Diplomarbeit

The ASR Implant Recall: A Single Center Experience

Metal Ion Concentrations And Revision Rates For Metal-on-Metal Hip Arthroplasty

eingereicht von

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zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde
(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Orthopädie und orthopädische Chirurgie

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Graz, am 09.06.2016

Affidavit

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 09.06.2016 Peter Höfler, eh.

Danksagungen

An dieser Stelle möchte ich mich bei all jenen Menschen bedanken, die mir bei der Erstellung dieser Diplomarbeit halfen.

Zuvorderst gilt mein Dank Hr. Prof. Dr. Andreas Leithner und Hr. OA Dr. Werner Maurer-Ertl für die Themenstellung und die Begutachtung meiner Arbeit. Weiters danke ich Hr. Ass. DDr. Jörg Friesenbichler der mich während der Diplomarbeit betreut hat. Er war es, der mich mit meinem Thema vertraut gemacht hat und ohne dessen stetes Engagement und Umsicht meine Arbeit in dieser Form nicht zustande gekommen wäre. Darüber hinaus wurde er mir in jener Zeit nicht nur ein Freund, sondern auch ein Vorbild in mancherlei Belangen.

Im Übrigen danke ich all meinen Freunden, die mich Zeit meines Lebens begleitet haben und mein Leben stets aufs Neue bereichern. Stellvertretend für all jene, sei hier der Name von Markus Kieler genannt, den ich schon lange Jahre einen meiner besten Freunde nennen darf.
Darüber hinaus danke ich meinen Brüdern Gernot und Robert für ihren unermüdlichen Zuspruch und die Freuden durch allerlei Späße. Meiner Freundin Jördis Fuchs danke ich für das Korrekturlesen, ihre Anteilnahme an meinem Leben, ihre Hingabe und Motivation sowie ihr Verständnis.
Vor allem aber danke ich meinen Eltern, Maria und Nikolaus Höfler, die mich in allen Lebenslagen unterstützt und begleitet haben, mir dieses Studium ermöglichten und deren Erziehung mich zu jenem Menschen werden ließ der ich nunmehr bin.
Eingedenk Kästners Epigramm an die Moral will ich diesen Prolog enden: ”Es gibt nichts Gutes, außer: man tut es!”[1]

[1](Kästner, Erich: Doktor Erich Kästners lyrische Hausapotheke. Dtv, 2005, 21.Auflage, S.30.)

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Glossary and Abbreviations

AAOS	American Academy of Orthopaedic Surgeons
AOA	Australian Orthopaedic Association
ALVAL	Aseptic Lymphocyte-Dominated Vasculitis Associated Lesions
ALTR	Adverse Local Tissue reactions
ARMD	Adverse Reaction to Metal Debris
ASR	Articular Surface Replacement
BHR	Birmingham Hip Resurfacing
BMI	Body Mass Index
cm	Centimetres
Co	Cobalt
CoC	Ceramic-on-Ceramic
CoP	Ceramic-on-Polyethylene
Cr	Chromium
CT	Computed Tomography
dl	Decilitre
EDTA	Ethylene Diamine Tetraacetic Acid
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
ET-ASS	Electrothermal Graphite Furnace Atomic Absorption Spectrometry
Fig.	Figure
HA	Hydroxyapatite
HRA	Hip Resurfacing Arthroplasty
L	Litre
LOT	Batch Number
MARS	Metal Artefact Reduction Sequence
MHRA	Medicines and Healthcare products Regulatory Agency

Mo	Molybdenum
MoM	Metal-on-Metal
MoP	Metal-on-Polyethylene
MRI	Magnetic Resonance Imaging
NJR	National Joint Registry
Tab.	Table
THA	Total Hip Arthroplasty
RPM	Rounds per minute
UHMWPE	Ultra-High Molecular Weight Polyethylene
UHXLPE	Ultra-High Cross-linked Polyethylene
µg	Microgram
µl	Microliter
µg/L	Microgram per Litre

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Legend to Tables

Zusammenfassung

Hintergrund:

Die dritte Generation von Hüftgelenksoberflächenersatz mit einer Metall-Metall-Gleitpaarung und großem Durchmesser wurde zu Beginn des 21. Jahrhunderts eingeführt und erfreute sich großer Popularität. Diese Endoprothesen wurden vor allem bei jungen und physisch aktiven Patienten implantiert. Innerhalb weniger Jahre jedoch, verzeichneten einige nationale Endoprothesenregister einen Anstieg von Revisionszahlen für fehlgeschlagene Metall-Metall Oberflächenersätze. Dies führte dazu, dass DePuy seinen Oberflächenersatz, das Articular Surface Replacement™ System (ASR™), weltweit vom Markt nehmen musste. In dieser Studie berichten wir über die Komplikations- sowie Revisionsraten von Patienten, die mit dem ASR™ System in unserem Institut behandelt wurden.

Methoden:

In unserem Institut wurden zwischen 2005 und 2008 insgesamt 64 ASR™ Prothesen in 56 Patienten implantiert. Zwanzig Patienten erhielten einen ASR™ Resurfacing Oberflächenersatz und 44 ein ASR™ XL-Head Implantat. Der durchschnittliche postoperative Nachbeobachtungszeitraum betrug 90 Monate (Spanne: Zwischen 20 und 109 Monate). Folgendes Procedere wurde bei jedem Patienten im Rahmen der Rückholaktion durchgeführt: Klinische Untersuchung, Bestimmung der Serum Metallionen-Konzentrationen und Röntgenbilder der Hüfte. Weiters wurden all jene Patienten mit erhöhten Serum Metallionenspiegel oder Schmerzen in der Hüfte zur Kernspintomographie überwiesen.

Resultate:

Insgesamt betrug die Revisionsrate in der ASR™ XL Head Gruppe 32% und in der ASR™ Resurfacing Gruppe 30%. Die mittlere Zeitspanne ab der Erstoperation bis zur Revision betrug 48 Monate. Die Revisionen wurden durchgeführt aufgrund erhöhter Serum Metallionenspiegel, Luxation oder Subluxation, aseptischer Lockerung des Femurschaftes, ARMD und Infektionen. Jedoch war während unserer Studie nach einer Revisionsoperation keine weitere Revision mehr notwendig. Bei den Revisionen konnten alle ASR™ Pfannen durch Press-fit Pfannen sowie die Metall-Metall-Gleitpaarung durch Keramik-Keramik-

Gleitpaarung ersetzt werden. Die berechnete Überlebensrate der ASR™ Implantate betrug in der ASR™ XL Head Gruppe 79% und in der ASR™ Resurfacing Gruppe 90% nach 60 Monaten.

Schlussfolgerung:

Unsere Studie zeigte hohe Revisionsraten beider ASR™ Implantat Typen. Wir empfehlen bei symptomatischen Patienten, einerlei ob mit oder ohne erhöhten Serum Metallionenspiegel, eine Kernspintomographie durchzuführen, um eine ARMD auszuschließen. Eine Revision sollte erwogen werden bei Patienten mit hohen Serum Metallionenspiegel, lokalen Schmerzen oder bei einer manifesten ARMD.

In Anbetracht der hohen Revisionsraten des ASR™ Systems, wäre eine engmaschige Überwachung von neuen Implantaten angebracht, um künftig einem solchen Implantatversagen entgegenzuwirken. Weiters spiegelt der Rückruf des ASR™ Systems die Wichtigkeit nationaler Endoprothesenregister wieder.

Abstract

Introduction:

The third generation of metal-on-metal hip arthroplasties with large diameter heads were brought up to the market within the last decade and gained wide popularity. These metal-on-metal devices were especially implanted in young and physically active patients. However, in the short run national joint registries observed an increment of revision rates due to ineffective metal-on-metal hip arthroplasties. The circumstance of increasing revision rates of failed metal-on-metal devices induced DePuy to a voluntarily recall of its Articular Surface Replacement™ (ASR™) hip prostheses. In this survey we reveal the number of adverse events and revision rates of patients treated with the ASR™ system at our institute.

Patients & Methods:

In our institute, a total of 64 ASR™ hip prostheses were implanted in 56 patients, beginning in 2005 until 2008. Twenty patients received an ASR^{TM} Resurfacing and 44 an ASR^{TM} XL-Head device. The mean postoperative follow-up was 90 months, ranging from 20 to 109 months. Within the scope of the recall following proceedings were realised in every patient: clinical examination, plain radiographs and serum metal ion determination. Furthermore MRI scans were performed in all patients who showed increased serum metal ion levels or who complained about pain.

Results:

The cumulative revision rate in the ASR^{TM} XL Head cohort was 32% and 30% in the ASR^{TM} resurfacing cohort. The average time from index surgery to revision was 48 months, regardless from the complication. Revisions have been performed due to increased metal ion levels, dislocation or subluxation, aseptic loosening of the femoral stem, adverse reaction to metal debris (ARMD) and infection. However, it has to be said that after revision surgery no further re-revision had to be done. During revision surgery all ASR^{TM} cups were revised into a press-fit cup and the metal-on-metal bearing was replaced by a ceramic-on-ceramic liner. The

calculated implant survival for the ASR™ Resurfacing devices was 90% after 60 months, whereas the survival was 79% in der ASR™ XL Head group.

Discussion:

According to the current literature, our study revealed unsatisfying results of the ASR™ system with high complication- and revision rates. Overall, we suggest that symptomatic patients, regardless whether they have high or low serum metal ion levels, should receive magnetic resonance imaging to rule out ARMD. Revision surgery should be considered if patients complain about local pain, if they have high serum metal ion levels or if formation of ARMD can be detected. Considering the high revision rates of the ASR™ system, it would be advisable to implement an appropriate surveillance program of new launched devices to avoid such complications. Hence, the voluntarily recall of the ASR™ systems illustrates the importance of national implant registries.

1. General Part

1.1. History of orthopaedic devices

Themistokles Gluck was one of the greatest pioneers in the history of artificial joint replacement. He first conducted an artificial knee joint made of ivory in 1890 (Figure 1). Unfortunately, the device had to be removed due to an early prosthetic infection. Afterwards there was a lot of progress in the knowledge of surgical techniques, joint biomechanics, implant design and fabrication.

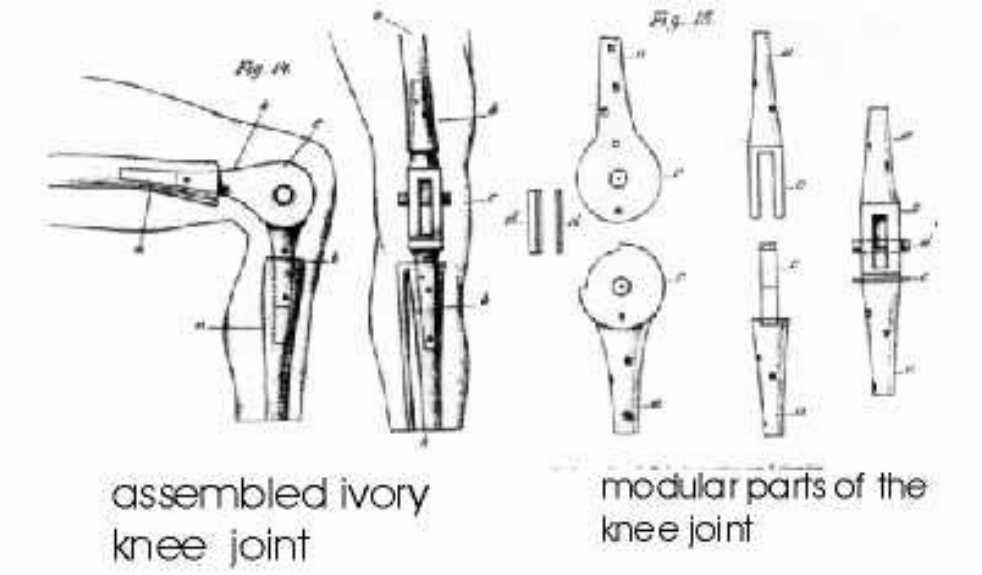

Figure 1: Drawing of Themistokles Gluck's artificial arthroplasty (Picture from http://www.thecascadiacourier.com/2013/04/my-knee-hurts.html).

In 1928 Smith-Petersen performed an artificial reconstruction of the hip joint for ostheoarthritis utilizing a glass cap. (1,3,4) Despite the improvement of the patients' pain, the clinical results of this treatment were unsatisfactory and many of this glass caps cracked. Afterwards, the design was modified several times by using other materials but also with unsatisfying clinical results (Figure 2). (1,3–5)

Figure 2: The evolution of Smith-Petersen's caps (Picture from M. Smith-Petersen, Evolution of mould arthroplasty of the hip joint, J Bone Joint Surg Br, 1948, 59-75, (1))

Sir John Charnley designed a new promising hip resurfacing arthroplasty (HRA)-device made of Teflon in the 1950s. Unfortunately this design also failed due to high wear rates, followed by early loosening and necrosis of the femoral head (Figure 3). (3,6)

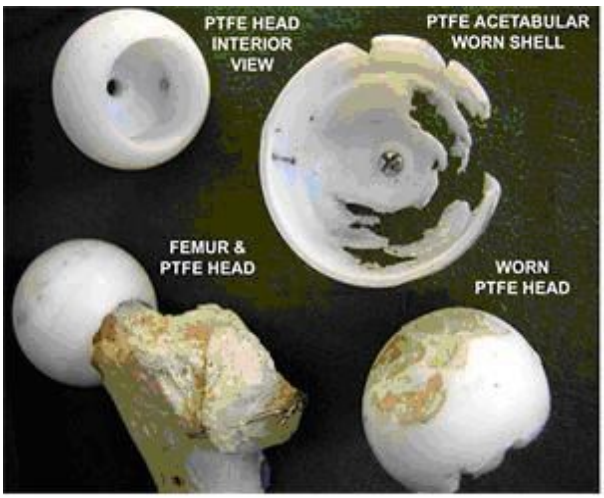

Figure 3: Picture of Charnley's HRA (Picture from www.kon.org/urc/v5/ravichandran.html).

At the beginning of the 1960s, Charles O. Townley designed a hip resurfacing arthroplasty device composed of metal backed femoral cup and a polyurethane socket (TARA, Figure 4), likewise with catastrophic outcome due to high wear rates. (3,7)

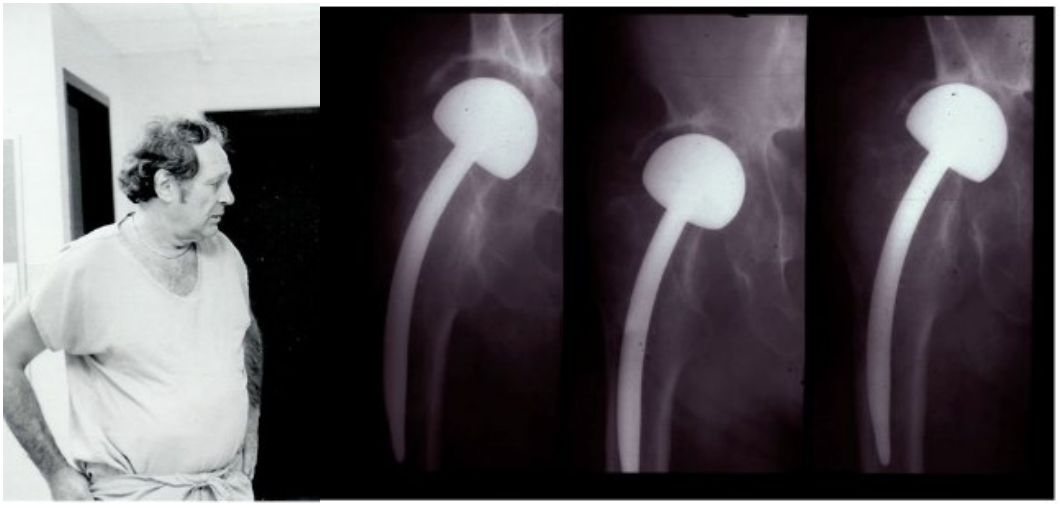

Figure 4: Charles O. Townley and a picture of his HRA called TARA on the right. (Pictures from http://seattlejointsurgeon.com/pdf/journals/townley.pdf).

Until the 1970s, this design had been modified into a metal backed cup with a polyethylene socket, but long-term results have not been published. (3)

M.E. Müller developed an implant based on a re-cap design in 1967, which was one of the first metal-on-metal (MoM) devices. (3,8,9) This type of hip replacement was implanted in 18 patients. Despite good early results, about 50% of the implants had to be revised due to insufficient migration/osteointegration of the components, later the design was changed into a metal-on-polyethylene (MoP) pairing. (3,8,9)

The implementation of the first known performing total hip replacement by Sir John Charnley led to the continuous development of new total hip arthroplasties but it also led to less interest in the evolution of hip resurfacing devices (Figure 5). (3,10)

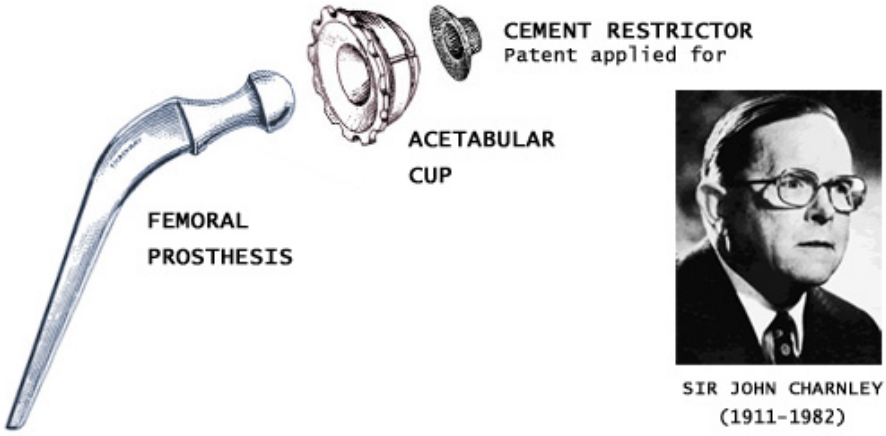

Figure 5: Sir John Charnley and a picture of the Charnley THA system (Picture from www.almuderis.com.au/hip-surgery/hip-arthroplasty/141-information/history-of-hip-replacement).

Nevertheless, every new generation of THA devices showed complications and a variety of different reasons for revision, that is why interest in resurfacing revived in the seventies. (3)

In 1970, Gerard published the results of a bipolar double-cup arthroplasty comprising of matching cups and uncemented components. (3,11) The design was changed from metal-on-metal (MoM) pairings to metal-on-polyethylene (MoP) articulation due to high wear rates, whereas this problem could not be resolved despite this kind of modification (Figure 6). (3,11)

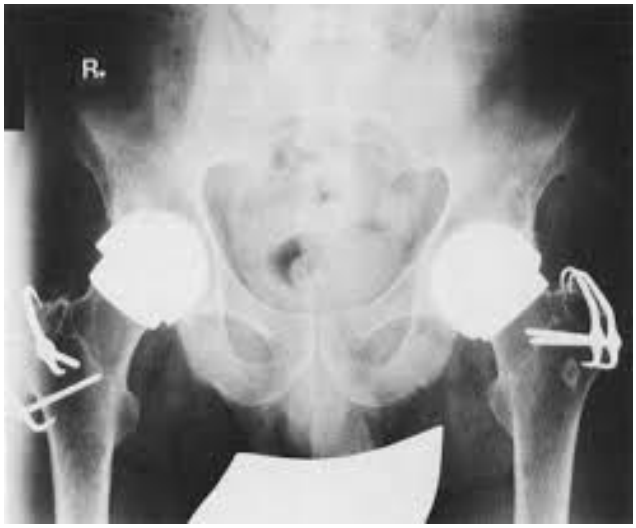

Figure 6: Picture of a patient treated with a bilateral HRA, developed by Gerard (Picture from W. Willems et al.; Gerard cup arthroplasty in inflammatory arthropathy of the hip, Clinical orthopaedics and related research 1986, (210): 179-84,(2)).

In the seventies, various designs and materials were utilized, mainly comprising two congruous elements joined to the femoral head and the acetabular cavity. (3,12) In general, MoP bearings were used, but also other materials like ceramics were introduced. (3,12) This treatment was named double-cup arthroplasty and widely used in several nations, for instance in Japan, the USA, Germany and Italy. (3,12–19)

The double-cup arthroplasties were primarily conceptualized for young patients, due to the benefit of femoral bone stock retention. (12) These early designs revealed unsatisfactory long-term results likened to THA. (20–25)

The Wagner cup may serve as an example. (3,16) It was first implanted in 1974 in Germany and consisted of a polyethylene acetabular component combined with a femoral cup made out of cobalt (Co)/chromium (Cr) alloy or ceramic (Figure 7).

(3,16) The Wagner cup was widely used in Europe, but the preparation of the femoral head was inaccurate and the revision rates were high due to aseptic loosening. (3,4,12)

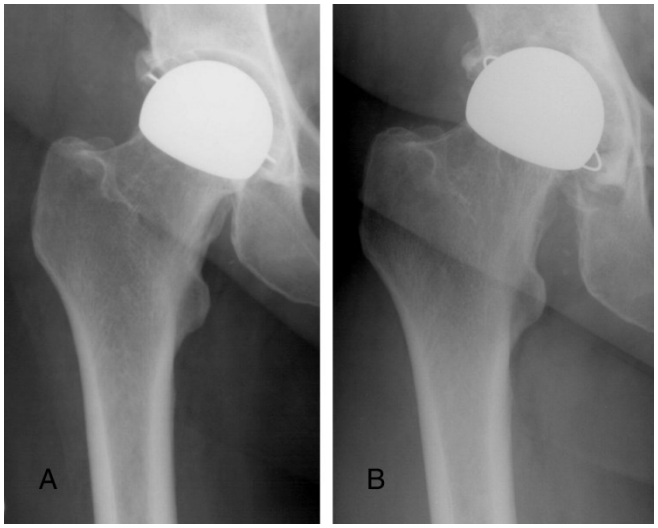

Figure 7: Picture showing a Patient treated with a RHA developed by Wagner, (A) postoperative anteroposterior radiography and (B) the same patient after 11,5 years (Picture from http://www.arthroplastyjournal.org/article/S0883-5403%2809%2900109-0/fulltext).

The first generation of hip resurfacing arthroplasties had high failure rates and therefore the idea of resurfacing was abandoned by many surgeons and the orthopaedic community. (12)

The main reason for high failure rates was massive polyethylene wear debris, produced by the large femoral head articulating with a cemented acetabular ultra-high molecular weight polyethylene-inlay (UHMWPE), which led to an accelerated formation of osteolysis and subsequent to prosthetic loosening. (12,26)

Further reasons for high failure rates were incorrect implantation techniques and design, as well as insufficient implantation equipment. (3)

In the early 1990s the idea of hip resurfacing arthroplasty revived because of new promising metal alloys which showed good wear behaviour in total hip arthroplasties (THA).(3,4,12) Weber's development of a new alloy named “Metasul” (Zimmer Inc. Warsaw, Indiana, USA) in 1988, consisting of Co and Cr, as mentioned, renewed the interest in the second generation of MoM devices. (3,27,28)

On one hand, the Metasul MoM bearing was widely used in Europe and showed promising early results. (3,29-31) On the other hand, dislocation was a rising

complication due to the usually used head size of 28 mm. (3,29–31) Wagner and Wagner implemented a new design for a HRA in Germany in 1991, whereby the acetabular socket consisted of a titan alloy combined with a Metasul-inlay. (3,32) Nevertheless, problems arose with the implants, because there were only four sizes available and the implantation tools were insufficient. (3)The first generation of this cup design was fixated with screws, later this design was changed to a press-fit system. (3) Only few of these press-fit devices were implanted and therefore long-term results were not published, to the best of our knowledge. (3) Simultaneously, McMinn et al. developed an articular surface replacement also made of a CoCr-alloy in the United Kingdom (Figure 8). (3,33) Due to high loosening rates of this design, McMinn modified the implants several times as well as its fixation arrangements. (3)

Figure 8: Picture showing some of McMinn's early design concepts of his HRA developed in 1991 (Picture from www.mcminncentre.co.uk/response-dispatches-program.html).

In 1996, Amstutz et al. published the first results of their MoM HRA consisting of a Co-Cr alloy, reporting promising short-term results. (3,12,34)

Since the beginning of the 21st century, a various number of MoM resurfacing designs have been implemented on the international market, also known as the so called third generation MoM devices. (3) Unlike the conventional MoP or ceramic-on-ceramic (CoC) implants, theoretical advantages should be: less volumetric debris (35–37), increased stability and a better range of motion (ROM) (37–41). Therefore these devices were widely used in young and physical active patients.

(3) One example for such a device was the Birmingham Hip Resurfacing (BHR™, Smith & Nephew, MA, US), designed by McMinn, which was introduced on the European market in 1997 (Figure 9). (42)

Figure 9: The Birmingham Hip Resurfacing (BHR, Smith & Nephew) designed by McMinn as it came on the market in 1997 (Picture from www.mcminncentre.co.uk/response-dispatches-program.html).

In 2003, DePuy (Johnson & Johnson, IN, US) launched their MoM bearing on the European market, which is better known as the Articular Surface Replacement (ASR™) system with a Resurfacing device and the XL Head System. (4,42)

1.2. History of tribological bearings

At the onset of artificial hip replacements various materials were used for joint replacement. For instance, different tissues like fasciae, fat and muscle were used to cover lesions of the femoral head caused by osteoarthritis. (3) Since these attempts failed, caps made out of glass and/or vitallium were used for replacement, also with unsatisfying outcome. (1,3,4) For decades, MoP remained the golden standard and showed good early results. (3,12) But on the long run, high failure rates were detected due to the polyethylene wear which led to periprosthetic osteolysis followed by aseptic loosening of the implant. (3,12,43) Improvements like the introduction of high cross-linked polyethylene (HXLPE) and ultra-high cross-linked polyethylene (UHXLPE) dissolved this formerly mentioned issues and were proven by various publications. (12,44) Also the implementation of CoC bearings was a noteworthy development, minimizing the issues of inlays made of

polyethylene, even though current published studies revealed varying findings. (45–48) Advantages of CoC bearings are substantial lower rates of revision, dislocation, periprosthetic osteolysis and aseptic loosening, although the design is vulnerable to squeaking noises and fracture of the tribological bearing during the implantation. (45,47,48) The question whether CoC bearings are better than CoP remains unclear, as exhibited in recent studies. (45,48) Amstutz et al. (12) revealed that further research on cross-linked polyethylene utilized in bearings and CoC bearings is needed. Another noteworthy development in the area of tribological bearings were MoM pairings that used high-carbon Co/Cr-alloys. (3)

1.3. Advantages of hip resurfacing arthroplasties

In general hip resurfacing arthroplasties (HRA) were introduced with the advantages of preserving femoral bone stock, larger femoral heads with lower rates of dislocation, reconditioned hip biomechanics, restoring leg length and easier revision to a THA. (12,49–53) These advantages designated HRAs as a primary intervention especially suitable for young and physical active patients since there is the possibility of revision surgery. (12)Usually, modern HRA used MoM bearings due to assumed low abrasion rates and the materials' strength. (12)

1.4. The history of Articular Surface Replacement

As mentioned before, several modern hip resurfacing arthroplasty devices using a MoM bearing were introduced on the market in the 1990s. Good short-term results, together with the revaluation of alternative bearings, made hip resurfacing arthroplasties popular again. (12,54–62) Several manufacturers of orthopaedic devices included a metal-on-metal bearing in their portfolio and the registry data revealed an increment of hip resurfacing arthroplasties being done until 2006. (12,63–65)

Derek McMinn evolved the Birmingham Hip Resurfacing (BHR) in the United Kingdom. (42) This device was launched in 1997 on the European market and quickly gained popularity. Later on, the BHR was authorised by the Food and Drug Administration (FDA) in 2006. (42)

Smith and Nephew purchased the BHR™ design, and the economic competition between those two producers forced DePuy, a Johnson & Johnson company, to develop a new MoM HRA on their own, in order not to forfeit market shares. (42)
The Articular Surface Replacement (ASR™) Resurfacing System is a modern third generation MoM device. (4) The bearing consists of a cast Co-Cr alloy (Figure 10). (4) The ASR™ had not been tested in patients before it was launched on the European market in 2003, since resurfacing implants were categorized as a category 2b device. (42) In the guidance document of the European Commission that classifies medical devices, IIb devices were classified as follows:" All implantable devices and long-term surgically invasive devices are in Class IIb." (206) At that time, DePuy met the requirements of the European Commission and carried out simulator studies before they brought the ASR™ to the European market. (42)
Worldwide, the systems were introduced in 2004, both devices available in various sizes matching to the existing anatomy and more than 100.000 implantations were performed. (4,42,66)
In 2005 DePuy received a 510(k) clearance from the FDA and therefore, the company was allowed to launch their product on the US market without performing a clinical study on the ASR™ XL head system. (42,67)

Figure 10: The ASR™ Resurfacing System (Picture from http://www.depuysynthes.com/asrrecall/malaysiapatient.html).

Clearance is the distance between the hinged articulating surfaces of an implant. The clearance has also an influence on the implants wear rates, the lower the clearance the better the lubrication is and the lower the wear rates are. (204,205) DePuy postulated an optimized clearance by joining a large head diameter and a lower clearance, hoping for a better lubrication and therefore better tribological behaviour. (4) The clearance of the ASR Resurfacing System was commended to be up to threefold lower compared to other hip resurfacing devices (Figure 11). (4)

Figure 11: Optimized clearance of the ASR^{IM} Resurfacing System (Picture from a DePuy advertising brochure)

In general, the HRA designs per se were already bone preserving implants. This effect was enhanced by the inside of the femoral component, which was 3º conic (Figure 12). (4) This fact enabled a lower diameter of the femoral head and might lower the chance of femoral neck notching. (4)

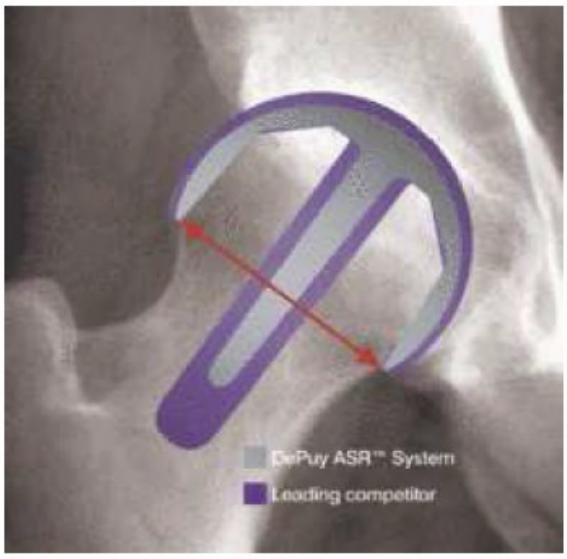

Figure 12: Conic shape of the ASR^{TM} femoral component (Picture from a DePuy advertising brochure)

Further, DePuy propagated that the design of the ASR™ Resurfacing System, was conceptualized to grant an ideal lubrication despite intraoperative deformation during implantation, which was calculated to ensure that the implant's clearance always remained high. (4)

If the osseous requirements of the ASR™ Resurfacing System could not be met intraoperatively, the ASR™ XL Head System acted as a suitable option, although the benefit of femoral bone stock preservation got lost. (4) On the other hand, the ASR™ XL Head System should have maintained all other merits of the ASR™ Resurfacing System (Figure 13). (4)

Figure 13: The ASR™ XL Head System (Picture from a DePuy advertising brochure)

1.5. Indications for total hip arthroplasty and resurfacing hip arthroplasty

Generally speaking, there were the following indications for a MoM THA (4):

- Osteoarthritis: primary vs. secondary
- Collagen disease
- Avascular necrosis
- Rheumatoid arthritis
- Innate dysplasia of the hip
- Acetabular protrusion
- Epiphyseal coxa vara

- Posttraumatic arthritis
- Disablement because of former arthrodesis

The indications for a MoM HRA are primary or secondary osteoarthritis of the hip. (4)

Contraindications for MoM HRA were as follows (4):

- Posttraumatic arthritis
- Grave dysplasia of the femoral head or the acetabulum
- Epiphyseolysis of the femoral head
- Allergies to metal and an arthritis of the hip post-osteotomy

1.6. Investigated Characteristics of metal ions and serum metal ion levels

Cobalt (Co) is known as a heavy metal belonging to the 8th group in the periodic system of elements and its naturally occurring isotope is Cobalt 59. (68) Co is widely used in the industry, e.g. in steel-alloys or low abrasion materials. Further, it is a component of vitamin B12. (68) Therefore, it is also an essential trace element. (68) The average Co plasma concentration of a naturally exposed adult is 0,06 to 0,07 µg/L, whereas a normal serum cobalt level is <0,45 µg/L. (68) In case of Co poisoning, acute symptoms like nausea, vomiting, colics and respiratory depression can be observed. (68) Chronic symptoms of Co intoxication are struma, polycythaemia, cardiomyopathy and metabolic acidosis. (68–70) Poisoning by Co is known among alcoholics because in former times it was used as a foam stabilizer in beer, additionally. (71) Furthermore, poisoning has been observed in industrial workers and in patients. (71) Further symptoms of Co intoxication, also called cobaltism, as described by Tower et al. (72), are: headaches, vertigo, hypothyroidism, tinnitus, peripheral neuropathy, deafness, convulsion, blindness and optic nerve atrophy.

Chromium (Cr) is known as a transition metal belonging to the 6th group in the periodic system of elements and its naturally occurring stable isotopes are ^{52}Cr, ^{53}Cr and ^{54}Cr. Cr is widely used in the industries e.g. in steel alloys due to its high corrosion resistance and hardness. Furthermore, it is an essential trace element. (73) Cr is absorbed by the skin, the gastrointestinal tract and lungs. A

normal serum Cr level is less than 0,40 µg/L. (68) High oral Cr doses can cause acute intoxication with the following symptoms: affection of the gastrointestinal tract, vomiting, diarrhoea, hepato-renal-damage, shock and even death. Chronic symptoms of poisoning with Cr, especially hexavalent Cr, are for instance: conjunctivitis, gastritis, gastric ulcers, allergies, eczemas and bronchial carcinomas. Treatment of choice of a systemic intoxication is dimercaptopropanesulfonic acid (DMPS), and also Chrome (VI) can be reduced via ascorbic acid to a less toxic Cr (III).

In regard to total hip arthroplasty, the literature reveals 5 cases of intoxication due to increased Co and Cr concentrations. (70,71,74–77) All cases occurred due to third body wear following breakage of a CoC bearing and revision to a MoP bearing. Treatment of choice is revision arthroplasty and chelation therapy, where the symptoms should improve. (70,71,74–78)

Wear and corrosion of MoM bearings might cause an elevation of plasma metal ion levels of Co and Cr. (74,79–82) Therefore, they are nowadays used as a surrogate direct or indirect marker for component wear.(83) A number of authors demonstrated the relation between Co and Cr concentrations measured in blood or serum and failure of hip resurfacing arthroplasty, especially due to the evolution of adverse reactions to metal debris (ARMD). (12,84–88)

Otherwise, worries that the activity of patients with MoM devices could lead to elevated serum metal ion levels were refuted by the findings of Heisel et al. (89).

At present, there is a discussion, if metal ion analysis is accurate to detect ARMD and how to set the threshold at which further investigations and even interventions should be done. (90,91) For instance, De Smet et al. (83) reported that metallosis was related to Cr serum levels higher than 17 µg/L or Co serum levels higher than 19 µg/L, whereas Hart et al. (92) suggested the optimal cut-off serum level of 4,97 µg/L for both Co and Cr. In April 2010, the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) applied a threshold of 7 µg/L for Co and Cr in their safety alert (91,93,94), whereas Hart et al. (95) recently suggested that a threshold of 7 µg/L both for Co and Cr should not only be utilized to prognosticate the indication for revision. There is a broad number of studies approaching the subject of high metal ion concentrations in the hip joint, the periarticular soft tissues and systemically in blood and urine generated by MoM bearings. (74,96–101) Nevertheless, there is a consensus that Co concentrations

higher than 10 µg/L are at concern and require accurate follow-up in asymptomatic patients. (12) On the other side, the correlation between metal ion levels and malfunction of implants is not linear, therefore, it is difficult to adopt an absolute threshold of ion levels that could be used as a "screening tool" indicating an ARMD. (12,90,102)

Several studies showed that there are various other reasons that affect the metal ion serum levels, like implant design, size and geometry of the bearing, individual biological response as well as the approach and component malposition (inclination, anteversion, arc of cover) and, additionally, variations in metallurgy and production. (12,74,97,103,104)

Further, Amstutz et al. (12) attributed problems in MoM bearings not to the material but to insufficient design and operative procedure. De Haan et al. (105) postulated that higher metal ion blood concentrations are found in patients with steeply-inclined (abduction angle >55°) MoM resurfacing components. Furthermore, edge-loading of MoM devices might cause inadequate lubrication resulting in elevated blood metal ion concentration due to increased wear. (105–110) De Haan et al. (105) also showed that a reduced arc of cover less than 10mm increased the risk of elevated metal ion levels in serum. On the contrary, Maurer-Ertl et al. (103) did not find a significant correlation between Co and Cr concentrations, arc of cover and inclination, neither in the THA nor in the RHA group. Macnair et al. (91) related that small head sizes, mainly used in women, cause higher Cr levels compared to men. Langton et al. (111) also indicated that patients with large femoral components bigger than ≥53 mm had substantial lower serum Cr and Co levels than those having a small femoral component (≤ 51 mm). Furthermore, these authors postulated that the serum metal concentrations substantially correlate with the acetabular anteversion angle. (111)

Another characteristic of MoM bearings is the "running in phase", in which Cr and Co levels increase due to wear, during the first 3 months to 2 years. (74,96,103,112–121) The "running in phase" is followed by the "steady state phase". (121–124) In that phase, levels of wear decrease. Apart from that, Imanishi et al. (125) referred that the serum levels of Cr and Co did not increase significantly between the third month and one year postoperatively. On the other hand, Sauvè et al. (122) reported in their 30 years follow-up study on the Ring THR (MoM) threefold and fivefold higher Co and Cr levels compared to four

reference groups. A 10-yearsperiod study on MoM resurfacing, approached by deSouza et al. (126), showed an increment of metal ion concentrations during the first 18 months following implantation, a slow decrement towards the fifth year and subsequently again an increment. Furthermore, these authors postulated that the metal ion concentrations measured in women were not significantly higher compared to men, whereas Moroni et al. (127) postulated that Cr-concentrations in women were significantly higher than those of men. As mentioned before, one of the main problems of MoM HRA and modular MoM THA are elevated metal ion concentrations. (4,74,126) Therefore, it is interesting that both implant types show the same wear rates and increased blood levels, as shown by Matthies et al. (128). Based on these findings, Matthies et al. (128) assumed that the mechanism of high wear in all types of large-diameter hip arthroplasty and hip resurfacing was the same. These observations were also made by Moroni et al. (127) during their 2- and 5-year follow-up study. The mean levels of Co, Cr and Mo did not differ in patients with MoM THA and MoM HRA, although the metal ion concentrations were 7-fold to 10-fold higher compared to the control group ($p<0.001$). (127)

Several studies in the literature contradict the afore shown results, by revealing significant higher concentrations of blood metal ions in patients with MoM THA compared to those with a MoM HRA. (103,112,129) Another source of metal ion debris, elevated metal ions release and therefore ARMD, may be the wear between a modular stem and head in the setting of a THA. (12,101,130–133) Furthermore, recent studies showed that micromotions of implant surfaces, at hinged articulations and in case of press-fit junctions (e.g. MoP, CoC, MoM or modular devices), might produce additional wear (=fretting corrosion). (128,134) This fretting corrosion might also lead to ARMD and is generally known as tribocorrosional effect. (128,134) Additionally, Amstutz et al. (12) revealed problems in modular femoral THA components and urged not to combine parts of MoM HRA and MoM THA with large femoral heads since they are designed differently. Furthermore, there are uncertainties about taper geometry and corrosion at the junction side. (12)

1.7. Effects and consequences of elevated serum metal ion concentrations

Hart et al. (135) showed decreased peripheral blood counts of T- and B-lymphocytes in patients with MoM hip replacements compared to the control group with non-metal debris producing hip replacements (CoC and MoP hip replacements). High Co and Cr levels may also increase the incidence of chromosomal aberrations as shown by Ladon et al. (136). These authors demonstrated a 1.5-fold higher risk of chromosomal translocations and a 2-fold to 4-fold higher risk of aneuploidy in peripheral blood within 2 years after MoM arthroplasty likened with preoperative values. Nevertheless, the Agency for Research on Cancer postulated in two reports in 1999 and 2003 that orthopaedic implants are not classifiable as carcinogenic due to the fact that there is an insufficient evidence in humans regarding the carcinogenicity of orthopaedic devices. (137–139) Contrariwise, Visuri et al. (140) lately revealed a significant increment in the prevalence of melanoma and prostate cancer in patients with total hip arthroplasty.

Mavrogenis et al. (141) stated that, if patients suffered from pain after implantation of a total knee prosthesis or increasing masses in the knee, the orthopaedic surgeon should have different pathologies in mind, first soft tissue and bone sarcomas, as well as metastatic carcinomas to the bone, followed by aneurysms, cystic infections, deep vein thrombosis, or cellulitis. (142,143) This principle can be extended to hip arthroplasties as well. Furthermore Mavrogenis et al. (141) included the differential diagnoses such as wear debris, metallosis and aseptic loosening of the knee arthroplasty. This principle extends to hip arthroplasties as well. For instance, Ring et al. (144) showed that metallosis is a known complication among MoM bearings used in joint arthroplasty originating to the attrition of the bearings surfaces followed by a release of metal debris that affects the periprosthetic tissue, causing local tissue inflammation and elevated systemic serum metal ion levels. (145) Ottaviani et al. (146) attributed the formation of metallosis to the chemical and toxicological effects of wear generated by MoM arthroplasties and presumed that the periprosthetic tissue defects correlated with the implants size. (147) Berry et al. (148) showed in their study that the attrition of MoM surfaces correlated with wear debris, loss of joint height and implant failure. Furthermore, these authors stated that the metal wear may provoke an immune-

mediated inflammation involving different cytokines such as tumour necrosis factor-alpha 1 (TNF-alpha1), matrix metalloproteinase-1 (MMP1), interleukin-1 (IL-1), interleukin-6 (IL-6), and prostaglandin E2 (PGE2). (148-150) Ultimately, this inflammatory reaction might provoke pain, osteolysis, pannus development and loosening of the device. (148) Singh et al. (151) observed increased levels of interleukin-1 beta (IL-1ß), interleukin-5 (IL-5), interleukin-10 (IL-10), and granulocyte macrophage colony stimulating factor (GM-CSF) in the surrounding tissues of revised MoM THA with lymphocyte-dominated tissue reactions.

Fary et al. (100) explained that metal wear can induce inflammatory soft tissue reactions which have been given various names: ARMD (adverse reaction to metal debris, 152), ALVAL (aseptic lymphocytic vasculitis associated lesion, 153), inflammatory pseudotumor (154), adverse local tissue reactions (ALTR, 155) and metallosis (156). There is also a difference regarding the definition of pseudotumors. Chang et al. (157) termed “any periprosthetic collection, regardless of size or quality” as pseudotumor, knowing that they might “inlcude periprosthetic collections not related to an adverse reaction to metal debris.“ Controversially, several authors stated that this observation can be interpreted as “a capsular weakness owed to the capsulotomy.” (157–159)

The orthopaedic community has struggled for a long time to agree on an umbrella term and since 2012, there has been some consensus between the AAOS and EFORT that all kind of local soft-tissue reactions are categorized as ARMD. (37,97,152,157,160–163) Anderson et al. (164) implemented a magnetic resonance imaging (MRI) classification for ARMD comprising five grades which are defined by the damage of the periprosthetic soft tissue as well as osseous and neurovascular structures.

At present, little is known concerning the origin and pathogenesis of ARMD, it might be a type four hypersensitivity reaction to the MoM debris. (74,96,100,165)

Moreover, it is uncertain if adverse reactions are dose-dependent, immune mediated or if adverse reactions are provoked directly by the metal wear. (74)

Malek et al. (90) declared that wear not only leads to ARMD but also to implant loosening, osteolysis, bone necrosis or fracture. (166–170) Patients with ARMD may present with different symptoms. Fary et al. (100) investigated that patients with ARMD might complain about discomfort or pain in the operated area, and in some cases, these sensations can spread out in the groin, the upper leg, the flank

or the bottom. (154) Further, symptoms are a noticeable swelling around the hip, the feeling of a mass in the groin, clicking noises of the implant and “giving way” of the hip. (100,154) As reported in the literature ARMD may also cause symptoms by compression of the neuro-vascular bundle next to the joint (= femoral nerve and or artery). (100,153,154,171)

Beneath the evaluation of metal ion levels to detect an ARMD, plain radiographs, ultrasound, cross sectional imaging using computed tomography (CT) and/or MRI can be used for diagnosing, whereby Fary et al. (100) showed that each of these procedures has its limitation.

In general, the golden standard in treatment of an ARMD induced by metallosis is a revision surgery combined with the replacement of the MoM bearing to another type of bearing, e.g. CoC, and resection of all inflammatory tissue. (104,172)

There is always the question if surgery is indicated in every case. At present, little is known about the natural course of ARMD and its progression, but recent case series indicated a possible further progression during conservative treatment. (100,173,174) Recently, Grammatopoulos et al. (171) showed in their study that in case of revision for ARMD the outcome is weak and they affirmed surgeons to reconsider a timely revision to avoid further progress of soft-tissue degradation. They further postulated that after revision complication rates still remain high. (171)

2. Special Part

2.1. The ASR Recall

In 2003, DePuy launched their MoM bearings on the European market and in 2004 the ASR™ systems were launched worldwide. (4,42,66) In 2005, DePuy received a 510(k) clearance from the FDA and brought the ASR™ XL Head system to the US market. (67)

Both devices were available in various sizes and more than 100.000 implantations were performed. (4,42,66) Nonetheless, the 7th annual report of the National Joint Registry (NJR) for England and Wales in 2010 revealed increasing revision rates for both ASR™ systems with revision rates higher than 10% at five years.(4,42,175) In addition to that, the annual report of the Australian Joint Registry in 2009 also showed higher than anticipated numbers of revision for these devices. (176,177) The dispatch and the raising doubts induced the Medicines and Healthcare products Regulatory Agency (MHRA) to release warnings in April 2010 (MDA/2010/033) and in May 2010 (MDA/2010/044) regarding MoM hip replacements in general and particularly, the ASR™ XL Head and the ASR™ Resurfacing systems. (4,42,91,94,178) In the end, DePuy realized the problematic nature of their MoM devices and performed a voluntary international recall in 2010. (42)

The aim of the current series was to report the official recall process at our department with complications and revision rates associated with these devices. Furthermore, the implant survival was calculated according to the method of Kaplan-Meier.

2.2. Patients and Methods

Between 2005 and 2008 a total of 64 ASR™ devices have been implanted in 56 patients at our institution. Out of this group, 20 patients received an ASR™ Resurfacing device and 44 patients an ASR™ XL Head prosthesis. Eight patients were treated with a bilateral MoM THA, likewise using an ASR™ XL Head implant. At the time of operation the patients were between 29 and 68 years old, the

average age at implantation was 51 years. There were 27 female and 29 male patients. The demographic data is shown in Table 1 and Table 2 (Appendix).
The majority of the patients that received an ASR^{TM} device participated in an ongoing prospective postmarketing surveillance study which assessed the serum metal ion concentrations. In this study, the blood serum concentrations were evaluated at intervals of 6 to 12 months depending on whether the metal ion concentrations were higher or lower according to the threshold of 7 µg/L. The results have recently been published by Trennheuser et al. (4) and Maurer-Ertl et al. (103).
Since DePuy published a voluntarily recall of their ASR^{TM} devices in August 2010, all patients who received an ASR^{TM} device were approached.(42) The patients were asked to attend clinical follow-up that evaluates potential implant associated complications. The follow-up included: clinical examination, plain radiographs, evaluation of serum metal ion concentration as well as cross sectional imaging with a Metal Artefact Reduction Sequence (MARS) MRI. The MARS MRI was particularly performed in patients who had pain in the hip or who had serum metal ion levels above the suggested threshold of 7 µg/L. (12) A few patients (n=21) denied the cross sectional imaging with the MARS MRI because they did not suffer from pain or had any other adverse event.

2.2.1. Privacy of the postmarketing surveillance study

Every participant of the prospective postmarketing surveillance study entrusted with this study obligated themselves to apply patient data and results of documentation absolutely confidential. Therefore all published data of this survey are applied anonymously.

2.2.2. Criteria of inclusion and exclusion

2.2.2.1. General inclusion criteria

All patients, men and/or women, with primary or secondary osteoarthritis of the hip between the age of 18 and 70 receiving a THA were asked to participate in the postmarketing surveillance study observing a MoM device. Patients who did not

fulfil the osseous requirements on femoral side for MoM HRA but for a cementless acetabulum received a large-head MoM THA.
The participants of the series agreed and understood the terms of the survey and were willing to collaborate. Further, the patients had to sign an informed consent.

2.2.2.2. General exclusion criteria

Patients who were not in the state of participating survey and follow-up as well as patients with the following criteria were not considered for the survey:

- Metal sensitivity
- Impaired kidney function
- Contagious disease
- Gravidity or planned gravidity within two years after surgery
- Drug and alcohol addiction
- Mental diseases
- Attendance in another survey within the last twelve months
- High dose or long term cortisone therapy
- Acute or recent joint sepsis

Exclusion criteria according to the manufacturer:

- Substantial osteoporosis and poor bone grade
- Distinct atrophy and malformations of the proximal femur
- Immature skeleton
- Neuromuscular disease
- Anatomic stem-shaft-angle under 120°
- Radiotherapy of the affected hip

2.2.3. Metal ion analysis

Blood samples were taken from all patients to examine the serum metal ion concentrations of Co and Cr. The procedure was done on equal setting conditions for all patients. The needles we utilized were forged out of stainless-steel and linked to no additive vacuum blood collection tubes with 9 ml capacity (VACUETTE®). The utilized tubes were no additive tubes in order to receive

accurate data of serum metal concentrations since additives like EDTA might falsify the results. All parts of the used equipment were manufactured by the same producer (VACUETTE®) and had the same LOT numbers. Additionally it should be mentioned that no patient in this survey suffered from renal impairment.
Within two hours after taking blood, all samples were processed in a centrifuge for ten minutes at 4300 rpm, afterwards the supernatant fluid was charged in two cryo-tubes with 5 ml capacity and the tubes were stored at 4° Celsius in a refrigerator until the evaluation of serum metal concentrations was done. One of the two samples was sent for evaluation at an off-site laboratory (Medical and Chemical Laboratory Diagnostic Lorenz & Petek GmbH, Graz, Austria). As procedure to investigate the serum metal ion concentrations electrothermal graphite furnace atomic absorption spectrometry (ET ASS) has been chosen, due to increased sensitivity and reduced matrix effects (Zeeman Effect). The second blood sample was stocked at -20° Celsius in our institute for further application if needed.
Each of our blood samples were processed by rarefying 300 microliters (µl) of the specimen with 50 µl modifier and 550 µl of distilled water (Rotipuran). Fifty microliters modifier and 850 µl distilled water (Rotipuran) served us as blank value. Afterwards the specimens for evaluation have been vaporised in an atomization machine and were converted into atomic status. As aforementioned, we utilised the electrothermal graphite furnace atomic absorption spectrometry (ET-ASS) for analysis. Therefore the rarefied specimens were filled in graphite tubes, using a micro pipette, and were liberated of dissolvers and other concomitant agents by applying incremental heat on the specimens subsequently the specimens were atomized. The ET-ASS generated a signal with an area which should be proportional to the element we wanted to determine, whereas the concentration of the rarefied specimen was computed by utilizing the dose volume of the specimen.

2.2.4. Statistical analysis

The acquired data was used to generate statistics to show differences between ASR^{TM} XL Head and ASR^{TM} Resurfacing groups and to evaluate differences in the serum metal ion concentrations of revision and non-revision groups. We observed an asymmetric distribution of all parameters and therefore non-parametric tests

(e.g. Kolmogorov-Smirnov test, Mann-Whitney-U test) were used. Furthermore, the implant survival was calculated in correspondent to the method of Kaplan-Meier. A p-value of <0.05 was assumed to be statically significant. For statistic evaluation the PASW Statistics 16.0 program (SPSS Inc., Chicago, IL) was utilized.

3. Results

3.1. Results of the *ASR™* XL Head Group

The ASR™ XL Head group consisted of 36 patients with a total of 44 ASR™ XL Head devices implanted. Eight patients of the group were treated with a bilateral MoM THA. The demographic data of the patients is shown in Table 1. The average follow-up after the initial surgery was 78 months, ranging from 20 to 98 months. Two patients were lost to the follow-up due to death of hepatocellular carcinoma (HCC) 20 and 67 months following initial surgery, respectively. MARS MRI was conducted in a total of 24 patients, whereas in seven patients (29%) an ARMD was ascertained. In the ASR™ XL Head group three revisions had to be done already before the recall, two due to a persisting infection (5%) in one patient 61 months after implantation and one due to dislocation (2%) after missed closed reduction 39 months following implantation. Due to increased serum metal ion concentrations, eight ASR™ XL Head devices (18%) were revised at an average follow-up of 56 months, ranging from 38 to 83 months. Furthermore, three revisions were made owed to aseptic loosening of the femoral stem (7%), which were conducted at an average follow-up of 41 months, ranging between 14 and 56 months. The overall revision rate for any complication was 32%.

3.2. Results of the ASR™ Resurfacing

Twenty patients, treated with unilateral HRA, joined the ASR™ Resurfacing group. See Table 2 for demographic data. After the initial surgery the average follow-up was 86 months, ranging from 68 to 109 months. MARS MRI was particularly performed in 11 patients who had discomfort in the hip or who had serum metal ion levels above the suggested threshold of 7 µg/L. (12) Overall, in five patients (45%) an ARMD was ascertained.

Three patients (15%) had a revision because of an ARMD, whereby one patient had two revisions due to the development of a pseudotumor before the ASR™ device was changed against another tribological paring 12 and 13 months following the initial surgery, respectively. The second patient needed a revision due to ARMD combined with an impending fracture of the femoral neck 69 months

following index surgery. One patient required revision surgery due to dislocation (5%) instantly after primary implantation of the ASR™ resurfacing device, whereby a significant increment of metal ions in the serum and detection of an ARMD in the MRI (5%) led to revision of the tribological paring 74 months after initial surgery. Another patient needed revision surgery due to subluxation (5%) owed to malposition of the ASR™ cup 72 months following initial surgery. The cumulative revision rate for all complications was 30%.

3.3. Revisions of the ASR™ Resurfacing and ASR™ XL Head

An antero-lateral approach was used in all revision surgeries, with removal of all ASR™ components.

During the study we observed that the femoral stems (Corail™ or Future™, DePuy Orthopaedics Inc.) of those patients treated with an ASR™XL Head system were well integrated except of the three revision cases for aseptic loosening, therefore no further revision of the femoral stems was necessary. In every case of revision surgery we observed blackish-grey colouring of the soft tissue generated by metallosis, as we had assumed (Figure 14).

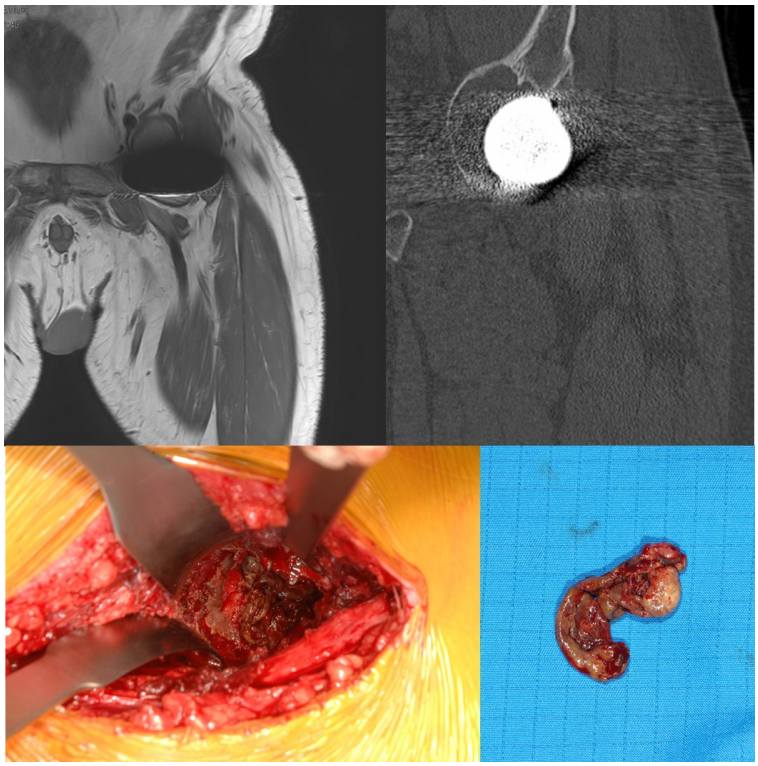

Figure 14: MRI and CT scan of an ASR™XL Head device showing an ARMD and a supraacetabular osteolysis as well as photographs of the resected ARMD intraoperatively.

Intraoperatively resected tissue, e.g. cystic formations (ARMD), was sent for histopathologic analysis. In case of a supra- and peri-acetabular osteolysis the bony defects were treated by padding the lesion with allogenic cancellous bone grafts. Every ASR™ cup was changed to a press-fit implant e.g. Pinnacle Sector or Pinnacle Gription™ (DePuy Orthopaedics Inc.). The tribological bearings were revised to a conventional 36mm ceramic-on-ceramic bearing. Patients treated with an ASR™ Resurfacing received a press-fit, HA-coated Corail™ stem during their revision. The revision surgery was followed by a rehabilitation in which the participants began to mobilize with partial weight bearing on the operated side for a period of six weeks, thereafter the weight bearing was raised in accordance to clinical and radiological results.

3.4. Serum metal ion evaluation

The evaluation of serum metal ion concentrations of patients treated with the ASR™ resurfacing revealed the following results: an average Co level of 18,7 µg/L (range, 0-190,5 µg/L) and an average Cr level of 12,9 µg/L (range, 0,3-125 µg/L) at the date of the recall in 2011. Likened to the resurfacing group the mean Co concentration was considerably higher in patients treated with an ASR™ XL Head ($p<0.001$). In case of Cr the mean concentration was considerably higher in the ASR™ resurfacing group compared to the ASR™ XL devices group ($p=0.006$). See Table 3 for the results.

Variable	**Overall**	**ASR™ XL Head**	**ASR™ Resurfacing**	***p-value***
Number of hips	64	44	20	
Number of patients	56	36	20	
Male:female	29:27	17:19	12:8	0.205
Follow-up	81 (20-109)	78 (20-98)	86 (68-109)	0.046
Age at operation (years)	51 (29-68)	52 (29-67)	49 (33-68)	0.187
Diameter acetabular cup (mm)	53 (44-64)	51 (44-58)	55 (46-64)	0.003
Femoral head diameter (mm)	47 (39-57)	45 (39-51)	49 (41-57)	0.003
Serum metal ion concentrations (µg/L)				
Co	18.7 (0-190.5)	20.1 (0.3-190.5)	16.0 (0-171.8)	0.001
Cr	12.9 (0.3-125.0)	12.8 (1.0-89.8)	13.1 (0.31-125.0)	0.006
Revisions (number of hips)	19	13	6	
Revision rate (%)	31	32	30	
Time to revision (months)	49 (0-83)	53 (14-83)	40 (0-74)	
Failure mode (number of hips)				
Serum metal ion elevation/ARMD	12 (19%)	8 (18%)	4 (20%)	

Aseptic femoral loosening	3 (5%)	3 (7%)	0	
Infection	2 (3%)	2 (5%)	0	
Cup malposition with subluxation	1 (2%)	0	1 (5%)	
Dislocation	2 (3%)	1 (2%)	1 (5%)	

Table 3: Data of the ASR™ XL Head and the ASR™ Resurfacing group as well as results of serum metal ion determination. Furthermore, statistical significant differences between the implant groups under investigation are shown.

The average Co and Cr concentrations were higher in patients who were revised compared to those patients that did not need any revision, whereby the divergences in the resurfacing cohort were statistically not significant. See Table 4 and Figure 15 for the results.

	ASR™ XL Head		**ASR™ Resurfacing**	
Status	**revised**	**non-revised**	**revised**	**non-revised**
Number of hips	12	32	6	14
Serum metal ion concentrations (µg/L)				
Co	54.7 (7.1-190.5)*	5.0 (0.3-27.3)*	93.4 (0.5-171.8)#	1.5 (0-6.0)#
Cr	30.4 (5.0-89.8)°	5.1 (1.0-23.6)°	68.8 (0.7-125.0)+	2.6 (0.3-10.7)+
p-value	*<0.001	°<0.001	#0.109	+0.359

Table 4: Comparing metal ion levels of the ASR™ XL Head and the ASR™ Resurfacing groups, again segmented in revised and non-revised implant groups.

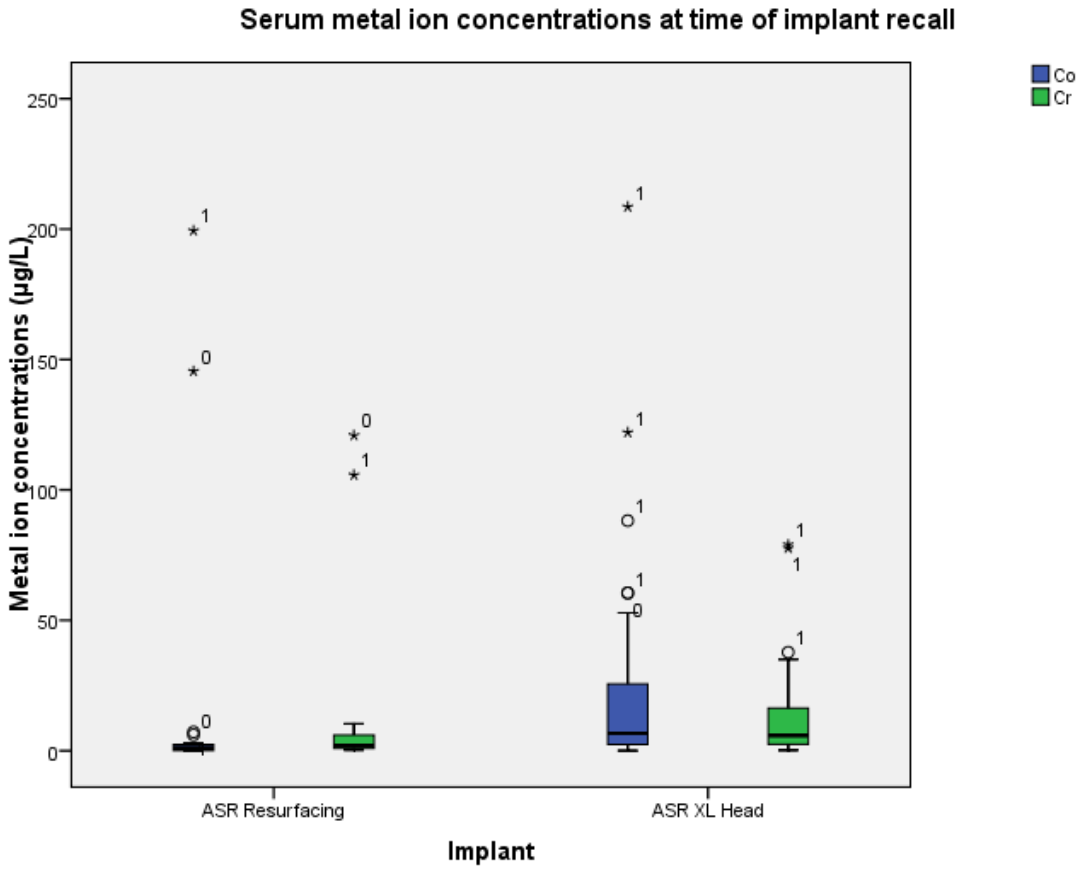

Figure 15: Box plot showing the Co and Cr serum metal ion levels in the ASR™ XL Head and the ASR™ Resurfacing groups. Patients with ASR™ Resurfacing had lower concentrations of Co and Cr compared to those of patients treated with ASR™ XL Head implants.

3.5. Implant survival

The implant survival was calculated according to the method of Kaplan-Meier, whereas revision for any reason was the end point. The calculated overall implant survival for both ASR™ devices was 83% at 60 months and 73% at 96 months, respectively (Figure 16). The implant survival of the ASR™ Resurfacing implant was 90% at 60 months, which reduced to 79% at 96 months (Figure 17). The implant survival of the ASR™ XL Head implant was 79% at 60 months, which reduced to 69% at 96 months (Figure 17). The divergence in implant survival was statistically not significant (log rank: 0.455).

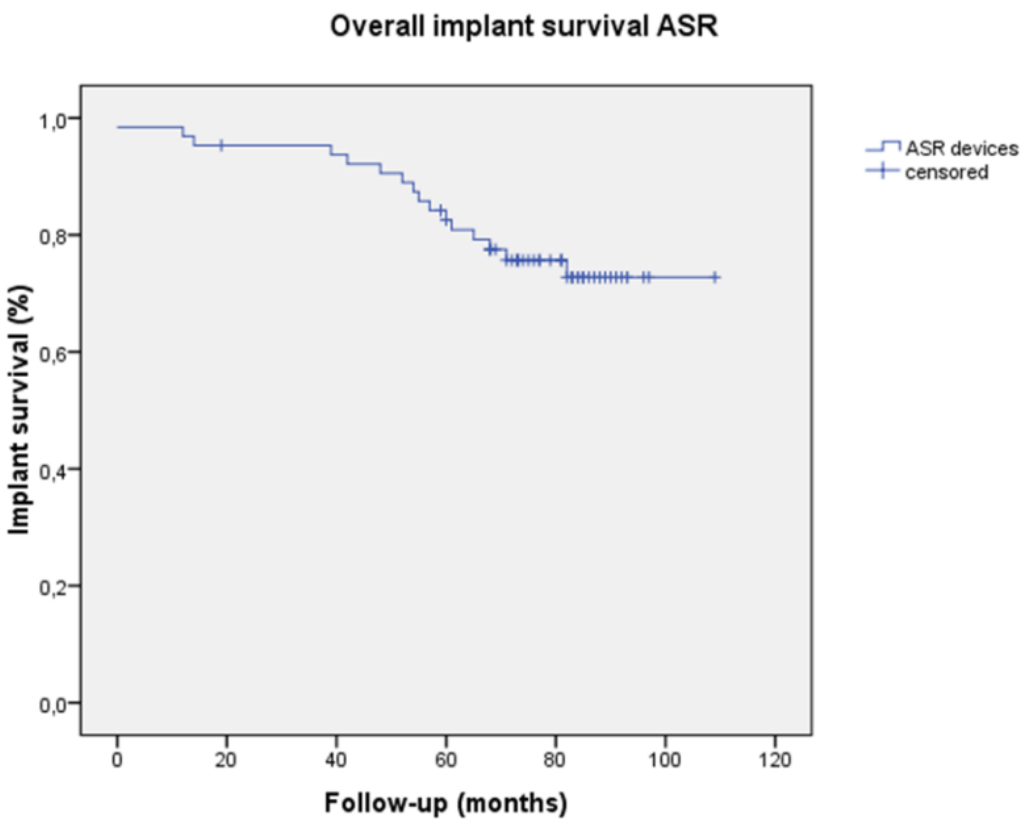

Figure 16: Implant survival of all ASR™ devices.

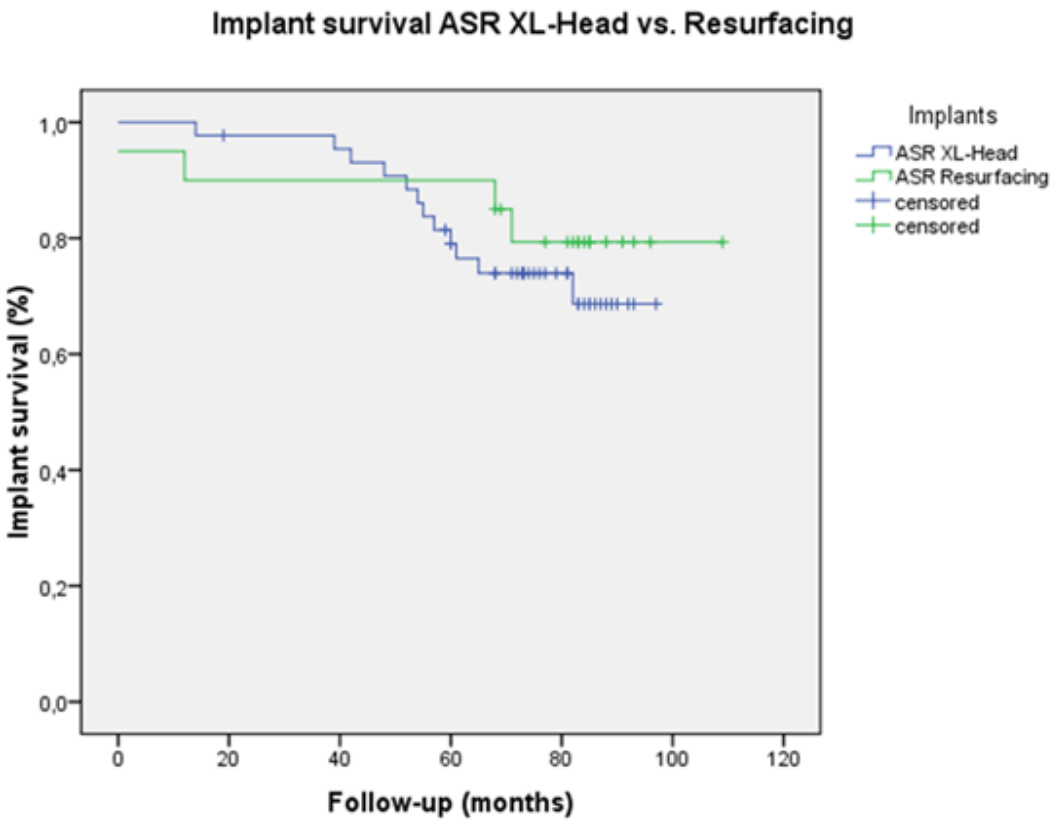

Figure 17: Implant survival of both ASR™ groups divided by type of device.

4. Discussion

In the late 90´s and early 2000s, large diameter MoM bearings have awaken interest in the orthopaedic community and were commonly used for young and physically active patients needing an artificial joint replacement of the hip. (12) Proclaimed benefits of these devices were less volumetric debris and enhanced range of motion. Unfortunately the number of revisions of abortive MoM bearings increased in the last years. (37,72,136,140,162,179–183) Additionally, there are persisting doubts whether elevated systemic metal ion concentrations might have long-term consequences. (37,72,136,140,162,179–183)

The ASR^{TM} Resurfacing and ASR^{TM} XL Head systems have been proven as the most inefficient MoM designs compared to other modern MoM bearing devices, with higher than anticipated revision rates. (37,97,152,157,158,162,185,203) Therefore, the implant systems have been recalled by the manufacturer. (157,160,184) For instance, Langton et al. (185) revealed revision rates of 25% and 49% for the ASR^{TM} resurfacing device and ASR^{TM} XL Head systems, respectively, at an interval of six years.

The current series showed an intolerable high revision rate for a modern orthopaedic device, namely the ASR^{TM} XL Head system (32%) and of the ASR^{TM} Resurfacing device (30%). The study revealed an implant survival of 79% for the ASR^{TM} XL Head system and 90% for the ASR^{TM} Resurfacing systems, at an interval of five years, respectively.

Serum metal ion determination

The determination of metal ion concentrations is subject of discussions in the orthopaedic community. For example the evaluation of metal ion concentrations in blood, serum, plasma and urine has been proven as a rough “screening tool” for the quantity of wear of MoM implants. (83,181,182) Interestingly, the recent literature showed varying data regarding increased or decreased metal ion concentrations in patients treated with ASR^{TM} devices. (157,185,186)

Moreover, it has been proven that the evaluation of metal ion concentrations might be insufficient in order to determine an ARMD. (91,92,97,157,160,181,187)

Chang et al. (157) proposed that abnormal plasma metal ions are not related to the patient´s pain or mechanical failure of the device and they showed a correlation between elevated Co concentrations and periprosthetic lucency as well as the formation of ARMD ($p<0.05$), although this correlation was statistically not significant. Malek et al. (90) showed that there is no correlation between high metal ion levels and the formation of ARMD in symptomatic patients determined in MARS MRI. Therefore they advised to combine blood metal ion measurement with symptoms, radiological findings and cross sectional imaging. Fox et al. (101) stated that radiologically determined periprosthetic pathologies were not associated with metal ion levels or inclination angles of the acetabular component, thus the relationship of these factors remain unclear, which adds even more complexity on how to manage patients with ASR implants.

Hart et al. (188) stated in their recent study that elevated blood Co- and Cr-ion levels were associated with failed MoM THA and MoM HRA. Additionally, they revealed that the threshold of 7 µg/L, as proposed by the MHRA (94), had inadequate sensitivity to be solely used as screening tool for failed arthroplasties, but allowed almost ideal misclassification rates. Since there is no safe lower level for blood metal ions, they dissuaded surgeons from conducting revision surgery based on blood metal ion levels solitary. (188) For that reason and in accordance to the AAOS's and EFORTs guidelines, we combined blood metal measurement, clinical examinations, plain radiographs and cross sectional imaging using MARS MRI. (189–191)

The current MHRA guidelines suggested measuring Co and Cr levels in the blood of asymptomatic patients treated with a MoM implant, but lacked specific instructions on how to execute them. (192,193)

To the best of our knowledge, there are no optimal follow-up protocols available at present, particularly regarding the determination of blood metal ion levels. (192) We therefore sympathize the notion of Reito et al. (192) that new standardized guidelines on how to manage patients treated with MoM arthroplasties are needed since the guidelines by DePuy, AAOS and EFORT are rather vague and so are the results of studies approaching the metal ion levels in patients. (189–191)

Several studies revealed that there is a correlation between high metal ion levels and implant size (< 50 mm) as well as malposition (steep inclination with reduced arc of cover and edge loading) and female gender. (37,105,111,162,163,182)

Reito et al. (184) determined multiple risk factors that may lead to the formation of ARMD, e.g. increasing femoral size and stem type. Additionally, they stated that larger head sizes may be responsible for more micromotion in the taper trunnion interface. Hence the femoral components taper trunnion interfaces might be a supplementary source of metal ion release due to fretting corrosion. (37,163,194) In the current study this circumstance was likewise noticed in the ASR^{TM} XL Head cohort.

Reito et al. (181) recently stated that there is a weak correlation between intraoperative histopathological findings and preoperative determined Co and Cr levels in joint fluid aspirate of patients with failed MoM implants. Hence they dissuaded surgeons from collecting joint fluid since this procedure has poor predictive ability and is not appropriate to foresee an ARMD. Therefore no joint fluid has been collected during our recent study, although intraoperatively resected tissues were sent in for histopathologic analysis. The best way to significantly decrease Co and Cr metal ion levels is revision surgery, as we observed in our current study and which has been proven also by other studies. (187,195)

The revision rate of MoM devices is also affected by the surgeons' or hospitals' different approach on how to set the indication for revision, which explains the significantly varying prevalence of revisions as Reito et al. (192) observed.

In the last years the focus of most studies has been to evaluate higher than anticipated failure rates of MoM implants due to ARMD, but studies on complication rates after revision surgery are still underrepresented. (187,192,196)

Stryker et al. (196) observed in their study on revisions on MoM THAs, which were manufactured by four different producers, a high early complication rate of 20% and a reoperation rate of 16% for patients after revision surgery. Munro et al. (195) reported a complication rate of 38% post revision surgery amongst patients that have been treated with a large-head MoM THA.

Adverse reaction to metal debris (ARMD)

The formation of ARMD is also an object of intensive research. ARMD is an umbrella term for all occurring soft-tissue reactions e.g. pseudotumours, aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL), metallosis, corrosive osteolysis and large sterile hip effusion.
(37,97,152,157,160,162,163,180,181,183,187)

Nevertheless, the pathogenesis of ARMD is still unknown, so far, it is hypothesized that it comprises a cytotoxic response as well as a delayed hypersensitivity reaction (Type IV) to Co and Cr debris. (100,153)

Several procedures are used in order to diagnose ARMD, e.g. blood metal ion measurement of Co and Cr can be used as a “rough screening tool”. (12)

Macnair et al. (91) reported significantly higher incidences of ARMD if the blood levels for Cr were risen above the threshold of 7 µg/L ($p = 0.02$). Moreover, they stated that the formation of ARMD might also appear in patients with normal metal ion levels. Hence, we did not only take blood samples during our study, but combined it with clinical examinations and cross-sectional imaging, using MARS MRI.

Various radiological examinations can be used in order to diagnose an ARMD as Fary et al. (100) described, but every procedure has its pros and cons. Plain radiographs might only show advanced pathologies complicated by osteolysis and/or soft tissue reaction but lack the ability to show early stages of ARMD. (100,197) Ultrasound scanning has several advantages, it is a very effective screening tool by enabling surgeons to diagnose ARMD without radiation exposure and is inexpensive, but disadvantages of this procedure are that it is time consuming, needs an experienced musculoskeletal radiologist to interpret the images and in some circumstances a smaller ARMD can be missed. (100,187,198) Cip et al. (187) stated that the computed tomography (CT) is usable as a rough screening tool, but lacks the accuracy of determining periprosthetic ARMD due to metal artefacts. Therefore, this group of authors as well as Macnair et al. (91) recommended MARS MRI for diagnostic reasons. On the other hand, CT can also serve as an alternative for those who have contraindications to MRI or if ultrasound scanning is not available. (91)

Anderson et al. (164) published a grading system for the evaluation of ARMD, but as far as we know, this grading system has not yet been widely used. Unfortunately, MARS MRI is also a rather expensive procedure as stated by Reito et al. (183). Therefore, it is not surprising that Reito et al. (192) found in their meta-analysis of 122 studies a rather low overall incidence of ARMD, since most of them used plain radiography and clinical examination in order to diagnose ARMD.

Interestingly, Reito et al. (192) noticed in their meta-analysis that the prevalence of ARMD was not affected by the follow-up time. Additionally, Reito et al. (183)

pointed out in a further publication that there is an absence of international guidelines on how to specifically define ARMD, moreover there is no agreement in the orthopaedic community on how to set the indications for revision surgery.

The prevalence of ARMD, calculated in studies using cross-sectional imaging, varied from 7% to 69% as Briant-Evans et al. (199) observed. (86,88,200) This wide range is hardly surprising since varying imaging modalities with different sensitivities and varying MARS MRI protocols have been utilized, even enhanced by the fact that there is no agreement regarding a specific definition of ARMD. (199,201,202)

In 35 out of 56 patients treated with an ASR^{TM} device we conducted a MARS MRI and determined ARMD in 12 cases (34%). All of these patients showed one or more of the following symptoms: increased Co and Cr concentrations in the serum, pain or clicking noises produced by the implant. A total of six revision surgeries, three within the ASR^{TM} Resurfacing and three within the ASR^{TM} XL Head group, were conducted premised on serum metal concentrations, results of the MARS MRI and clinical findings.

Whitwell et al. (66) also advised this procedure to be done in all patients with an ASR^{TM} device, moreover they suggested to adopt this procedure in patients with well-functioning implants. Interestingly, Whitwell et al. (66) solely performed an MRI in patients with increased Co and Cr levels or with symptomatic hips in their study. Nonetheless, a higher rate of ARMD is presumable, if each patient is included in the assessment by cross sectional imaging as proposed by Macnair et al. (91).

Revision surgery in ASR patients

The current literature shows a broad spectrum of revision rates, ranging from low rates as shown by Langton et al. (97) (HRA 3.2%, THA 6%), the NJR (175) (HRA 12%, THA 13%) and Hug et al. (37) (HRA 12%, THA 13%), to increased rates as revealed by Bernthal et al.(177) (THA 17.1%) and Whitwell et al.(66) (HRA 19%, THA 19%), up to high rates published by Langton et al.(185) (HRA 25%, THA 48,8%). Our revision rates were within this upper range reported. The revision rate for the ASR^{TM} Resurfacing was 30% and the ASR^{TM} XL Heads was 32%, respectively. The overall revision rate was 31%.

The implementation of novel screening methods, e.g. MARS MRI, and the growing knowledge regarding ARMD has affected the revision rates remarkably. (100,192) Furthermore, Reito et al. (192) revealed the tendency towards positive results regarding the ASR™ Resurfacings and ASR™ XL Heads revision rates until the recall in studies before 2010. This circumstance was followed by studies whose primary aim was to achieve “higher than anticipated” revision rates. (192)

All patients treated with an ASR™ device at our institute received a clinical, laboratory and radiographic assessment as proposed by DePuy, AAOS and EFORT, this procedure has proven practicable and assures the recent series. (189–191)

To the best of our knowledge, little has been published about the progression of ARMD and the outcome for those patients needing revision surgery due to ARMD. So far, the current literature supports the notion that ARMD is likely to progress and that the outcome for patients who had revision surgery due to ARMD was inferior compared to other reasons. (100,171,173,174) Fary et al. (100) recommended early revision surgery to prevent further progress of soft tissue destruction and osteolysis.

Cip et al. (187) reported in their recent study one major complication, namely a femoral nerve palsy, which occurred subsequently after revision surgery but did not require a second revision. Furthermore, one re-revision had to be done eight months following first revision due to a periprosthetic infection. In our series, none of the revised patients needed another revision surgery.

Aseptic loosening

Reito et al. (194) and current literature demonstrated that there was a greater chance of aseptic loosening and also a greater chance of complications related to ARMD in patients treated with an ASR™ XL Head implant paired with a stem out of the portfolio of DePuy (HA-coated Corail™, proximally porous-coated Summit®, S-ROM®) or of another manufacturer (Proxima™). (37,91,97,163,177,184,185) This afore mentioned circumstance might be explained by the reduction of the stems hydroxyapatite (HA) coating and release of HA-flakes and subsequent probable third-body wear. In our ASR™ XL Head cohort we also noticed three cases of aseptic femoral loosening (7%) that required revision surgery. On the other hand, Cip et al. (163) observed in their study that the revision rate of patients

treated with an ASR™ XL Head device paired with a stem of another manufacturer than DePuy like the CoxaFit™ or the ARGE Geradschaft™ (K-Implant, Hannover, Germany) was 24.5%.

Thus it can be concluded, that the femoral stem per se does not directly influence the failure rate and therefore the pathogenesis persists unknown.

DePuy (189) suggested in accordance to the MHRA´s device alerts (94,178) that every patient treated with an ASR™ device should join a five year follow-up after index surgery with annual examination. Thereafter, a follow-up can be further pursued in accordance to the locally agreed protocols. Patients with radiographic changes due to imminent implant failure should be contacted. During the follow-up DePuy advised to assess the serum metal ion concentrations in patients whose hip replacements are at concern. Furthermore, DePuy suggested that in patients who are symptomatic or with inclination angle higher than (>45°), a serum metal assessment and/or cross sectional imaging comprising MRI or ultrasound scan should be performed, especially in those who received small femoral and acetabular components. The threshold for Co and Cr was set for both metals at 7µg/L. If the measured concentrations where above this threshold, further blood tests should be performed to decide which patient needs closer surveillance and radiological examination. Patients with identified pathologies in MRI or sonography should be considered for revision surgery.

In our department we amended the advised procedure by DePuy. During our follow-up we assessed changes in the extent of periprosthetic soft tissue and fluid collections in asymptomatic patients using MARS MRI. If the extent of periprosthetic masses and fluid was consistent and the patient remained asymptomatic, we did not perform revision surgery. If asymptomatic patients became symptomatic or if the tissue masses or fluid masses expanded, we considered revision surgery.

Limitations

Our current survey has a number of limitations: 1) The data of this non-randomised retrospective survey has been gathered prospectively. 2) Patients with unilateral but also bilateral hip arthroplasties were enclosed in this study whilst it is questionable if it is adequate to enclose patients with bilateral MoM devices in the survival study. Thus it can be concluded that patients with bilateral arthroplasties

and an experienced implant correlated failure on one side are at risk of failure at the contralateral side, even though the arthroplasties components were implanted regularly. (180)

5. Conclusion

Considering the last published guidelines from the AAOS, EFORT and British Hip Society, we propose an accurate and constant follow-up of every patient treated with a MoM THA implant with focus on serum metal ion concentrations of Co and Cr as well as plain radiographs. Furthermore, we suggest that symptomatic patients, regardless of whether they have elevated metal ion concentrations or not, require an MRI once to rule out ARMD. If elevated metal ion concentrations are detected, the patients suffer from local pain or an ARMD was confirmed in MRI, a revision surgery should be considered. In our currently performed survey we observed substantial revision rates within both ASR^{TM} implant cohorts, although it has to be said there was no case of re-revision. The tribological bearings were revised to conventional CoC bearings in all revision cases. Further, press-fit cups were used during revision and all femoral stems were kept since they were well integrated. To foresee and prevent high failure rates of new implants like those of the ASR^{TM} design, we suggest accurate surveillance of new implant designs and innovations in the future. Further, the authorization procedure should be optimized in order to prevent such incidents. Moreover, the recall of the ASR^{TM} design illustrates the relevance of national implant registries.

Appendix

Table 1:
Demographic data of the ASR XL Head group

Number	Age at the operation	Sex	Date of the operation	Operated side	Head-size	Cup- size	Revision 1	Date of the first revision	Causes for the revision	Revision 2	Date of the second revision	Causes for the revision	MRI done	ARMD detected	Follow-up (months)	Last Co level	Last Cr level
1	29	f	18.10.2005	r	39	44							y	n.a.	108	13,3	14,88
2	49	m	18.04.2008	r	49	56							y	y	83	2,7	5,93
3	60	m	21.02.2008	r	47	54							n	n.a.	20	0,5	1,1
4	50	m	25.04.2007	l	49	56							n	n.a.	92	11,2	10,24
5	51	m	21.03.2008	r	46	52							n	n.a.	81	n.a.	n.a.
6	53	m	05.11.2007	r	n.a.	n.a.							y	y	84	4,5	4,6
7	54	f	23.03.2007	r	47	54							y	n.a.	97	8,2	9,18
8	54	f	25.10.2007	l	47	54							y	n.a.	89	n.a.	n.a.
9	49	f	25.10.2006	l	43	48	y	27.10.2011	metal ion elevation				y	n.a.	97	45,1	22,76
10	57	m	18.03.2008	l	47	54							y	y	79	13,7	11,8
11	44	f	08.02.2008	r	45	50							n	n.a.	81	2,5	4,23
12	59	f	02.05.2007	l	46	52							y	n.a.	88	1,1	1,19
13	67	f	24.07.2008	l	46	52							n.	n.a.	72	3,6	0,64
14	58	f	27.11.2007	r	41	46	y	01.12.2011	metal ion elevation				y	n.a.	87	1,3	10,48
15	58	m	29.07.2008	r	47	54							n	n.a.	75	6,5	9,61
16	43	f	26.04.2006	r	43	48							y	n.a.	105	22,5	28,9
17	43	f	22.11.2006	l	43	48	y	05.04.2012	metal ion elevation				y	y	98	n.a.	n.a.
18	61	m	18.04.2007	l	46	52							y	n.a.	88	26,4	14,13
19	43	m	23.05.2008	r	49	56							n	n.a.	73	6,2	6,48
20	51	m	07.03.2007	l	49	56							n	n.a.	96	1,9	0,96
21	54	m	08.01.2008	l	49	56							n.	n.a.	77	7,7	9,74
22	51	m	22.03.2007	l	47	54							y	n.a.	93	5,2	9,4
23	52	m	07.04.2008	r	47	54	y	07.10.2011	metal ion elevation				y	n.a.	80	n.a.	n.a.
24	60	f	11.12.2006	r	41	46	y	25.02.2010	dislocation				n.a.	n.a.	80	20,3	15,9
25	53	f	01.06.2006	r	41	46							y	n.a.	100	2,3	3,59
26	53	f	15.11.2006	l	43	48	y	09.03.2011l	loosening (stem)				y	y	95	n.a.	n.a.
27	57	f	02.01.2007	r	45	50	y	28.07.2011	loosening (stem)				y	n.a.	67	0,2	1,3
28	55	f	11.04.2007	r	45	50	y	12.06.2008	loosening (stem)	y	36.07.2011	metal ion elevation	y	y	95	0,2	0,34
29	46	m	26.03.2008	l	51	58	y	17.01.2015	pseudotumor; osteolysis				n	n.a.	84	13	3,16
30	45	f	04.10.2006	r	43	48							n	n.a.	94	2,3	2,8
31	42	f	07.12.2006	r	45	50							y	n.a.	91	11,2	3,3
32	60	m	18.10.2007	r	47	54							n	n.a.	81	3,4	2,3

33	38	m	26.09.2006	r	46	52							y	n.a.	93	7	4,75
34	40	m	13.02.2008	l	46	52							y	y	76	/	/
35	47	f	15.02.2008	l	41	48							n	n.a.	81	4,6	4,03
36	50	f	18.04.2007	r	43	48							y	n.a.	92	20,8	10,18
37	50	f	18.04.2007	l	43	48	y	12.01.2012	metal ion elevation				y	n.a.	92	/	/
38	63	f	21.11.2005	r	45	50	y	04.12.2010	infection	y	23.12.2010	infection; revision festulation	n	n.a.	105	2,6	3,38
39	64	f	16.08.2006	l	45	50							n	n.a.	96	n.a.	n.a.
40	59	m	06.01.2008	r	51	58							n	n.a.	86	17,5	7,91
41	59	f	26.04.2007	l	41	46	y	20.10.2011	metal ion elevation				y	n.a.	96	0,5	9,51
42	48	m	27.03.2008	r	47	54							n	n.a.	77	5,3	3,17
43	45	f	13.06.2007	l	41	46							n	n.a.	83	5,6	4,65
44	63	m	27.07.2006	r	49	56							n	n.a.	90	0,8	0,7

f=female; m= male; l=left;r=right; y=yes; n=no;n.a.=not applicable.

Table 2:

Demographic data of the ASR Resurfacing group

Number	Age at the	Sex	Date of operation	Operated side	Head-size	Cup- size	Revision 1	Date of the first revision	Causes for the revision	Revision 2	Date of the second revision	Causes for the revision	MRI done	ARMD detected	Follow-up (months)	Last Co level	Last Cr level
1	49	m	18.05.2007	r	49	56							y	y	94	6,25	6,39
2	47	m	20.04.2007	r	51	58							y	y	95	4,2	3,03
3	46	m	30.01.2007	r	49	56							n	n.a.	99	0,5	0,89
4	61	m	22.11.2006	l	53	60							n	n.a.	92	1,0	0,97
5	54	m	13.12.2005	r	55	62							n	n.a.	103	0,8	0,59
6	33	m	08.10.2007	r	51	58							n	n.a.	86	0,3	0,85
7	53	f	12.12.2007	r	46	52							y	n.a.	78	1,1	1,63
8	68	m	11.09.2006	r	51	58							n	n.a.	94	0,7	0,91
9	35	f	31.07.2006	r	45	50							n	n.a.	98	1,2	1,1
10	51	m	25.10.2005	l	51	58							y	n.a.	108	4,8	8,39
11	52	f	10.10.2006	r	46	52							n	n.a.	101	10,8	8,91
12	48	m	25.05.2005	l	53	60							y	n.a.	109	1,5	1,51
13	36	f	20.11.2007	l	45	50							y	n.a.	80	1,5	2,05
14	66	f	30.05.2006	r	45	50							y	n.a.	105	1,2	2,22
15	52	m	08.08.2006	l	4	56							n	n.a.	97	0,4	0,28
16	55	f	06.06.2006	l	41	46							n	n.a.	98	1,7	3,89
17	57	m	19.11.2007	l	51	58	y	09.10.2013	subluxation				y	n.a.	84	1,0	2,59
18	40	f	13.12.2005	l	46	52	y	19.12.2005	dislocation	y	12.01.2012	metal ion elevation	y	y	107	1,1	6,11
19	37	f	09.11.2005	l	46	52	y	01.12.2006	pseudotumor	y	10.12.2007	pseudo-tumor	y	y	114	/	/
20	42	m	20.09.2005	l	57	64	y	16.05.2011	pseudotumor; impending fracture				y	y	104	0,6	7,5

f=female; m= male; l=left;r=right; y=yes; n=no;n.a.=not applicable.

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