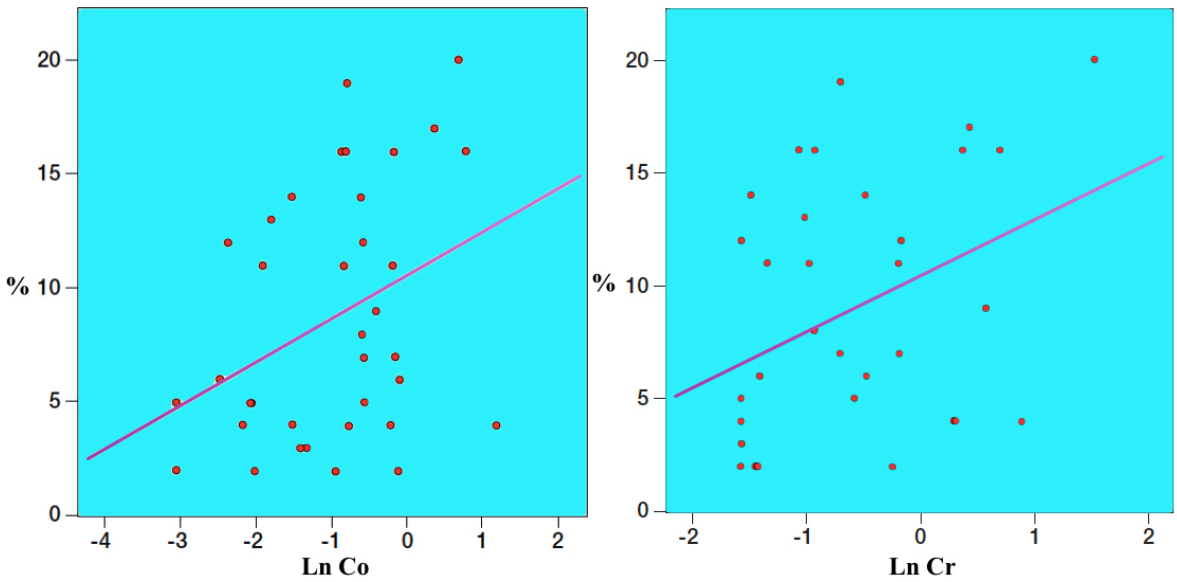
Table 5. *Immunological parameters. Mean differences of cells in numbers per nL, percentages or concentration of immunoglobulins in g/L, between the two bearing groups. Positive differences indicate higher values in the MoM group; negative indicate lower values in the MoM group.*

	Mean difference	95% CI	p-value*
Leukocytes	–0.4	–1.3–0.5	0.4
Lymphocytes	0.1	–0.4–0.5	0.8
T-cells CD3	0.0	–0.4–0.4	0.9
T-cells CD3 (%)	0.8	–4.6–6.2	0.8
T-cells CD4	0.0	–0.3–0.2	0.7
T-cells CD4 (%)	–3.1	–9.5–3.3	0.3
T-cells CD4 HLA DR+	1.5	–1.3–4.2	0.3
T-cells CD8	0.1	–0.1–0.3	0.4
T-cells CD8 (%)	5.0	–1.6–11.5	0.1
T-cells CD8 HLA DR+	3.9	0.3–7.4	**0.03**
CD4/CD8 ratio	–1.9	–4.8–1.1	0.2
B-cells CD19	0.0	–0.1–0.0	0.2
B-cells CD19 (%)	–3.7	–6.5–0.9	**0.01**
NK-cells CD16/CD56	0.1	0.0–0.2	0.1
NK-cells CD16/CD56 (%)	3.2	–1.8–8.3	0.2
IgG	0.2	–1.7–2.1	0.84
IgA	0.1	–0.9–1.1	0.79
IgM	–0.1	–0.5–0.2	0.39
IgG1	0.3	–0.7–1.3	0.55
IgG2	0	–1.2–1.2	0.99
IgG3	–0.2	–0.5–0.2	0.31
IgG4	0.1	–0.2–0.3	0.56

**derived from independent t-test. Bold numbers indicate p<0.05.*

A statistically significant positive correlation of the percentage of HLA DR^+ $CD8^+$ T-cells with logarithmically transformed concentrations of Co (r=0.36, p=0.03) and Cr (r=0.39, p=0.02) was found (Figure 4). No significant correlations were found for other subsets.

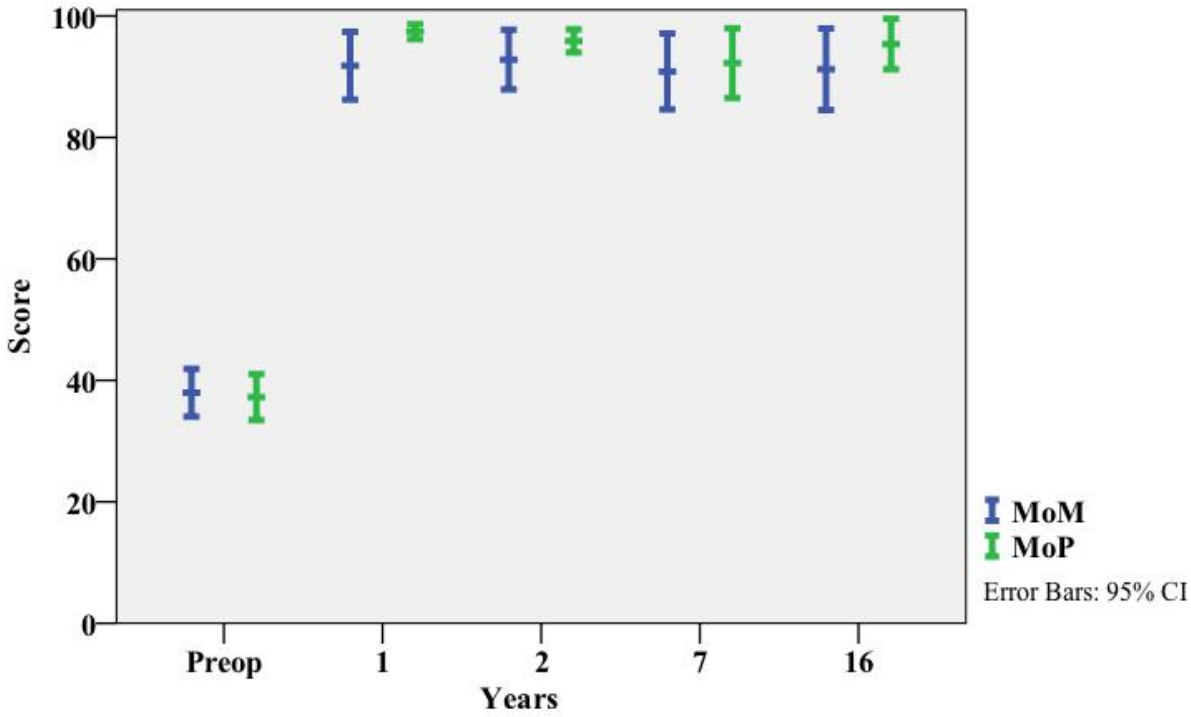
Figure 4. *Correlation between the percentage of HLA DR^+ $CD8^+$ T-cells and metal ion concentrations.*



4.4 CLINICAL PERFORMANCE OF STUDIED IMPLANTS, PAPERS II-IV

The Harris hip score increased after surgery and remained at a high level during follow-up (Figure 5). No statistically significant differences were seen between groups.

***Figure 5**. Harris hip score for metal-on-metal (MoM) and metal-on-polyethylene (MoP) THAs.*



The SF-36 at one and two years showed increased values for all eight domains in both groups compared to preoperative values (Table 6, next page). There were no statistically significant differences between the groups.

Table 6. *SF-36 preoperatively and at the 12- and 24-months follow-up.*

		MoP N=23		MoM N=27	
		Mean	SD	Mean	SD
Physical scores (5 dimensions):					
Physical functioning	Preop	40.0	24.6	32.6	22.6
	12 months	79.4	16.3	70.0	25.2
	24 months	77.0	19.3	67.2	26.9
Social functioning	Preop	71.2	26.8	71.8	23.4
	12 months	91.8	15.4	82.4	23.6
	24 months	88.0	20.5	83.3	27.1
Role limitations -Physical	Preop	23.9	35.0	15.7	28.7
	12 months	70.7	38.2	61.1	44.6
	24 months	69.6	39.9	60.2	44.0
Role limitations -Emotional	Preop	46.4	43.5	46.9	43.6
	12 months	78.2	38.4	64.2	44.3
	24 months	53.6	26.1	48.2	28.3
Bodily pain	Preop	39.3	19.2	33.3	19.4
	12 months	90.0	18.6	76.1	29.3
	24 months	76.7	27.9	67.9	31.7
Mental scores (3 dimensions):					
Mental health	Preop	69.2	21.8	69.0	20.5
	12 months	83.1	18.4	76.6	24.5
	24 months	80.2	18.9	73.8	20.4
Energy/Vitality	Preop	50.9	19.0	53.9	23.3
	12 months	77.6	22.1	67.8	26.2
	24 months	71.3	23.7	62.8	26.1
General health perceptions	Preop	69.1	20.8	68.3	23.0
	12 months	75.0	21.7	71.5	24.9
	24 months	70.0	20.8	66.1	26.0

4.5 RADIOLOGICAL OUTCOME, PAPERS II-IV

The mean cup inclination angle measured at 16 years was similar in both groups (MoM 45° vs. MoP 48°, p=0.33), and none of the stems had migrated beyond five mm. No major difference regarding radiographic outcome was seen between the two groups at neither two-, seven- or 16-year follow-up. The frequency and distribution of radiolucent lines at the last follow-up are shown in Table 7 and 8. There was no statistically significant difference between the groups.

***Table 7**. Presence of radiolucent lines at 16 years.*

Lucencies per patient (n)	MoM (n=13)	MoP (n=16)
Cup		
No lucency	7	6
1 zone	2	1
2 zones	4	7
3 zones	0	2
Stem		
No lucency	8	11
1 zone	4	3
2 zones	1	2

p=0.23 in DeLee zones and p=0.85 in Gruen zones using Mann-Whitney U test on independent samples.

***Table 8**. Distribution of radiolucent lines at 16 years.*

	MoM (n=13)	MoP (n=16)
No lucency in any DeLee zone	7	6
DeLee zone 1	4	8
2	2	4
3	4	6
No lucency in any Gruen zone	8	11
Gruen zone 1	3	3
2-5	0	0
6	1	2
7	2	2

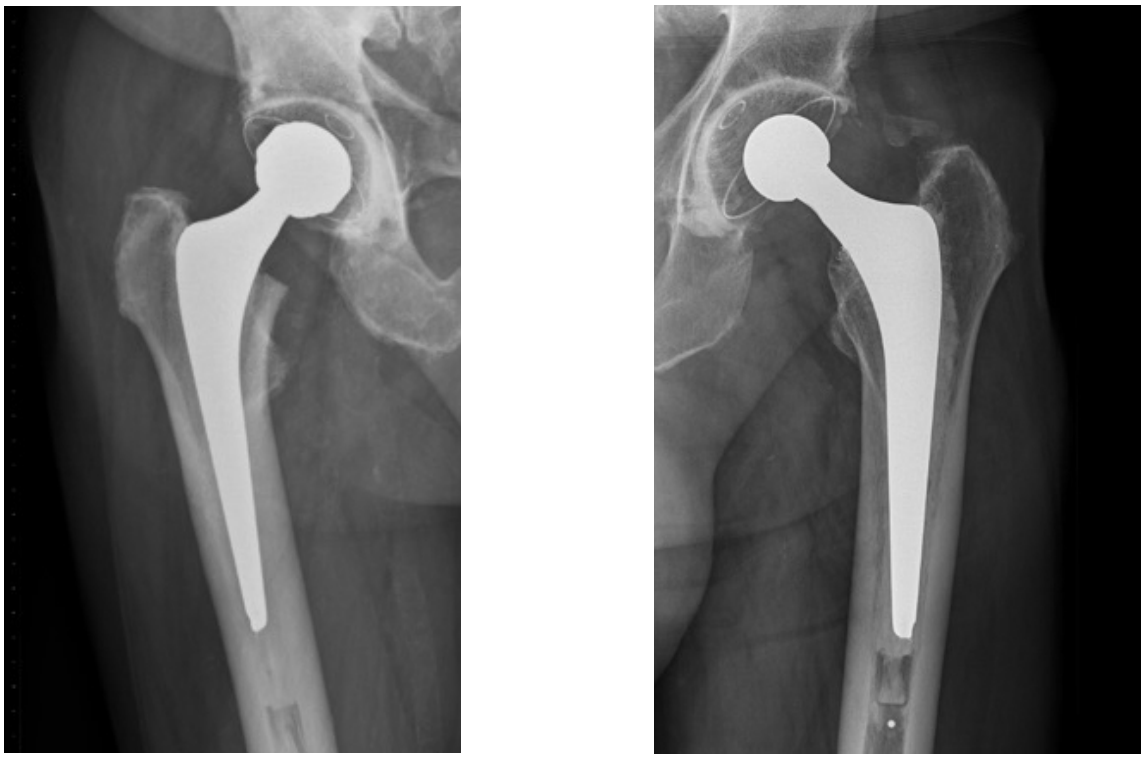


***Figure 6.** The Metasul MoM THA on the left and the Protasul MoP THA on the right.*

4.6 LONG-TERM SURVIVAL OF STUDIED IMPLANTS, PAPER IV

No patient suffered any complication, including deep infection, that needed surgery in the first two years after the index operation. A total of four patients underwent revision surgery during the study period, two in each group. Of these, one in each group had revision surgery due to aseptic loosening. Details of all revisions are shown in Table 9.

***Table 9**. All revision cases in chronological order.*

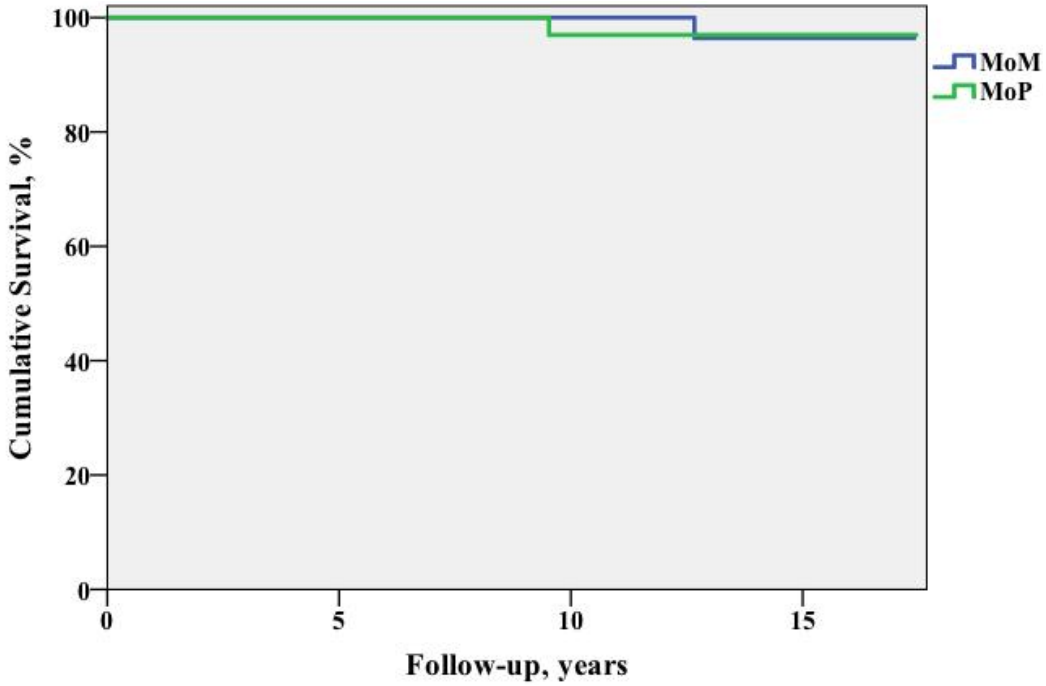
Patient / sex	Years to revision	Bearing	Aseptic loosening	Details
1 / F	2.1	MoP	No	Cup revision (recurring dislocations). No signs of loosening.
2 / M	9.5	MoP	Yes	Cup and stem revision (aseptic loosening).
3 / M	12.7	MoM	Yes	Cup and stem revision (aseptic loosening).
4 / M	13.0	MoM	No	Cup and stem revision (periprosthetic fracture). No signs of loosening.

MoM=metal-on-metal, MoP=metal-on-polyethylene. There were no macroscopic signs of metallosis or pseudotumours during revision surgery in any case.

Even though patients were not screened for pseudotumours with ultrasonography, CT or MRI, none presented with symptoms that indicated its presence at any time during follow-up.

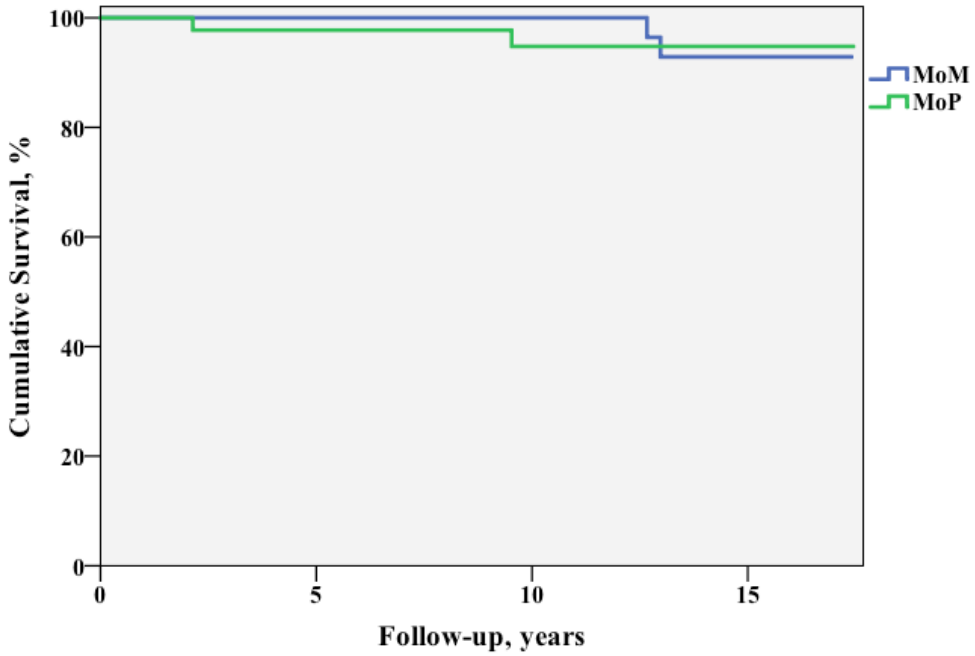
Long-term survival of the studied implants with aseptic loosening as the endpoint at 15 years was similar in both groups. The survival rate was 96 % in the MoM [95%-CI: 88-100%] and 97 % in the MoP cohort [95%-CI: 91-100 %]. No statistically significant difference was seen between the groups (p=0.99) (Figure 7).

***Figure 7**. Kaplan-Meier-analysis of metal-on-metal (MoM) and metal-on-polyethylene (MoP) articulations with revision for aseptic loosening as the endpoint.*



Survival with revision for any reason as the endpoint was 93 % [95%-CI: 83-100 %] and 95 % [95%-CI: 87-100 %] in the MoM and MoP group, respectively. There was no significant difference between the groups (p=0.99) (Figure 8).

Figure 8. *Kaplan-Meier-analysis of metal-on-metal (MoM) and metal-on-polyethylene (MoP) articulations with revision for any reason as the endpoint.*



5 DISCUSSION

We evaluated a MoM THA with a 28-mm head both in a joint simulator and in a clinical setting. In a unique prospective, randomized study with long-term follow-up (mean 16 years), we compared the MoM bearing with a conventional MoP THA with identical properties except for the articulating surface.

5.1 SURVIVAL AND CLINICAL OUTCOME OF THE 28-MM METASUL SYSTEM

A Medline-search in December 2016 revealed nine long-term studies evaluating the 28-mm Metasul bearing (Table 10).[52-60] Most of these studies were of a retrospective design, reporting the results of uncemented components in patients mostly younger than our cohort. Implant survival rates with revision for any reason as the endpoint were in most studies in line with our findings. Moreover, the proportions of patients revised due to aseptic loosening were also found to be similar when compared to our findings (Table 10).

Table 10. *Studies of long-term outcome (>12 years) of the 28-mm Metasul THA.*

Author	Year	Fixation	Age, mean	Study design	Control group/ randomization	n op./ n evaluated	Follow-up, years	Survival rate, %*	A.L. n/total
Dastane	2011	Uncement.	62	Retrospect.	No	127/69	13	91	1/69
Randelli	2012	Uncement.	50	Retrospect.	No	149/138	14	94	4/138
Saito	2010	Uncement.	56	Retrospect.	No	114/90	12	94	1/90
Delaunay	2016	Uncement.	42	Retrospect.	No	110/83	13	96	2/83
Tardy	2015	Hybrid	56	Retrospect.	No	106/60	13	79	5/60
Lass	2014	Uncement.	56	Retrospect.	No	105/83	18	87	4/83
Malek	2015	Cemented	66	Prospective	No	89/69	13	92	1/69
Innmann	2014	Uncement.	42	Retrospect.	No	100/79	12	92	1/79
Migaud	2011	Uncement.	40	Prospective	MoC/No	39/39	13	100	0/39
Dahlstrand	2017	Cemented	65	Prospective	MoP/Yes	41/41	16	93	1/41

** Survival rate with revision for any reason as the end-point. A.L.= Revision due to aseptic loosening.*

There were only two other studies comparing the 28-mm MoM Metasul articulation with alternative bearings using a prospective randomized study design.[57, 61] Bjørgul et al. reported a significantly lower survival rate and more radiolucent lines compared with the MoP and metal-on-ceramic (MoC) cohort after seven-year follow-up.[61] Eight of the 112 MoM THAs were revised after seven years, of which four were due to aseptic loosening. The mean age of Bjørgul's cohort (63 years) was comparable to that of our cohort and all implants were cemented. Migaud et al. compared uncemented MoM with MoC bearings in patients with a mean age of 40 years at the index surgery and a follow-up of 13 years. None of the 39 MoM THAs were revised, compared to 13 of 39 in the MoC control group.[57] The results from these two studies are diverging, however our results support the findings of Migaud et al., showing good long-term survival of the 28-mm Metasul THA.

5.2 TRIBOLOGICAL FINDINGS AND WEAR

A run-in phase of higher wear rates produced by MoM implants in a laboratory setting using a hip simulator has been described by others.[62-64] The results in our clinical study did not clearly show a similar early phase with higher concentrations of metal ions in patient serum during the first year compared to later time-points. Our findings are consistent with those of other studies.[65, 66] A theory that may explain these findings, is that an initial uptake of metals in the adjacent tissues with would prevent an actual accelerated early wear phase from causing elevated systemic metal concentrations compared to later time-points, when tissues are saturated. This hypothesis has not yet been investigated.

In paper I, we found that two pairs of head-cup couplings showed higher wear rates compared to the other four pairs and never reached a steady state wear-phase. This may suggest that there could be patients exposed to higher loads of metal ions from metal wear because of microscopical characteristics or flaws of their individual implants. This has not been confirmed in failed implant retrieval studies, where instead outliers with high metal ion concentrations and above average wear were more likely to have mal-positioned implants.[67]

MoM implants with larger head sizes have been shown to produce less wear than smaller diameter bearings in simulator studies.[26] This may be explained by the wider surface area over which contact stresses are distributed and the formation of a thicker fluid film between head and socket under ideal circumstances, i.e. in a laboratory setting. The in vitro finding of increasing wear with diminishing head size, stands in contrast to the findings in clinical studies and retrieval studies. [16, 67, 68] In these studies, hip resurfacing systems and large head MoM THAs showed considerably more wear and higher systemic metal ion concentrations compared to smaller diameter MoM systems. One large retrieval study by Hart et al., reporting the examination of 276 revised large diameter MoM implants showed a high proportion of wear from edge loading on the bearings of the failed implants.[67] This correlated only to some extent with a high cup inclination angle, which is known to cause edge loading.[69] Hart et al. showed that in cases with a normal or low cup inclination angle, other factors may explain the edge-loading. Those factors could be e.g. impingement or peri-operative deformation of cups with thin acetabular metal wall by design, such as the Articular Surface Replacement system (ASR, DePuy, Warsaw, IN, USA). A slightly deformed cup would result in equatorial loading of the articulating surfaces. This factor may in part explain the finding of high wear and failure rates in certain withdrawn resurfacing prostheses and mega head systems. The most common cause for revision in the study of Hart et al. was unexplained joint pain and most of the implants from these patients did not show extensive wear. This led the authors to speculate that they might suffer from a none dose-dependent hypersensivity to metal ions.

Thus, there are conflicting results from in vitro studies of wear rates related to head diameter compared with in vivo studies of the same implants. This may generate the hypothesis that MoM THAs with small diameter heads, like the 28-mm head investigated in our study, may be more “forgiving” regarding implant positioning compared to large caliber head systems.

This, combined with the finding that some designs of large head systems have a higher risk of component deformation during implantation, indicates the need for further investigation in future studies.

5.3 CONCENTRATIONS OF COBALT AND CHROMIUM

The concentrations of Co and Cr in our clinical study were in accordance with other reports evaluating patients with the same 28-mm MoM articulation or similar small diameter MoM bearings from other manufacturers.[53, 55-57, 70-72]

Some authors presented metal ion concentrations from whole-blood while others measured concentrations in serum or plasma. There is no evidence of the superiority of one method over the other.[73] We measured concentrations in plasma until the seven-year follow-up, but had to change to serum at the 16-year follow-up due to a change of methodology at the external laboratory used throughout the study. In a study comparing the concentrations of metal ions in the different blood fractions, serum and plasma was found to be interchangeable regarding concentrations of Co and Cr.[74] The same study showed that Co and Cr were found in lower concentrations in erythrocytes in patients with a MoM THA, resulting in lower concentrations of these ions in whole blood compared to plasma and serum. In healthy controls there were two to three times higher concentrations of Cr in erythrocytes compared to serum, in contrast to the distribution of ions found in MoM patients.[74] This is explained by the fact that Cr is found physiologically in small amounts intracellularly, especially in erythrocytes. Plasma and serum in patients with a MoM THA contain according to one study, on average 1,5 times the amount of Co and Cr found in whole blood.[75] The observed pattern of a higher concentration of Cr in extracellular fractions of blood after MoM THA indicates that Cr released from MoM bearings is of the less biologically active trivalent form, not being able to penetrate cellular membranes. Co is predominantly found extracellularly in both healthy controls and MoM THA patients.[68, 74]

The significant elevation of Cr in both groups of our study at the follow-up at 16 years was not accompanied by a rise in Co. This may be the result of corrosion or wear from the head-neck junction, so-called trunnionosis.[76] An alternative explanation could be the change of method of sample collection and equipment at the latest follow-up, an undesired and unfortunate side effect of the long-term setup.

There are guidelines stating that patients with MoM implants should be monitored and screened for elevated metal concentrations regardless of symptoms.[40-42] This screening is recommended to detect early cases of ARMD that may need revision surgery. A cut-off level of seven μg/L for Co and Cr in whole-blood has been set by the FDA and MHRA, above which further action should be taken. Even though ion concentrations are believed to reflect the amount of wear from bearings, and elevated levels are associated with a higher risk of revision, there is little evidence to support this screening method as the only predictor of the patients' risk of revision due to implant failure.[20, 77-79] There are reports stating that above-average concentrations of Co and Cr may correlate with the development of pseudotumours

and there are yet other studies contradicting such a relationship.[21, 80, 81] The findings of pseudotumours is not a certain predictor for clinical symptoms or mechanical failure leading to revision.[79, 82]

5.4 SYSTEMIC EFFECTS OF COBALT AND CHROMIUM FROM METAL-ON-METAL IMPLANTS

The effect on lymphocyte counts in relation to the concentration of circulating Co and Cr ions after THA has been investigated, but the results are inconclusive.[83-85] Retrospective studies indicate that higher metal concentrations correlate with a decrease in circulating $CD8^+$ lymphocytes.[83, 84] The only prospective, randomized study including baseline levels of cellular immunology and metal ions showed a small but statistically significant depressive effect of Co ions on the general T-cell count.[85] This is in contrast to the findings of our study, which documented a correlation between an increase of the sub-group of $CD8^+$ cells expressing HLA-DR and higher metal concentrations. The clinical significance of this finding is however unclear.

In a recent study, tissues from pseudotumours of patients with failed ASR implants were shown to exhibit a macrophage dominated reaction in patients with higher systemic concentrations of Co and Cr.[86] In the same study, patients with lower systemic concentrations of metals, comparable to the level seen in our study, showed a lymphocyte driven inflammation. This would suggest two separate types of failure mechanisms; one caused by a cytotoxic reaction to high level of metals driven by macrophages and one with the characteristics of a delayed-type hypersensitivity reaction, mediated by lymphocytes.[86]

Co and the hexavalent form of Cr are known to have various biological effects and even cause morbidity in humans at high concentrations.[31-33, 36, 87-92] Hence, it has been motivated to investigate their potential role in the development of cancers after MoM THA. In several Nordic studies, data from the national hip arthroplasty registries was analyzed and matched with data from national cancer registries. Cancer incidences in patients with MoM and MoP hip implants were compared with each other and with the cancer burden in a selected, matched population without prostheses, as well as with that of the general population. Even though studies did not show an increased total risk of cancer or mortality for other reasons associated with MoM implants, there are indications of a higher rate of basal cell carcinomas.[93-96] This type of cancer is known to be more common in patients with a compromised immune system following organ transplantation and is believed to be especially related to a lower $CD4^+$ T-cell count.[97] Another recent study of the first seven years after implantation of a MoM THA, based on the National Joint Registry in Great Britain, showed no increased risk of cancer.[98] Since the registry did not start collecting data until 2003, the follow-up is shorter than those of the Nordic studies.

Although metal ions at concentrations normally seen after MoM THA are not believed to cause systemic morbidity, there are case reports of severe conditions in patients with extremely elevated concentrations of Co and Cr after THA surgery.[18, 99, 100]

Toxic concentrations of 100-5,000 times the levels seen in our study, are not uncommon in those case reports and patients often show various symptoms and conditions associated with Co poisoning, e.g. peripheral neuropathy, sensorineural hearing loss, visual impairment, cardiomyopathy and hypothyroidism.[19] Poisoning from extreme levels of Co associated with a MoM THA can even be fatal.[89, 101] Some of the cases with ultra-high levels of Co and Cr are revised patients where a THA with shattered ceramic bearings have been replaced with a MoM or MoP THA.[100] In these cases, friction from microscopic ceramic shards between the articulating surfaces will lead to large amounts of metal wear.

6 LIMITATIONS

The power calculation that was performed prior to our clinical study revealed the need of a cohort of at least 20 patients in each arm to detect significant differences concerning the primary outcome (metal concentrations during the run-in phase). With time, other outcomes were added to the study, e.g. long-term survival and immunological analyses, with the risk of a type two error as the number of patients diminished during follow-up due to death and other causes. Regarding the difference in immunological parameters between groups at seven years, there was both a risk of type one and type two error.

Because only 30 of 85 patients could be evaluated at the 16-year follow-up, we chose not to exclude patients that had received additional implants. This should be considered when comparing the metal ion concentrations of this study to those of other studies, even though none of the patients had an additional MoM implant and the presence of additional implants was similar in both groups at 16 years (MoM=nine out of 14 patients vs. MoP=10 out of 16 patients; p=0.61).

The small differences in the method of gathering blood and the preparation of serum for the measurement of metal ion concentrations at the 16-year follow-up compared with earlier time-points may have resulted in a potential methodological error. This could affect the comparison of Cr concentrations with earlier follow-ups but not the comparisons between groups at this time-point.

The analysis of immunological differences between groups would have greatly benefitted from preoperative baseline values of the immunological status of the patient cohort, which our study lacked.

The patient cohort and exclusion of patients was not fully described in paper II and not presented in accordance with the CONSORT statement. This was not a requirement at the time of publication. The cohort is described more accurately in the patients and methods section of this thesis.

The acetabular components of both the MoM and the MoP were made from UHMWPE, a predecessor to the highly crosslinked PE which was first introduced into the market soon after the initiation of our clinical study. Since most cups today are made from highly crosslinked PE, the use of a cup made from this material in the MoP control group of our clinical study would have been preferred.

7 CONCLUSIONS

This thesis concludes the following:

1. MoM implants show a wear pattern in vitro consisting of an early high wear run-in phase, followed by a steady-state phase with a significantly lower wear rate.
2. Patients with a MoM THA have significantly higher systemic concentrations of Co and Cr compared to patients with a MoP THA at all time-points during 16 years of follow-up.
3. There is evidence suggesting that increasing systemic concentrations of Co and Cr correlate with changes in lymphocyte subsets.
4. The over-all clinical performance and long-term survival of a 28-mm all-cemented Metasul MoM THA is similar to that of a comparable conventional Protasul MoP THA.
5. There is no superiority of any of the investigated bearings when compared with each other, hence we recommend the use of the MoP articulation to avoid the subsequent life-long exposure of biologically active metal ions from MoM THAs.

8 FUTURE PERSPECTIVES

As mentioned previously, it is estimated that over one million patients worldwide presently live with a MoM implant. Many of these patients were operated at a relatively young age. The matter of what happens to them in the event of future kidney failure has not been thoroughly investigated.[102] Since the circulating metal ions from MoM bearings are excreted via the kidneys, hopefully there will be future investigations shedding more light on this issue.

The concept of MoM implants has historically been introduced twice and both times been found to be inferior to other articulations. Since we all know the saying that the third time is a charm, it would not be surprising if a re-introduction of MoM is seen some twenty years from now. The take-home message from this thesis to future manufacturers would be to remember that:

- tribological findings in vitro do not always correspond to actual performance in vivo
- metals with known biological activity and toxicity are not suitable in alloys of rigid bearing surfaces
- clinical series with long-term follow-up are essential in the introduction of new implant systems, preferably before they are widely introduced on the market.

9 POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrunden till att mycket forskning ägnas åt att optimera de metoder och material som används vid höftproteskirurgi är det utgör ett av de vanligaste kirurgiska ingreppen i vårt land och i övriga västvärlden. I Sverige utförs årligen drygt 16 000 höftprotesoperationer.

På femtiotalet började operationer med konstgjorda ledproteser utföras i ökande skala på människor med smärtande höftleder. Höftproteskirurgi utnämndes redan efter några årtionden med rätta till ”århundradets operation”. I flera av de tidigaste protesmodellerna var både lårbenets ledhuvud och bäckenets ledpanna ersatta av protesdelar gjorda helt av metall, så kallade metall-mot-metall (M-M) proteser. Inom några år utmanades M-M modellen av andra protessystem, i vilka ett litet metallhuvud istället ledade mot en ledpanna av polyetylenplast. Den mest berömda protesen med ledytor av metall-mot-polyetylen (M-P) har uppkallats efter sin skapare, sir John Charnley. Med den så kallade Charnley-protesen erhölls minimal friktion mellan de rörliga delarna och en ”golden standard” sattes för höftproteser. M-P visade mycket goda initiala resultat och medförde att M-M-proteserna konkurrerades ut under sjuttiotalet. Det finns dock fortfarande människor i livet med välfungerade M-M-proteser från sextio- och sjuttiotalen kvar i sina höfter.

Materialet till denna avhandling kommer från innehållet i två studier. I den första har M-M-protesen Metasul testats i en höftsimulator och mängden nötning från sex protesers ledytor har mätts regelbundet under drygt fyra miljoner cykler, motsvarande fyra års normalt användande i kroppen efter operation. Resultatet visar att nötningen av ledytorna i de flesta fall var störst under det första året och därefter planade ut på en lägre nivå. Den andra studien är en klinisk studie som omfattar 85 patienter med höftartros. Hälften lottades till att opereras med en likadan M-M-protes som i den första studien och hälften lottades till en kontrollgrupp som fick liknande proteser men med slitytor av M-P. Grupperna följdes sedan under 17 år med regelbundna kontroller av höftfunktion, röntgenutseende och blodkoncentrationer av metallerna kobolt (Co) och krom (Cr) som ingår i höga halter i protesernas metallegeringar. Sju år efter operationerna kontrollerades även patienternas immunförsvar.

Resultaten visar att båda protestyperna gav en god och likvärdig funktion. Runt proteserna syntes röntgenförändringar i lika hög utsträckning i båda grupperna. Endast två patienter i varje grupp hade efter 15 år behövt opereras om i sina höfter, vilket anses vara ett gott resultat och i linje med andra studiers resultat avseende liknande proteser. Halterna av Co och Cr i blodet var högre i patientgruppen med M-M-proteser jämfört med M-P-gruppen vid alla mättillfällen efter operationen. Sju år efter operationen syntes små men mätbara skillnader i halterna av vissa typer av vita blodkroppar. Andra studier har också sett skillnader i immunförsvaret efter operation med M-M-proteser. Man vet sedan tidigare att Co och Cr, i betydligt högre halter än de vi fann i vår studie, kan medföra allvarliga sjukdomar.

Slutsatsen i denna avhandling är att man på grund av risken för oklara biologiska effekter i kroppen på lång sikt inte rekommenderar användande av M-M-proteser, trots goda och likvärdiga resultat jämfört med de traditionella modellerna med ledytor av M-P.

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