Serum metal ion concentrations following total knee arthroplasty using hinged prostheses:

Comparison between fixed and rotating hinge devices

Serum Metallionenkonzentrationen nach Kniegelenksersatz mit achsgeführten Totalendoprothesen: ein Vergleich zwischen Prothesensystemen mit einer fixed-hinge und rotating hinge Artikulation

submitted by

Dr. med. univ. Joerg Friesenbichler

for the Academic Degree of

Doctor of Medical Science

(Dr. scient. med.)

at the

Medical University of Graz

at the

Department of Orthopaedic Surgery

under the Supervision of

ao.Univ. Prof. Dr. Andreas Leithner

OA Dr. Werner Maurer-Ertl

Priv. Doz. Dr. Joanna Szkandera

2015

DECLARATION

I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of "Good Scientific Practice".

Graz, Date ……. *Signature*

ACKNOWLEDGEMENTS

First I would like to thank Professor Dr. Andreas Leithner for giving me the possibility to join his team as resident at the Department of Orthopaedic Surgery after finishing my medical studies. Furthermore, I would like to express profound gratitude to him for guiding me throughout this dissertation and the daily problems at the department, encouraging me to perform scientific research, as well as for his financial support to take part in national and international meetings, where I could present my scientific works and results.

Next I would like to thank my mentor and instructor Dr. Werner Maurer-Ertl for his support, encouragement, supervision and useful suggestions throughout my whole academic training. He encouraged me to develop independent and critical thinking. His continuous guidance and greatly assistance during my residency made it possible to learn the basics in orthopaedics and helped to enhance my surgical skills. Further, he became a good and trustful friend of mine.

I also want to thank Priv. Doz. Dr. Joanna Szkandera for being a member of my dissertation committee. Her critical guidance and supervision helped me finishing this thesis. She promoted my interests in oncology and additionally edged my spirit for teamwork.

Furthermore I want to give credit to all my colleagues at the department for their support and patience during my on-going residency.

Last but not least, I want to thank my family and friends for supporting me all time.

I. TABLE OF CONTENTS

II. ABBREVIATIONS

AAOS	American Academy of Orthopaedic Surgeons
ALVAL	Aseptic Lymphocyte-Dominated Vasculitis-Associated Lesions
AOA	Australian Orthopaedic Association
ASR	Articular Surface Replacement
ARMD	Adverse Reaction to Metal Debris
BMI	Body Mass Index
cm	Centimetres
Co	Cobalt
CoC	Ceramic-on-Ceramic
CoP	Ceramic-on-Polyethylene
Cr	Chromium
dl	Decilitre
EFORT	European Federation of National Associations of Orthopaedics and Traumatology
ET ASS	Electrothermal Graphite Furnace Atomic Absorption Spectrometry
Fig.	Figure
HMRS	Howmedica Modular Resection System
HXLPE	Highly CrossLinked PolyEthylene
ISO	International Organization for Standardization
KMFTR	Kotz Modular Femur Tibia Reconstruction System
KSS	Knee Society Score
L	Litre
LPS	Limb Preservation System
MARS	Metal Artefact Reduction Sequence
M.B.T.	Mobile Bearing Tibia
Mo	Molybdenum
MoM	Metal-on-Metal
MoP	Metal-on-Polyethylene
MRI	Magnetic Resonance Imaging

MSTS	Musculoskeletal Tumor Society Score
Mths.	Months
MUTARS	Modular Universal Tumour And Revision System
NJR	National Joint Registry
PMMA	Polymethylmethacrylat
RHA	Resurfacing Hip Arthroplasty
RHK	Rotating Hinge Knee
RL	Resection length
Tab.	Table
TDR	Total Disc Replacement
THA	Total Hip Arthroplasty
THR	Total Hip Replacement
TiN	Titanium Nitride
TKA	Total Knee Arthroplasty
UHMWPE	Ultra-High Molecular Weight Polyethylene
UHXLPE	Ultra-High Cross-linked Polyethylene
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
Yrs.	Years
µg	Microgram
µl	Microliter

III. LEGEND TO FIGURES

Figure 1: Sir John Charnley, *1911-1982†, pioneer of the total hip arthroplasty. Picture of the Charnley THA system on the right.

Figure 2: First generation of hinged knee prostheses: SHIERS, STANMORE and GUEPAR (from Manning et al.; Revision Total Knee Arthroplasty, 219-236).

Figure 3: SHEEHAN, HERBERT and ATTENBOROUGH prostheses (from Manning et al.; Revision Total Knee Arthroplasty, 219-236).

Figure 4: KINEMATIC rotating hinge knee and the schema of the NOILES total knee device (from Manning et al.; Revision Total Knee Arthroplasty, 219-236).

Figure 5: FINN Knee, S-ROM®Noiles™ and HMRS™ RHK prostheses from left to right (from Manning et al.; Revision Total Knee Arthroplasty, 219-236 and www.depuy.de).

Figure 6: The modular KMFTR™ and HMRS™ prostheses.

Figure 7: Components of the Limb Preservation System (from the LPS™ planning software and www.depuysynthes.com).

Figure 8: S-ROM®Noiles™ Hinged Tibial Insert Bearing and tibial component with metaphyseal sleeve (from Jones et al.; Clin Orthop Relat Res 2001, [1] and www.depuysynthes.com).

Figure 9: Tribiological bearings used for THA: metal-on-polyethylene (MoP) and ceramic-on-ceramic (CoC; from https://www.hipreplacement.com/technology/implants/bearings).

Figure 10: Modern metal-on-metal (MoM) resurfacing device.

Figure 11: Box plot showing the Co and Cr serum metal ion levels in the fixed hinge megaprosthesis group in proportion to the other RHK devices. Patients with fixed hinge devices had higher concentrations of Co and Cr in the plasma compared to patients with a

standard rotating hinge device. These results showed a statistically significant difference (Table 3).

Figure 12: HE stained sections and Berlin blue stained section of a cystic pseudotumor. Fibrous and fibro-hyalinized tissue with massive accumulation of macrophages (magnification, x10) containing visible metal particles (x400). The Berlin blue stained section showing no reaction for hemosiderin (x400).

Figure 13: Intraoperative photographs at the revision of a fixed hinge megaprosthesis in a 20-year-old male patient showing a marked metallosis in the periprosthetic soft tissues of the lower leg 119 months after implantation.

Figure 14: Photograph of the resected periprosthetic grey to black metallosis tissue.

Figure 15 showing a) the femoral and b) the tibial component of an explanted HMRS® megaprosthesis. At the side of the hinge there was a direct metal-on-metal articulation with clearly signs of metal debris (scratches and striation) following abrasion of the PE bushings.

IV. LEGEND TO TABLES

Table 1: Demographic data of the study population in the different prosthesis groups (yrs. /years; mths. months).

Table 2: Demographic data and results of serum metal ion determination divided by the implant groups.

Table 3: Results of statistical analysis comparing the measured serum metal ion levels of the different implant groups.

Table 4: Calculated Pearson correlation coefficient for all implant groups. In the S-ROM®Noiles™ group there was a significant correlation between Co and Cr concentrations (RL-resection length).

Table 5: The results of functional analysis as well as results of statistical analysis comparing all scoring systems. Differences in functional outcome between the HMRS® group and RHK patients are most likely due to the young age of these patients.

1. ABSTRACT

1.1 ENGLISH

Background: Serum metal ion concentrations of cobalt (Co) and chrome (Cr), indicating the wear behaviour of orthopaedic implants, are a critically discussed field of research due to potential harmful effects caused by their elevated systemic exposure. The aim of the study was to determine the values of cobalt, chromium and molybdenum (Mo) in the serum of patients after reconstruction of the knee using a fixed hinge megaprostheses following tumour resection. The metal ion concentrations of Co and Cr were then compared to those of patients treated with rotating hinge knee prostheses.

Materials &Methods:

Howmedica Modular Resection System (HMRS™):

Between 1998 and 2006, 19 patients were treated with wide resection and reconstruction of the lower extremity using the fixed hinge HMRS™ tumour prostheses for primary malignant bone tumours in the distal femur or the proximal tibia. Out of this group, 11 patients were available for the determination of serum metal ion concentrations.

Limb Preservation System (LPS™) and S-ROM®Noiles™:

Fifty-five patients underwent total knee replacement using the modular LPS™ megaprosthesis or the S-ROM®Noiles™ revision device from 2003 to 2008, after a tumour resection or revision TKA. Both implants consist of a rotating hinge articulation. Out of this group, blood was taken from 25 patients treated with these devices (LPS™: n=17; S-ROM®Noiles™: n=8).

Serum metal ion determination:

Blood was taken from all patients using stainless-steel needles attached to 9 ml no-additive plastic vacuum tubes (VACUETTE®). All needles and tubes were from the same batch and blood was taken under equal conditions by one observer. Furthermore none of the patients had a history of renal impairment. The concentrations of Co, Cr and Mo were determined using electrothermal graphite furnace atomic absorption spectrometry (ET ASS) at an external laboratory.

Results: Determining the serum metal ions concentrations in patients following megaprosthetic reconstruction with a fixed hinge articulation showed a mean concentration for Co of 0.47 µg/dl (range, 0.04-1.28 µg/dl), for Cr of 0.401 µg/dl (range, 0.148-0.891 µg/dl), and for Mo of 0.06 µg/dl (range, 0.01-0.09 µg/dl) after an average follow-up of 108 months (range, 67 to 163 months). The values for Co and Cr were tenfold and twofold,

respectively, increased compared to the upper values from the reference laboratory, while the Mo concentrations were within the limits.

Patients treated with a LPS™ megaprosthesis also showed fifteen-fold and twofold, respectively, increased Co and Cr concentrations after an average follow-up of 34 months (range, 9 to 67 months), while the concentrations in the S-ROM®Noiles™ rotating hinge group were within the limits after nearly the same time of follow-up (mean 37, range, 15 to 62 months). The differences for Co and Cr levels between the implant groups were statistically significant (Co: $p=0.010$, Cr: $p<0.001$).

Discussion: Determining the concentration of metal ions following fixed hinge total knee arthroplasty revealed significant increments for Co and Cr. The same effects could also be observed in the rotating hinge group but only in case of megaprostheses.

Referring to the most recent AAOS and EFORT guidelines released for total hip arthroplasties with metal-on-metal articulation, we recommend as well close and periodic follow-ups for all other orthopaedic devices with a metal-on-metal or metal-on-polyethylene articulation with plain radiographs and serum including metal ion determination at least once. Although there was no case of an adverse reaction to metal debris in the current series, the revision of fixed hinge implants should be considered in case of high serum metal ion levels.

1.2 GERMAN

Einleitung: Die Metallionenkonzentration von Kobalt (Co) und Chrom (Cr) im Blut, welche als indirekter Parameter für das Abriebverhalten von orthopädischen Implantaten gilt, ist derzeit ein kritisch diskutiertes Thema, da etwaige Spätfolgen einer Langzeitexposition nicht abschätzbar sind.

Das Ziel der aktuellen Studie war es, die unterschiedlichen Konzentrationen von Kobalt, Chrom und Molybdän bei Patienten nach erfolgter Tumorresektion im Bereich des Kniegelenks sowie Rekonstruktion mittels achsgeführter Tumorendoprothese (fixed-hinge) zu bestimmen. Die gemessenen Metallionen-Konzentrationen wurden in weiterer Folge mit den Kobalt und Chrom- Werten von Patienten verglichen, die mit einem anderen achsgeführten Knietotalendoprothesensystem (rotating-hinge) versorgt worden sind.

Material & Methoden:

Howmedica Modular Resektion System (HMRS^{TM}):

Im Zeitraum zwischen 1998 und 2006 wurden 19 pädiatrische Patienten nach erfolgter weiter Resektion eines primär malignen Knochentumors im Bereich des distalen Femurs oder der proximale Tibia mit einer HMRS^{TM} Tumorendoprothese versorgt. Aus dieser Patientengruppe standen 11 Patienten zur Bestimmung der Serum-Metallionenkonzentrationen zur Verfügung.

Limb Preservation System (LPS^{TM}) und S-ROM$^{®}$Noiles^{TM}:

Fünfundfünfzig Patienten wurden mit dem modularen Tumorendoprothesensystem LPS^{TM} oder dem Revisionsendoprothesensystem S-ROM$^{®}$Noiles^{TM} nach Tumorresektionen oder Wechseloperationen am Kniegelenk im Zeitraum von 2003 bis 2008 behandelt. Im Falle beider Implantate handelt es sich um Endoprothesen mit einem rotating-hinge Koppelungsmechanismus. Aus dieser Patientengruppe konnte 25 Patienten Blut zur Metallionenkonzentrationsbestimmung abgenommen werden. (LPS^{TM}: n=17; S-ROM$^{®}$Noiles^{TM}: n =8).

Metallionen-Bestimmung im Serum:

Das Blut wurde von allen Studienteilnehmern mit Edelstahl-Nadeln abgenommen und direkt über ein vakuum-assistiertes System (VACUETTE$^{®}$) in 9 ml no-additive Röhrchen abgefüllt. Alle Nadeln und Röhrchen stammen aus der gleichen Charge und die Blutabnahmen wurden immer unter den selber Voraussetzungen durchgeführt. Darüber hinaus konnte bei keinem der Patienten eine eingeschränkte Nierenfunktion festgestellt werden. Die Konzentrationen von Co, Cr und Mo wurden mittels elektrothermaler

Atomabsorptionsspektrometrie mit Graphitrohr Technik (ET ASS) in einem externen Labor bestimmt.

Ergebnisse: Die Bestimmung der Metallionen-Konzentrationen im Serum von Patienten nach erfolgter Kniegelenksrekonstruktion mittels achsgeführter, fixed hinge, Tumorendoprothese ergab eine durchschnittliche Konzentration für Co von 0.47 µg/dl (Bereich: 0.04-1.28 µg/dl), für Cr von 0.401 µg/dl (Bereich: 0.148-0.891 µg/dl), und für Mo von 0.06 µg/dl (Bereich: 0.01-0.09 µg/dl). Das mittlere postoperative Follow-up betrug 108 Monate (Bereich: 67 bis 163 Monate). Die Werte für Co und Cr waren zehnfach bzw. zweifach erhöht im Vergleich zu den oberen Referenzwerten des bestimmenden Labors, während sich die Mo Konzentrationen im Referenzbereich befanden.

Patienten, die mit einer LPS™ Megaendoprothese behandelt wurden, zeigten ebenfalls fünfzehnfach bzw. zweifach erhöhte Co und Cr Konzentrationen nach einem durchschnittlichen Follow-up von 34 Monaten (Bereich: 9 bis 67 Monate), während die Konzentrationen in der S-ROM®Noiles™ Gruppe im Normbereich waren. Die Unterschiede der Co und Cr Konzentrationen zwischen den Implantatgruppen waren statistisch signifikant (Co: $p= 0.010$, Cr: $p <0.001$).

Diskussion: Die Bestimmung der verschiedenen Metallionen-Konzentrationen nach tumorendoprothetischer Versorgung mit einer fixed hinge Scharniergelenksprothese zeigte eine signifikante Erhöhung der Co und Cr Werte im Serum. Dieselben Ergebnisse konnten auch in der rotating-hinge Megaprothesengruppe festgestellt werden, jedoch nicht nach Verwendung des Revisionsmodells.

Bezugnehmend auf die aktuellsten AAOS und EFORT Richtlinien für Hüfttotalendoprothesen mit Metall-Metall-Gleitpaarung, empfehlen wir engmaschige und regelmäßige Nachkontrolle aller orthopädischen Prothesensysteme mit einer Metall-Metall-Gleitpaarung oder Metall-Polyethylen Gleitpaarung. Bei den routinemäßigen Kontrollen sollten Röntgenaufnahmen in 2 Ebenen durchgeführt werden und zumindest einmal eine Bestimmung der Metallionen-Konzentrationen erfolgen. Wenngleich in der aktuellen Studie keine Komplikationen durch erhöhten Metallabrieb nach Kniegelenksersatz mit Tumor- oder Revisionsendoprothesen beobachtet werden konnten, sollte im Falle einer massiven Erhöhung der Metallionenkonzentrationen eine Revisionsoperation mit Änderung des Gleitmechanismus in Erwägung gezogen werden.

2. GENERAL PART

2.1 HISTORY OF ORTHOPAEDIC IMPLANTS

There have been several milestones in medical and orthopaedic history since the beginning of endoprosthetic replacement in 1890 by Themistocles Gluck, who first implanted an artificial knee joint made out of ivory. Additional, there were many advances in the knowledge of surgical techniques, joint biomechanics, implant designs and fabrication as well as an increasing knowledge in materials used for fabrication.

The first known performing hip prosthesis was implanted by Sir John Charnley (Figure 1) in the 1960s by replacing the acetabular cup, using a femoral stem and fixation of both components with polymethylmethacrylat bone cement (PMMA) [2-4]. Afterwards he spent about two decades refining this procedure.

Figure 1: Sir John Charnley, *1911-1982†, pioneer of the total hip arthroplasty. Picture of the Charnley THA system on the right.

Nevertheless, one of the first major complications was aseptic loosening of the cemented implants due to a lessened strength of the bond between cement and bone caused by micromotions and material debris. Therefore, the research and developments concentrated on anatomical shaped devices and cementless fixation supported by the introduction of special osteointegrative coatings on the surface of the prosthesis' components. Nowadays the probability of implant survival for cement free prostheses rose up to 96% at twenty years [5]. Additionally, progress could not only be observed in design and durability of the implant components, but also in the field of tribological pairings.

2.2 HISTORY OF HINGED KNEE PROSTHESES

The first constrained, fixed hinge knee prostheses had a metal-on-metal articulation (Figure 2) [6-10]. These prostheses allowed movement only in the sagittal plane with flexion and extension leading to high forces transmitted to the bone-cement-prosthesis interface. All in all, the mid- and long-term results showed high rates of component loosening, deep prosthetic infection, femoral fractures, particulate wear debris, subsidence and fatigue failures of the implants [11-17].

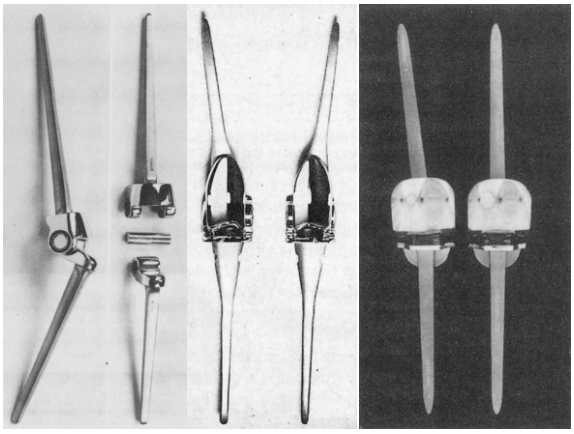

Figure 2: First generation of hinged knee prostheses: SHIERS, STANMORE and GUEPAR (from Manning et al.; Revision Total Knee Arthroplasty, 219-236).

In the early 1970s concepts of hinged and unconnected surface devices leading to the less constrained second generation implants due to the poor results of the first-generation were tried to be combined and modified (Figure 3) [12, 18]. Modifications of the implant designs allowed varus-valgus motion in the frontal plane and an axial rotation of the hinge in order to reduce the transmitted forces between the femoral and tibial component [12, 19].

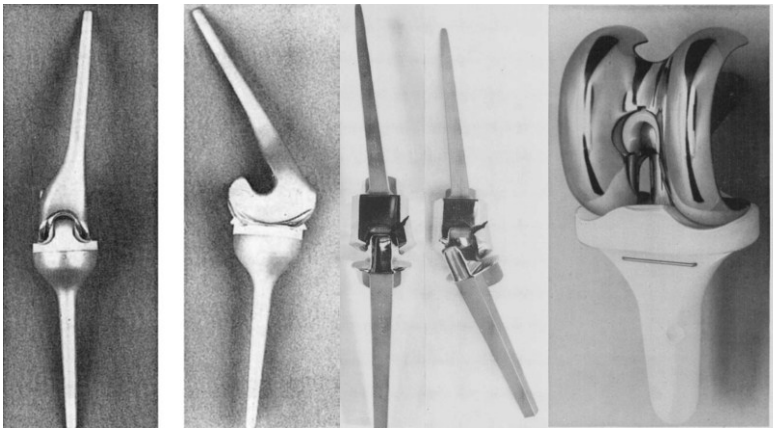

Figure 3: SHEEHAN, HERBERT and ATTENBOROUGH prostheses (from Manning et al.; Revision Total Knee Arthroplasty, 219-236).

The latest second generation designs were the NOILES and the KINEMATIC rotating hinge knee prostheses (RHK, Figure 4). The first promising short term results of all second generation designs were followed by disastrous complication rates [10-12, 18, 20-23]. Infection, fatigue failures and loosening were still the most common complications, although the second generation was already an improvement compared to the first one.

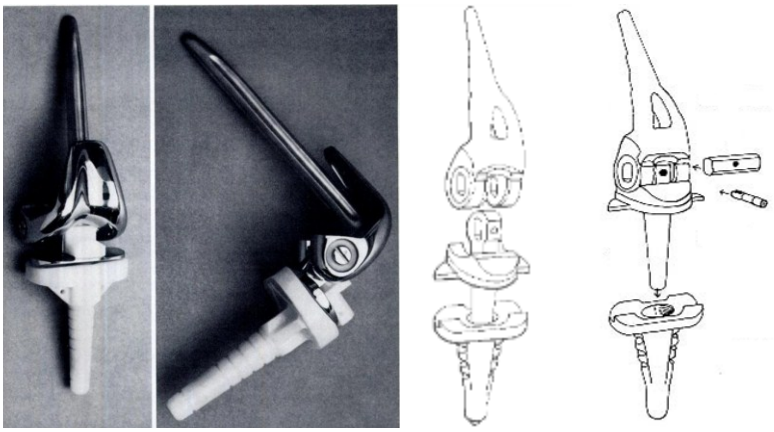

Figure 4: KINEMATIC rotating hinge knee and the schema of the NOILES total knee device (from Manning et al.; Revision Total Knee Arthroplasty, 219-236).

The third generation rotating hinge devices underwent once again several modifications concerning implant design and biomechanical features. The introduction of modular, anatomical sized "off the shelf" components facilitated the customized intraoperative reconstruction of osseous defects, as well as an easier revision of failed prostheses and the incorporated rotating hinge mechanism addressed complications like loosening or particular wear debris [24-26].

The first designs of the third generation were the FINN RHK and the S-ROM®Noiles™ RHK followed by several other devices like the NEXGEN RHK and the Howmedica Modular Resection System (HMRS™, Figure 5) [27].

Figure 5: FINN Knee, S-ROM®Noiles™ and HMRS™ RHK prostheses from left to right (from Manning et al.; Revision Total Knee Arthroplasty, 219-236 and www.depuy.de).

Up to now, the third generation RHK devices produced good results in the short- and mid-term follow-up [10, 13, 19, 23, 26, 28-35].

2.2.1 HOWMEDICA MODULAR RESECTION SYSTEM (HMRS™)

The Howmedica Modular Resection System (HMRS™, Stryker Howmedica Osteonics, Rutherford, NJ) was a further stage device of the fixed-hinge Kotz Modular Femur and Tibia Reconstruction System (KMFTR™) which was first introduced in 1988 (Figure 6) [27, 36-38]. The KMFTR™ system with a metal-on-polyethylene articulation was one of the first modular prosthetic systems, used for reconstruction after wide tumour resection or complex revision of total knee arthroplasty (TKA) [36-38]. Compared with earlier hinged megaprosthetic designs, infections, aseptic loosening and material fatigue failures of the hinge axle were still the most common complications.

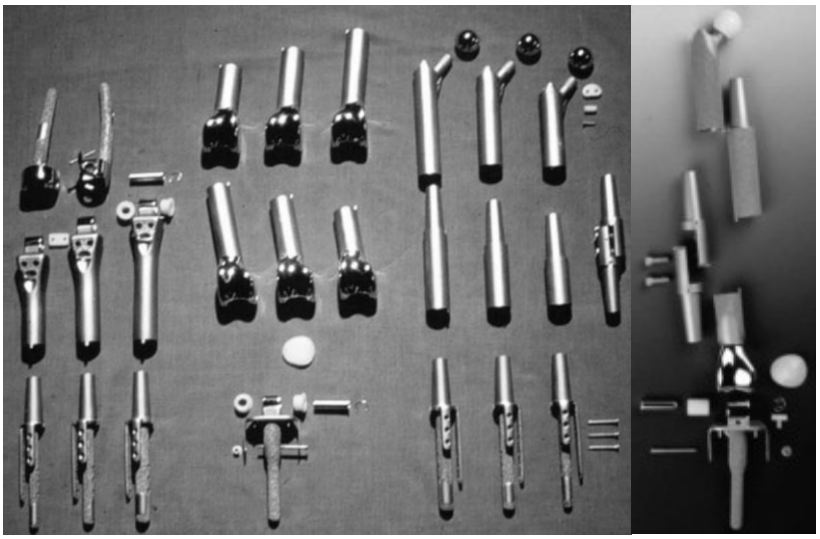

Figure 6: The modular KMFTR™ and HMRS™ prostheses.

The HMRS™ system was launched in 1988 following some modifications in function and implant design. Merely, the fixed hinge design was retained until 1996 and then converted to a rotating-hinge articulation due to high rates of aseptic loosening [39, 40]. Subsequently, the HMRS™ design was replaced by the launch of the Global Modular Replacement System (GMRS™, Stryker Howmedica Osteonics, Rutherford, NJ) in 2002 which was designed by the famous tumour surgeons Kotz, Mercuri, Eckardt and Malawer. In 2010, R. Kotz [27] showed no differences for implant survival between the KMFTR™ and the HMRS™ system for aseptic loosening and infection, although the revision rates for implant fatigue failures had reduced.

2.2.2 LIMB PRESERVATION SYSTEM (LPS™)

One of the modern rotating hinge devices, the Orthogenesis Limb Preservation System (LPS™) was introduced in 2001 by DePuy Orthopaedics (DePuy Orthopaedics Inc, Warsaw, IN, USA) and presented a "state-of-the-art" modular device, designed to facilitate limb salvage surgery. The modularity and the different configuration of the components allowed the reconstruction of the whole femur, the proximal, distal or total portion, or only the diaphyseal part and/or the proximal tibia (Figure 7). The LPS™ distal femoral component was designed to articulate with the M.B.T. mobile bearing tibial revision tray, the LPS™ proximal tibial replacement or the S-ROM®Noiles™ tibial tray by changing only the hinged insert.

Figure 7: Components of the Limb Preservation System (from the LPS™ planning software and www.depuysynthes.com).

2.2.3 S-ROM®Noiles™ ROTATING HINGE SYSTEM

The S-ROM®Noiles™ mobile-bearing hinge revision prosthesis, a third generation device, is mainly used for reconstruction in cases of deficient ligament stability or segmental bone loss at primary TKA or at complex revision TKA (Figure 8). Modular wedges, stem extensions and metaphyseal sleeves addresses the fit and fill philosophy of the device. The S-ROM®Noiles™ femoral component can be combined with the S-ROM® tibial tray, the M.B.T. revision tray or the LPS™ proximal tibial replacement.

The articulating surface of the S-ROM® Tibial Component is highly polished providing a broad mobile surface for the hinged polyethylene bearing insert.

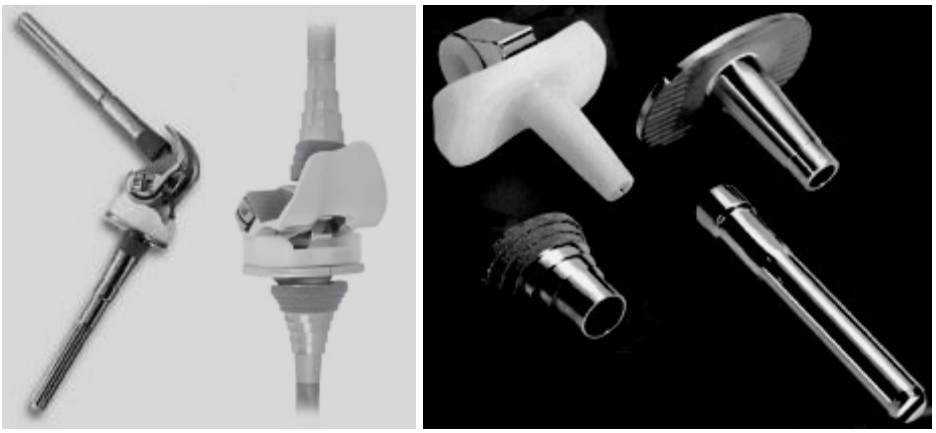

Figure 8: S-ROM®Noiles™ Hinged Tibial Insert Bearing and tibial component with metaphyseal sleeve (from Jones et al.; Clin Orthop Relat Res 2001, [1] and www.depuysynthes.com).

2.3 HISTORY OF TRIBOLOGICAL BEARINGS

At the beginning of artificial hip replacement, the metal-on-polyethylene (MoP) articulation represented the gold standard for many years with satisfying results. Otherwise, on the long run, unknown complications appeared with periprosthetic osteolysis and aseptic loosening due to polyethylene wear debris [4]. These problems were resolved by the introduction of high cross-linked polyethylene (HXLPE) and ultra-high cross-linked polyethylene (UHXLPE),shown in several studies [41]. Another substantial progress was the approach of ceramic-on-ceramic bearings (CoC), reducing problems with polyethylene inlays, although the literature shows different results when comparing these tribological pairings [42-45]. The use of CoC bearings significantly decreased the risks of revision, osteolysis, aseptic loosening and dislocation but increased as well the risks of squeaking and intraoperative implant fracture [42, 44, 45]. Furthermore, nowadays there is

no evidence that CoC is superior to ceramic-on-polyethylene (CoP) which was shown in some recent meta-analyses [44, 45].

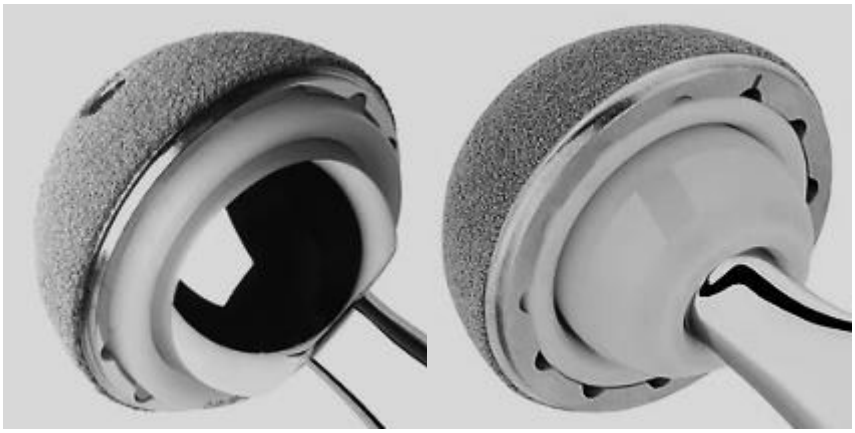

Figure 9: Tribiological bearings used for THA: metal-on-polyethylene (MoP) and ceramic-on-ceramic (CoC; from https://www.hipreplacement.com/technology/implants/bearings).

2.3.1 METAL-ON-METAL ARTICULATIONS

The first generation metal-on-metal (MoM) designs in the 1950s produced poor results due to high rates of aseptic loosening related to metal particle debris. August et al. [46] reported an outcome of the first generation McKee-Farrar metal-on-metal THA with an implant survival of 84% at 15 years, decreasing to 28% after 20 years. Since those experiences were made with MoM bearings, metal-on-polyethylene got the gold standard for several years resulting as well in high revision rates due to polyethylene wear [4, 47].

At the end of the 1980s, the second generation MoM bearing was introduced by Zimmer (Zimmer Inc., Warsaw, Indiana, USA) with the trade name “Metasul”. Several studies showed no advantage of this kind of MoM bearing compared to MoP bearings and identified higher revision rates, whereas dislocation was a rising complication due to the usually used head size of 28 mm [47-49]. Furthermore, a higher incidence of radiolucent lines could be observed than with other articulations like MoP or CoC [48].

In the first decade of the 21th century, MoM total hip arthroplasty and large diameter MoM resurfacing hip arthroplasty (RHA) became once again an accepted and widespread procedure for joint replacement since the introduction of the third-generation MoM bearings [50]. The early results revealed lower failure rates due to wear and aseptic loosening in contrast to the first- and second-generation [51-53]. Expected and propagated advantages of large head MoM bearings were less femoral bone loss with bone stock preservation in case of RHA as well as a higher range of motion with a reduced risk of

dislocation [50, 52, 54]. Therefore, this prosthesis' concept was thought to be suitable for the lifestyle of younger and physically active patients [50, 52, 54].

Figure 10: Modern metal-on-metal (MoM) resurfacing device.

However, the number of revisions of failed total hip arthroplasties using MoM articulations increased, after the first promising results, especially following hip resurfacing [50]. Several annual reports of different arthroplasty registers, such as the Australian Joint Replacement Registry, hosted by the Australian Orthopaedic Association (AOA), and the National Joint Registry (NJR) for England and Wales showed increasing revision rates [55-57].

The unexpected and underestimated disadvantage of modern metal-on-metal articulation was the production of metal wear debris leading to elevated concentrations of metal ions, especially of Co and Cr in the joint fluid, the periarticular soft tissues as well as systemically [50, 53, 58-60].

A various number of studies showed that there are several factors influencing metal ion concentrations such as the implant size, sex, component alignment, differences in manufacture and metallurgy as well as implant design and metal corrosion [50, 54, 58, 61, 62].

Several studies investigated the characteristics of Co and Cr in the human body following MoM total hip arthroplasty revealing increased concentrations associated with hypersensitivity reactions, neurological symptoms, teratological effects, cell death, reduced levels of CD 8+ lymphocytes, DNA damages, or even malignancies [50-53, 58-60, 63-77]. Additionally, local soft tissue reactions like pseudotumours, aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL), corrosive osteolysis and large sterile hip effusion

described, which are nowadays summarized as an adverse reaction to metal debris (ARMD) [50, 57, 60, 78-83].

On the contrary, Antoniou et al. [84] found that increased metal ion concentrations had no effect on oxidative stress makers. Grübl et al. [85] and Mäkelä et al. [86] showed additionally that there was no increased cancer incidence at 10-years follow-up after MoM THA [50, 60].

Almost every study in literature reporting the outcome, complications and survival of modern MoM devices reports the determination of metal ion concentrations in blood, serum, plasma and/or urine as an indirect marker for the amount of MoM wear [87, 88], although studies exist showing no correlation between measured metal ion levels and ARMD [50, 57, 79, 81, 89, 90].

Nowadays, a close and periodic follow-up of all MoM articulations investigating serum metal ion concentrations is strictly recommended by the worldwide biggest orthopaedic associations, American Academy of Orthopaedic Surgeons (AAOS) and European Federation of National Associations of Orthopaedics and Traumatology (EFORT), substantiated by unknown and unexpectable late-effects of long term high systemic Co and Cr exposure.

3. SPECIAL PART

3.1 INTRODUCTION

Bearing surfaces and press fit junctions of implants, for example MoP, CoC, MoM, and in case of modular prostheses the conical junctions between the components, are known to produce wear due to micromotions (= fretting corrosion) and release particles resulting in elevated local and systemical concentrations of metals or critical sized particles causing complications (= tribocorrosional effect) [62, 91].

Since several years, the potential harmful effects of elevated systemic Co and Cr concentrations and their long term exposure are of increasing concern in literature due to the higher than anticipated revision rates of modern third generation MoM hip devices, especially of RHA devices or large diameter heads [50, 92].

These bearings were introduced in an attempt to reduce implant wear due to bigger sized implants, modified implant designs and geometry, whereas the determination of Co and Cr levels in the blood are used for monitoring and evaluation of implant abrasion.

Numerous studies determining metal ion concentrations of patients with RHA or large diameter head THA devices showed that elevated Co and Cr levels in blood and urine represent the systemic exposure [50, 58, 60, 63, 64, 68, 70, 73, 76, 92, 93].

Furthermore, in literature there are several studies reporting complications with local adverse reactions against metal debris (ARMD) and high revision rates for MoM devices [58, 63, 64, 67, 68, 72, 92, 94]. There are also some cases of Co intoxication following THA with metal heads reported as serious complication [50, 60, 70, 73, 93].

Overall, within the last five years the number of revision surgeries due to high metal ion concentrations was rising, partially depending on the manufacturer and their device's performance. One manufacturer had to start a voluntary, worldwide recall of their implant due to extremely high revision rates [55, 75, 79].

Alternatively, less data is published concerning metal ion concentrations following endoprosthetic reconstructions of other anatomical locations than the hip, such as shoulder, vertebral column or knee. Only two studies exist in literature reporting metal ion concentrations after total knee replacement [60, 95, 96]. Further, there are two studies of Zeh et al. [97, 98] and one series of Bisseling et al. [99] which related metal ion concentrations following MoM total disc replacement (TDR).

The aim of the current study was to determine serum metal ion concentrations following fixed hinge total knee arthroplasty with modular megaprostheses. The measured metal concentrations were compared to the serum metal ion levels of patients with rotating hinge

devices. Furthermore, the functional outcome was compared using three different scoring systems.

The study's hypothesis was that the different metal ion concentrations in patients with fixed-hinge megaprostheses would be higher than in patients with RHK devices and that the function in patients with RHK prostheses would be superior compared to the fixed hinge ones.

3.2 MATERIALS AND METHODS

3.2.1 FIXED HINGE KNEE GROUP

From May 1998 to April 2006, 19 patients (12 male and 7 female) underwent total knee replacement using the fixed hinge Howmedica Modular Resection System (HMRS®, Stryker Howmedica Osteonics, Rutherford, NJ) following wide tumour resection around the knee. There were 14 distal femoral, four proximal tibial and one total femoral replacement for 13 osteosarcomas and six Ewing sarcomas. All patients got neo-adjuvant and adjuvant chemotherapy according to the corresponding protocol (COSS/EURAMOS, EUROWING). The mean age at operation was 14 years (range, 9 to 23 years) and the mean resection length was 20 centimetres (cm; range, 10 to 45 cm).

All prostheses were manufactured from a cobalt-chrome-molybdenum alloy according to ISO 2007-4-211.

At time of evaluation, out of these 19 patients, three had already died due to their underlying disease, three patients were lost to follow-up and another two did not want to participate in the current investigation. Overall, eleven patients with a mean postoperative follow-up of 108 months (range, 67 to 163 months) were available for the current series.

3.2.2 ROTATING HINGE KNEE GROUPS

From January 2003 to December 2008, 55 patients (26 male and 29 female) underwent artificial joint replacement of the knee using the Limb Preservation System (LPS™, DePuy, Warsaw, IN) or the S-ROM®Noiles™ (DePuy) rotating hinge prosthesis. Indications for replacement were reconstruction following tumour resection or revision TKA. There were 44 distal femoral, eight proximal tibial and three total femoral replacements. All prostheses were manufactured from cobalt-chrome-molybdenum alloy according to ISO 5832-4.

Eleven out of these 55 patients had died due to their underlying disease or due to an unrelated cause at time of evaluation. Furthermore, five patients were lost to follow-up and 14 patients did not want to participate in our investigation. All in all, blood was taken from 25 patients with a mean postoperative follow-up of 35 months (range, 9-67 months). Seventeen patients got a megaprostheses implanted (LPS™) and eight were treated with a standard rotating hinge device (S-ROM®Noiles™).

	HMRS®	S-ROM®Noiles™	LPS™
Number of patients	11	8	17
Mean age (yrs)	14 (10 to 23)	73 (60 to 81)	49 (15 to 83)
Sex ratio (m:f)	9:2	4:4	12:5
Mean follow-up (mths)	108 (67 to 163)	37 (15 to 62)	34 (9 to 67)
Mean resection length (cm)	20 (10 to 45)	3 (3 to 4)	17 (8 to 26)

Table 1: Demographic data of the study population in the different prosthesis groups (yrs, years; mths, months).

3.2.3 METAL ION SAMPLING

Blood for serum metal ion determination was taken from all patients on equal setting conditions by one observer (JF) using a vacuum assisted system with stainless-steel needles attached to 9 ml no additive vacuum tubes (VACUETTE®). All needles and tubes were used from the same batch and none of the patients had a history of renal impairment.

All specimens were centrifuged for 10 minutes at 4300 rpm within two hours following collection and stored in a fridge at 4°C until the analysis.

Metal ion determination was performed using electrothermal graphite furnace atomic absorption spectrometry (ET ASS) in an external laboratory (Medical and Chemical Laboratory Diagnostic Lorenz & Petek GmbH). This analytic method was chosen due to increased sensitivity and reduced matrix effects (Zeeman Effect). A second tube was stored in the laboratory of the department at -20° Celsius in order to elaborate further questions or to repeat metal ion determination.

Analytical path:

Three-hundred microliters (µl) of each serum sample were diluted with 50 µl modifier and 550 µl Aqua dest. (Rotipuran), whereas these reagents were used as blank values. The patients' samples and the samples of a control group were diluted in the same way.

All samples were evaporated in an atomization apparatus and transformed into atomic condition. The solved samples were charged in a graphite tube with a micro pipette and liberated from solvent and other concomitant agents by heating followed by atomization. Therefor the graphite furnace atomic absorption spectrometry technique was used. The analysis produced a signal with an area proportional to the element of interest and the concentration of the dilution could be calculated by using the dosed volume of the sample. Every ET ASS was repeated twice for each sample and the serum metal ion levels were recorded and expressed as µg/dl.

3.2.4 FUNCTIONAL SCORING SYSTEMS

Three different rating systems were used to evaluate the functional outcome following endoprosthetic reconstruction of the knee at time of investigation. For this purpose, the Knee Society Score (KSS), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC-Score) and the Musculoskeletal Tumor Society Score (MSTS Score) were used.

3.2.5 STATISTICAL ANALYSIS

The data of the current series was processed for statistical differences between the different implant groups concerning metal ion concentrations as well as the functional outcome. Due to the asymmetric distribution of all parameters, non-parametric tests (Kruskal-Wallis-Test, Mann-Whitney-U Test) were used. Additionally, the correlation between the metal ions was determined using the Pearson correlation coefficient. A p-value of <0.05 was considered to be statistical significant. For statistical analysis the PASW Statistics 16.0 program (SPSS Inc., Chicago, IL) was used.

This study was approved by the Ethics Committee and the informed consent was obtained from all patients.

3.3 RESULTS

3.3.1 METAL ION DETERMINATION

3.3.1.1 FIXED HINGE KNEE GROUP

At the time of the latest follow-up the average serum metal ion concentrations of Co, Cr, and Mo in patients with fixed hinge HMRS® megaprostheses were 0.47 µg/dl (range, 0.04 to 1.28 µg/dl) for Co, 0.401 µg/dl (range, 0.148 to 0.891 µg/dl) for Cr and 0.06 µg/dl (range, 0.01 to 0.09 µg/dl; Table 2) for Mo. Compared with the upper limits of the reference values from the laboratory, the levels of Co (normal range: 0 to 0.05 µg/dl) and Cr (normal range: 0 to 0.19 µg/dl) were nine-fold and two-fold, respectively, increased, while Mo (normal range: 0 to 0.10 µg/dl) was within the physiological limits.

3.3.1.2 ROTATING HINGE KNEE GROUPS

The mean results for Co, Cr and Mo in the serum of 17 patients with an implanted LPS™ rotating hinge device were 0.75 µg/dl (range, 0 to 4.70 µg/dl), 0.298 µg/dl (range, 0.012 to 2.49 µg/dl) and 0.04 µg/dl (range, 0 to 0.08 µg/dl). In this group the concentrations for Co and Cr were fifteen-fold and one and a half-fold increased, respectively, compared to the reference values from the laboratory. As observed in the fixed hinge group, Mo was within the physiological limits (Table 2).

In the S-ROM®Noiles™ group the measured levels of Co, Cr and Mo range from 0 to 0.07 µg/dl (mean, 0.03 µg/dl), 0.006 to 0.095 µg/dl (mean, 0.033 µg/dl) and 0.02 to 0.07 µg/dl (mean, 0.04 µg/dl; Table 2). Compared to the reference values of the laboratory, we could not observe any increments of serum metal ion levels.

	HMRS®	**LPS™**	**S-ROM®Noiles™**	**p-value**
Age at operation	15 (10 to 23)	49 (15 to 83)	73 (60 to 81)	p<0.001
Time of follow-up (mths)	108 (67 to 163)	34 (9 to 67)	37 (15 to 62)	p<0.001
Resection length (cm)	20 (10 to 45)	17 (8 o 26)	3 (3 to 4)	p<0.001
Serum metal ion levels (range)				
Co (µg/dl)	0.47 (0.04 to 1.28)	0.75 (0 to 4.70)	0.03 (0 to 0.07)	p=0.010
Cr (µg/dl)	0.401 (0.148 to 0.891)	0.298 (0.012 to 2.490)	0.033 (0.006 to 0.095)	p<0.001
Mo (µg/dl)	0.06 (0.01 to 0.09)	0.04 (0 to 0.08)	0.04 (0.02 to 0.07)	p=0.342

Table 2: Demographic data and results of serum metal ion determination divided by implant groups as well as statistical significances between the groups under investigation.

3.3.1.3 FIXED HINGE KNEE GROUP vs. ROTATING HINGE KNEE GROUPS

Overall, there was a statistical significant difference for Co and Cr concentrations between all three implant groups (Table 2), with higher concentrations measured in the megaprosthetic groups (Figure 11).

The serum concentrations of Co and Cr in patients with fixed hinge HMRS® prostheses were sixteen-fold and twelve-fold higher compared to the concentrations measured in patients with a S-ROM®Noiles™ rotating hinge device, respectively. The measured differences for metal ion levels were statistically significant (Co & Cr: $p=0.002$ and $p<0.001$, Mann-Whitney U test, Table 3).

Interestingly, the serum concentrations of Co were one and a half-fold higher in patients with the LPS™ rotating hinge megaprosthesis, while the Cr values in this group were one and a half-fold lower compared to the fixed hinge implant group. The difference between the Co concentrations was not statistically significant ($p=0.312$), while the Cr levels were significantly higher in the fixed hinge group ($p=0.002$, Mann-Whitney U test, Table 3).

The mean results for Co and Cr from patients treated with LPS™ megaprostheses were 25 and 9 times, respectively, higher compared to patients with the standard rotating hinge knee. These differences of serum metal ion concentrations were statistically significant (Co: $p=0.024$; Cr: $p=0.025$; Table 3).

There was no statistical difference for Mo concentrations in the serum between all tested implant groups under investigation (Tab.3).

Devices	Co	Cr	Mo
HMRS® vs. LPS™	0.312	0.002	0.210
HMRS® vs. S-ROM®Noiles™	0.002	<0.001	0.212
LPS™ vs. S-ROM®Noiles™	0.024	0.025	0.746

Table 3: Results of statistical analysis comparing the measured serum metal ion levels between the different implant groups.

Positive correlations between serum Co and Cr concentrations could be observed in all implant groups, but statistical significance was only observed in the S-ROM®Noiles™ group. Furthermore, there was no significant correlation between measured metal ion concentrations and resection length (Pearson correlation coefficient, Table 4).

Device	Co:Cr	p-value	Co:RL	p-value	Cr:RL	p-value
HMRS®	0.742	0.009	-0.041	0.904	0.027	0.938
LPS™	0.945	<0.001	-0.169	0.517	-0.132	0.613
S-ROM®Noiles™	0.764	0.027	0.068	0.872	-0.257	0.539

Table 4: Calculated Pearson correlation coefficient for all implant groups. In the S-ROM®Noiles™ group there was a significant correlation between Co and Cr concentrations (RL-resection length).

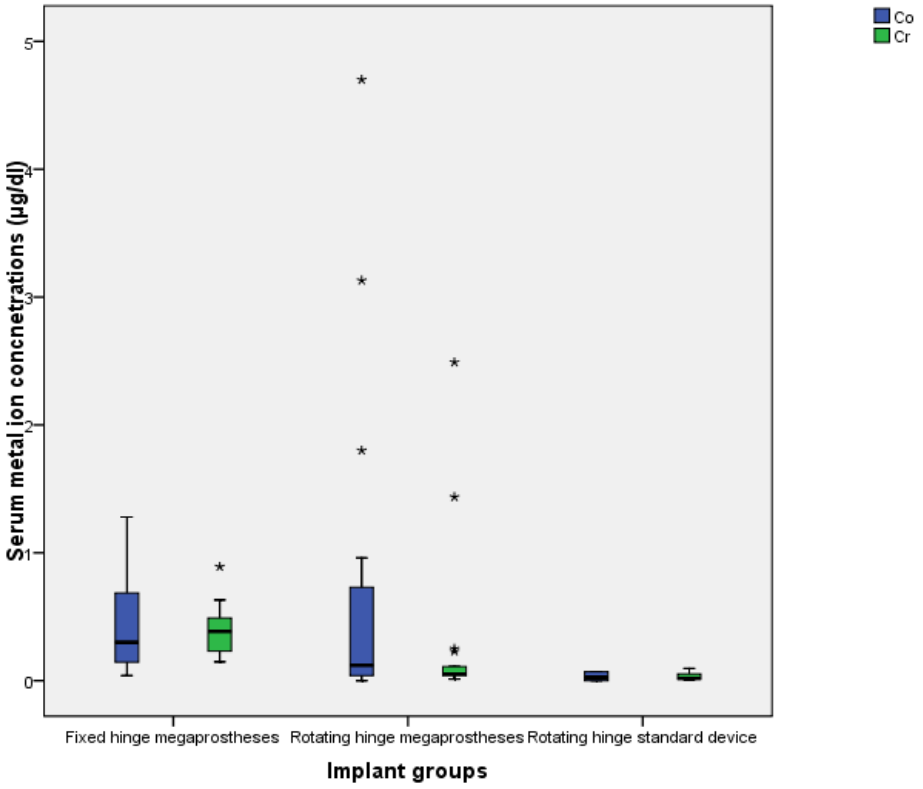

Figure 11: Box plot showing the Co and Cr serum metal ion levels in the fixed hinge megaprosthesis group in proportion to the other RHK devices. Patients with fixed hinge devices had higher concentrations of Co and Cr in the plasma compared to patients with a standard rotating hinge device. These results showed a statistically significant difference (Table 3).

A possible explanation for the differences between the implant groups could be the size respectively the surface of the implants as well as the conical junctions of the modular components as source of metal ion release.

Nevertheless, the average Co and Cr concentrations were within the international accepted limits of 0.20 µg/dl to 0.70 µg/dl, at which a regular follow-up is recommended [100, 101].

3.3.2 SCORING SYSTEMS

Patients with a fixed hinge HMRS® device had a mean WOMAC score of 4 points (range, 0 to 17), while patients with LPS™ megaprostheses had a mean score of 22 points (range, 0 to 88 points). Patients with S-ROM®Noiles™ knees had an average WOMAC score of 15 points (range, 1 to 37 points). Differences between the implant groups were statistically significant (p=0.009; Table 5).

The results of the first part of the KSS were satisfying in all groups (Table 5). The average scores were 89 (range, 64 to 100 points) and 87 points (range, 51 to 100 points) in the megaprostheses groups. In comparison to that, the mean KSS score for patients with a standard rotating hinge knee was 86 points (range, 65 to 99 points).

The second part of the KSS revealed worse results compared to the first one. Most patients had deductions for using walking aids like canes or crutches, especially in the LPS™ and the S-ROM®Noiles™ group. Patients in the HMRS® group produced quite better results with a mean score of 95 points (range, 80 to 100 points). The maximum score for the LPS™ group was 100 points and the worst result was 0 points (mean, 68 points). The results of the S-ROM®Noiles™ group were a bit worse with a mean score of 59 points (range, 30 to 80 points). Differences in functional outcome for the second part of the KSS were statistically significant (p=0.003, Table 5).

Evaluation of the MSTS score revealed a mean score of 27 points in the HMRS® group and 22 points in both RHK groups, respectively. Therefore it can be stated that the functional outcome was significant better in the HMRS® group (p=0.014, Table 5).

Outcome Scores (range)	HMRS®	LPS™	S-ROM®Noiles™	Significance
WOMAC	4 (0 to 17)	22 (0 to 88)	15 (1 to 37)	p=0.009
KSS Part 1	89 (64 to 100)	87 (51 to 100)	86 (65 to 95)	p=0.429
KSS Part 2	95 (80 to 100)	68 (0 to 100)	59 (30 to 80)	p=0.003
MSTS pts	27 (22 to 30)	22 (5 to 30)	22 (18 to 30)	p=0.014

Devices	MSTS	KSS 1	KSS 2	WOMAC
HMRS® vs. LPS™	0.013	0.382	0.016	0.003
HMRS® vs. S-ROM®Noiles™	0.009	0.182	<0.001	0.030
LPS™ vs. S-ROM®Noiles™	0.682	0.641	0.462	0.521

Table 5: The results of functional analysis as well as results of statistical analysis comparing all scoring systems. Differences in functional outcome between the HMRS® group and RHK patients are most likely due to the young age of these patients.

3.4 DISCUSSION

The current study revealed increased serum metal ion concentrations for Co and Cr in patients following fixed hinge total knee arthroplasty using the modular HMRS® megaprosthesis in comparison to a standard rotating hinge device (Table 2). Comparing these serum metal ion levels with the concentrations measured in the RHK megaprosthesis group (LPS™) resulted in lower Co levels but higher Cr concentrations, although these differences were statistically not significant (Table 2). Referring to previous published data, the values for Mo were within the limits in all implant groups under investigation as expected [58, 75, 85, 95, 102, 103].

Based on the results of the used scoring systems it can be stated that patients with fixed-hinge megaprostheses provided better functional outcome, whereas this might be caused by the younger age of the patients in comparison to the both RHK groups.

Overall, the hypothesis of this study regarding differences in serum metal ion concentrations with expected higher Co and Cr levels in the fixed-hinge group was not supported by the current results. However, a continued long-term follow-up is recommended because especially young patients might suffer from unexpectable late effects of chronic, high systemical metal ion exposure.

Regarding to the most recent official guidelines for MoM THA devices of the worldwide biggest orthopaedic societies, EFORT and AAOS, the concentrations of Co and Cr were within the accepted limits of 0.20 µg/dl to 0.70 µg/dl at which a regular outpatient care with routine serum metal ion determination is recommended [60, 100, 101], although there are no standards defined for other orthopaedic devices than the MoM hip prostheses.

The author's believe that these international accepted guidelines should also be accepted for other orthopaedic devices, especially for those with metal-on-metal articulation like in case of artificial TDR. Further, implants with metal-on-polyethylene articulation with the possibility of direct metal-on-metal contact due to wear of the PE-bushings, for example used at the articulation side of megaprostheses, as well as implants with multiple conical junctions in case of modular devices, should be investigated [60].

Continued follow-up investigations including blood metal ion determination should be obligatory due to the potential harmful effects of chronic high Co and Cr exposure. Further, the systemical toxicity of high Co and Cr levels is always the same and does not depend on the type of orthopaedic device.

Metal ions and prosthetic alloys:

Less is known concerning metal ion concentrations using implants manufactured from other prosthetic alloys or being covered with different surface coatings like titanium-nitride (TiN), silver or oxidized zirconium.

Garrett et al. [104] related a study determining differences in metal ion release following total knee arthroplasty using devices made of Co-Cr and oxidized zirconium. Despite the lack of Co and Cr in the oxidized zirconium control group, no statistically significant differences were found between the implant groups concerning serum ion concentrations. Due to these results the authors concluded that there is no significant increase of serum metal ion levels following TKA [104].

There are also studies reporting the wear behavior of TiN coated implants articulating with UHMWPE inlays [105-107]. Van Hove et al. [107] showed an improved oeteoconduction of TiN coated knee prostheses compared to Co-Cr devices in vitro suggesting better implant survival in TKA. On the other hand, the same author group referred that TiN coated implants did not influence the postoperative outcome indicating that these devices might not provide any clinical benefit compared to Co-Cr devices [108].

Mohammed et al. [109] related an implant survival of 99.1% for aseptic loosening 10 years following implantation of a TiN coated knee prosthesis. Park et al. [110] reported a case of a broken femoral component of a TiN coated total knee prosthesis suspecting a structural defect at the bone-cement interface causing that fatigue failure.

Dieckmann et al. [105] recently reported the wear properties of the new Modular Universal Tumour And Revision System (MUTARS®, Implantcast, Buxtehude, Germany) humerus inverse prosthesis used for reconstruction following tumor resection, being comparable to the results of normal reversed shoulder prostheses.

There are many studies reporting the functional outcome as well as complication rates after implantation of megaprostheses used for joint reconstruction and limp salvage surgery [105, 111, 112]. To the best of author's knowledge, there are no informations concerning serum metal ion concentrations following the usage of different megaprosthetic systems like the MUTARS® system, the Stanmore SMILES prostheses (Stanmore Implants, Hertfordshire, United Kingdom), the Endo Modell® (Waldemar Link GmbH & Co KG, Hamburg, Germany), the Megasystem C® (Waldemar Link, Germany) or the Biomet Orthopaedic Salvage System (OSS®, Biomet Inc., Warsaw, IN, United States).

Silver is known to be antibacterial and bacteriostatic. Therefore, this noble metal has been introduced in orthopedics as a surface coating for megaprostheses with the intention to

reduce complication rates based on early and late prosthetic infections [112, 113]. Otherwise, less is published about potential side effects of high blood silver concentrations and long term exposure as well as systemic silver concentrations in the blood. In 2013, Glehr et al. [114] firstly showed that there was no correlation between the development of local argyria and serum silver concentrations after the implantation of silver coated MUTARS® megaprostheses but at time there is no further study validating these observations.

Effects of serum metal ion elevation and intoxication:

In the literature there are numerous studies reporting elevated metal ion concentrations following MoM THA or RHA locally and systemically, especially in patients with mal-positioned implants [50, 52, 115]. Otherwise, some studies reported that the clinical significance of elevated metal ion concentrations remains unknown [51, 54, 77, 115].

Several author groups demonstrated the increment of Co and Cr levels within the first few months up to 2 years following MoM THA as so called "run-in" period [50, 53, 61, 63, 66, 72, 74, 77, 84, 103, 116-118]. In the further course, Back et al. [116] and Daniel et al. [63, 119] observed a decreasing trend within the first 6-years following implantation. On the other hand, deSouza et al. [65] related a second increment of metal ion concentrations 5-years after RHA. Sauvè et al. [76] reported three-fold and five-fold higher serum metal ion concentrations compared to a control group during a follow-up of 30 years.

Intoxications due to massively high Co concentrations are rare but serious complications and of increasing interest because biomaterials of orthopaedic devices were considered to be non-toxic, although some animal studies showed potentially carcinogenic effects of metals which are also used for the production of artificial devices [120]. At time, there are several cases of Co intoxications reported in the literature [70, 71, 73, 121, 122]. In all reported cases, the Co intoxication occurred following revision THA after breakage of the previously used CoC liner with exchange of the tribological bearing to a MoP articulation. At time of re-revision retained ceramic particles could be found in each case being responsible for massive third body wear associated with massive metal ion increments in the blood up to 600 µg/L for Co and 230 µg/L for Cr [70, 71, 73, 121, 122].

Reported symptoms associated with high Co concentrations were tachycardia, cardiomyopathia, hypothyroidism, exanthema, neuropathies of the acustic and optical nerve and irreversible polyneuropathia [70, 71, 73, 121, 122]. On the other hand, in most

cases the symptoms resolved following re-revision surgery in combination with chelation therapy with 2,3-dimercaptopropane-1-sulfonate (DMPS) [70, 71, 73, 121, 122].

Matziolis et al. [123] reported a case of massive metallosis following revision THA of a broken CoC bearing to a MoP articulation. The patient underwent another two-stage revision surgery due to aseptic loosening of the femoral stem caused by abrasion of the polyethylene liner. Therefore, the authors concluded that at time of revision of a broken CoC tribological bearing, the usage of a MoP articulation is contraindicated and further they recommended the application of a new CoC articulation pairing.

Keel et al. [120] reported the development of malignant tumours of soft tissue and bone associated with metallic implants although these are extraordinary rare. Due to the fact that malignancies arose next to metallic implants, this group suggested strong evidence and an important relationship concerning carcinogenic effects, which have not been proven until now.

Adverse Reactions to Metal Debris (ARMD):

Numerous authors related their observation of cystic and fluid masses around symptomatic and asymptomatic MoM hip arthroplasties [54, 64, 75, 94, 124-132]. These masses have been subtitled using headings like “aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL)” [133], “pseudotumors” [125, 134], “adverse reactions to metal debris (ARMD)” [51, 52, 77], metallosis and large sterile hip effusion until 2012. Since that time and following several consensus meetings of the worldwide biggest orthopaedic societies, AAOS and EFORT, these local soft tissue reactions are summarized as ARMD [57, 60, 78-83].

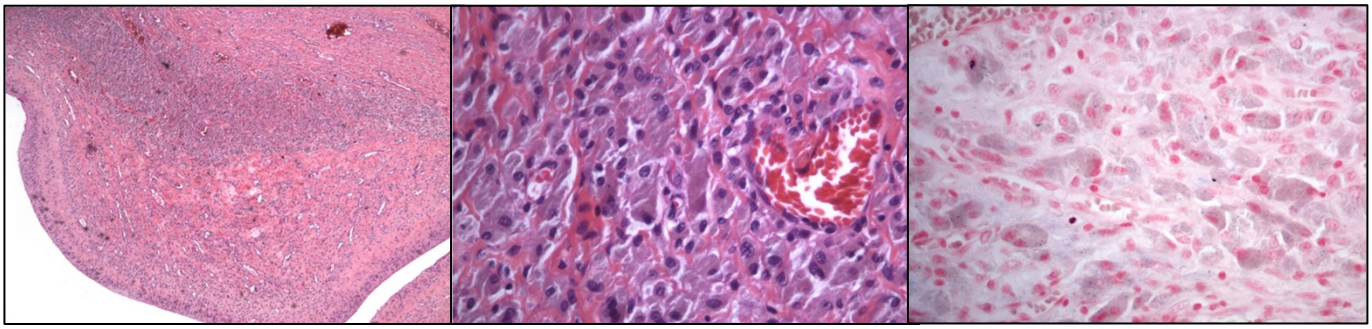

Figure 12: HE stained sections and Berlin blue stained section of a cystic pseudotumor. Fibrous and fibro-hyalinized tissue with massive accumulation of macrophages (magnification, x10) containing visible metal particles (x400). The Berlin blue stained section showing no reaction for hemosiderin (x400).

ARMD causes a wide spectrum of clinical symptoms ranging from small asymptomatic fluid masses up to massive local infiltrating lesions causing neurologic symptoms like par- or hypoesthesia and even paresis due to nerve compression. Furthermore, limb perfusion can be disturbed by compression of the major vessels of the lower extremities [51, 94].

Glyn-Jones et al. [128] and Langton et al. [58] postulated that the incidence of pseudotumors tends to increase with time and reported an incidence of 4% at 8 years of follow-up. Most recently, Wiley et al. [135] performed a systematical review reporting an incidence of ARMD spreading from 0% to 6.5% at a follow-up ranging from 1.7 to 12.3 years across all reviewed studies. Otherwise, Bayley et al. [136] detected ARMD in 20% of all investigated THAs.

Several author groups found that age (<40 years), sex (male<female), smaller implant size, implant mal-position and higher whole blood concentrations of Co and Cr had a significant influence on the revision rate for soft tissue masses [50, 58, 136, 137]. Overall, the origin and the pathogenesis of ARMD is still under investigation although delayed hypersensitivity reactions (Type IV) against metal debris are hypothesized to be in charge for these soft tissue reactions [52, 53, 138]. Natu et al. [77] related the histopathological features of periprosthetic tissues of failed MoM arthroplasties consisting of marked necrosis associated with a chronic lymphatic inflammation.

Actually, metal artefact reduction sequences MRI (MARS) is the gold standard in diagnosing such soft tissue reactions [126, 132, 137, 139]. Anderson et al. [140] introduced a grading system for ARMDs ranging from mild to severe depending on diameter, as well as soft tissue compromise, bone marrow involvement and involvement of the neurovascular structures.

Therapy of choice in case of ARMD due to metallosis is a revision surgery with resection of the cystic mass and exchange arthroplasty of the MoM implant to a THR with different tribological pairing [54, 94].

Metallosis:

There are several pathologic entities which have to be considered in case of painful and enlarging masses following joint replacement, whereas primary malignancies of soft tissue and bone, as well as metastatic disease have to be excluded. Further pathologies like aneurysm, infection, cellulitis or thrombosis have to be precluded, additionally [141]. Nevertheless, wear debris and metallosis are also potential differential diagnosis.

Metallosis is a combination of local chemical and toxicological reactions produced by metal debris of artificial devices, which is suspected to be proportional to the implant size [142, 143]. Metal debris is known to lead to a vicious cycle of implant failure with increasing abrasive wear of the articulation, as well as periprosthetic loosening by inciting a foreign body reaction mediated by several cytokines like tumor necrosis factor-alpha 1 (TNF-alpha 1), interleukin-1 and -6 (IL-1 & IL-6) and prostaglandin E2 (PGE2). This inflammatory process leads to continuous bone resorption with increasing micromotions at the implant interface with generation of particulate debris [141, 142, 144].

Local soft tissue reactions like ARMD seem to be unlikely following total knee arthroplasty using modular prostheses, neither with fixed hinge nor with rotating hinge articulation.

In the literature there are two cases of soft tissue masses posterior to the implant reported following MoM TDR and one case of a wear debris induced metallosis cyst 7 years following TKA [141, 145, 146]. In the case of Cavanaugh et al. [147] the pathologist found that the inflammatory reactions in the histologic specimen following revision of a MoM TDR were similar to the lymphocyte-dominated response found at revision of MoM hip devices. Berry et al. [142] reported a huge mass after MoM TDR with compression of the iliac vein.

On the other hand, at time of revision of the fixed hinge HMRS® megaprostheses for any reason, especially due to metal-on-metal impingement between the femoral and tibial component at the level of the hinge due to wear of the polyethylene bushes, which occurred in two cases, we observed massive periprosthetic metallosis, whereby metal debris was found in the joint fluid, the surrounding soft tissues including the synovial layer and the joint capsule (Figure 12 and 13). Further indications for revision surgery were aseptic loosening (n=2), periprosthetic fracture (n=1), femoral stem fracture (n=1), delayed wound closure (n=1) and implant revision to a rotating hinge device in case of a HMRS® growing prosthesis (n=1).

In all cases, partial or complete synovectomy was tried and performed in order to reduce the risk of infection or delayed wound closure. Further, all mobile parts, the PE bushings and the hinge axle, were changed.

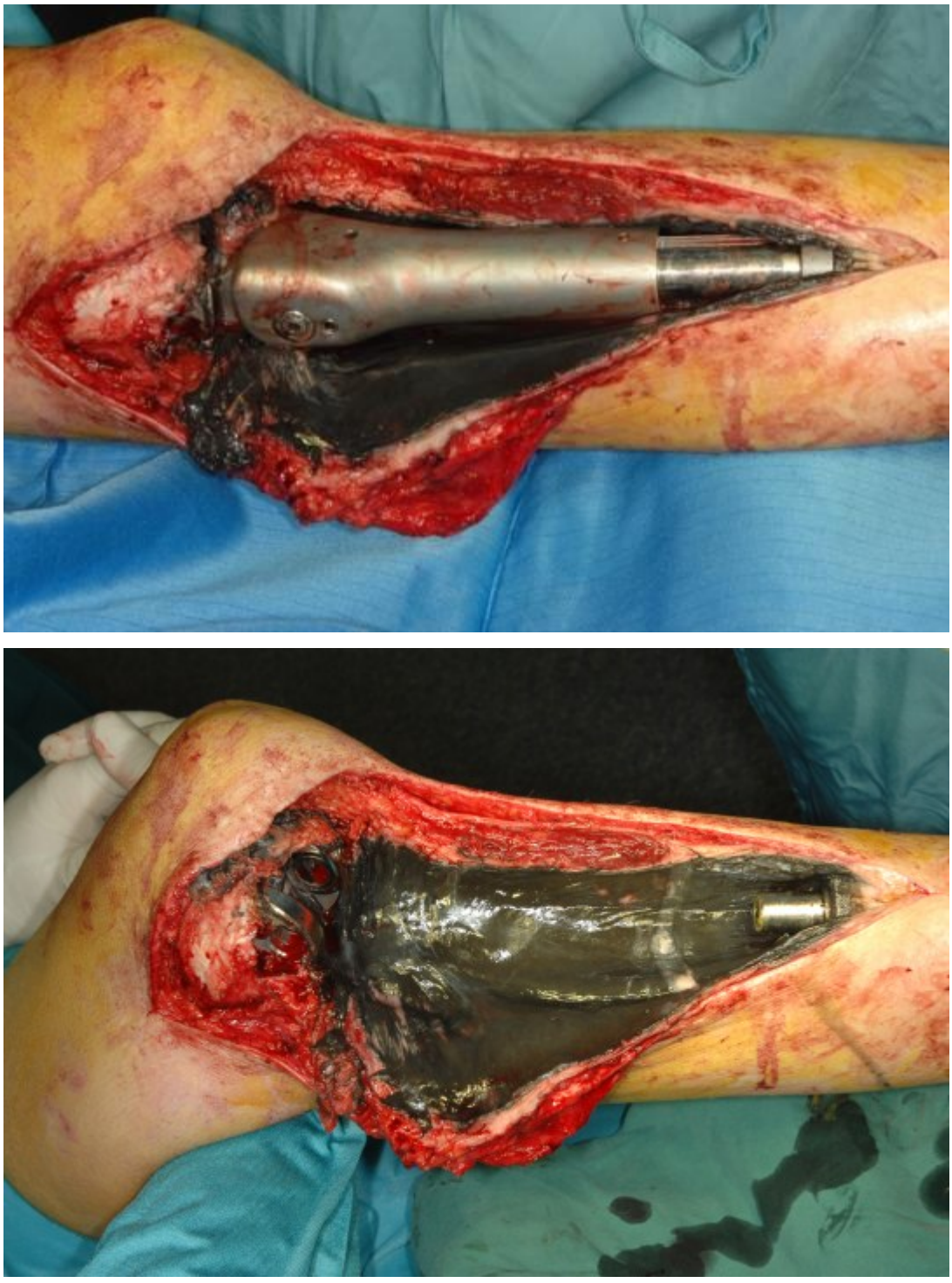

Figure 13: Intraoperative photographs at the revision of a fixed hinge HMRS® megaprosthesis in a 20-year-old male patient showing a marked metallosis in the periprosthetic soft tissues of the lower leg 119 months after implantation.

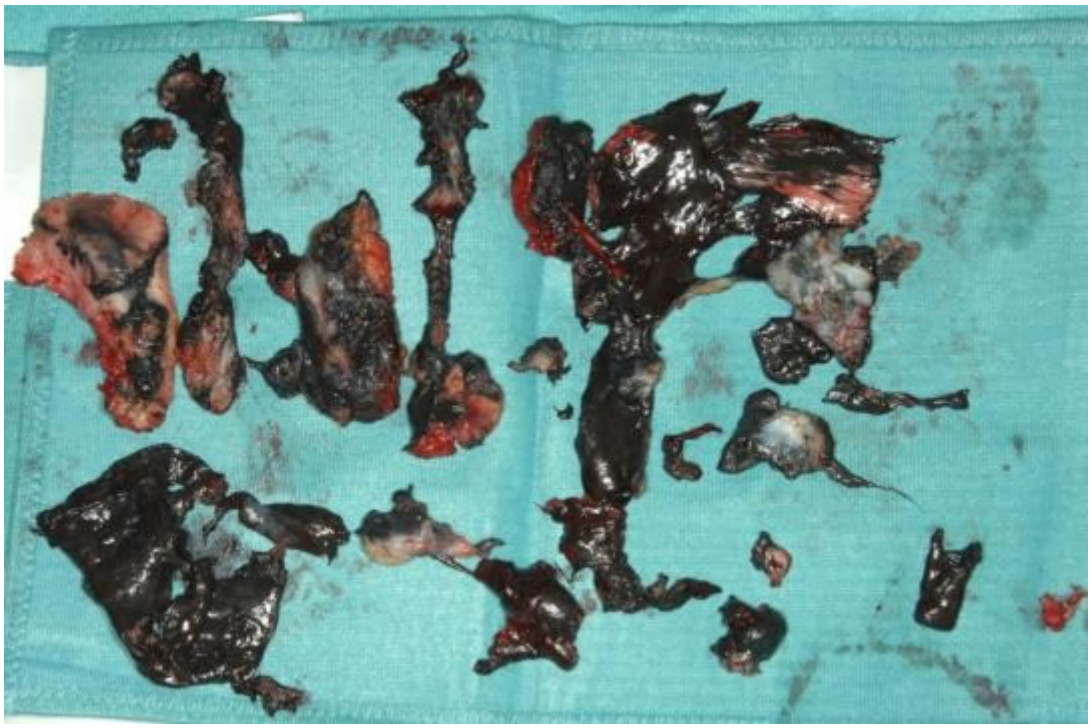

Figure 14: Photograph of the resected periprosthetic grey to black metallosis tissue.

Reported significant factors associated with metal wear of implants are patient's activity, weight and body mass index (BMI), type of articulation (constrained vs. non-constrained), implant's design and geometry, bearing surfaces, alignment and inlay's quality as well as high contact stresses and taper- and fretting corrosion of the implant [60, 141, 143, 148].

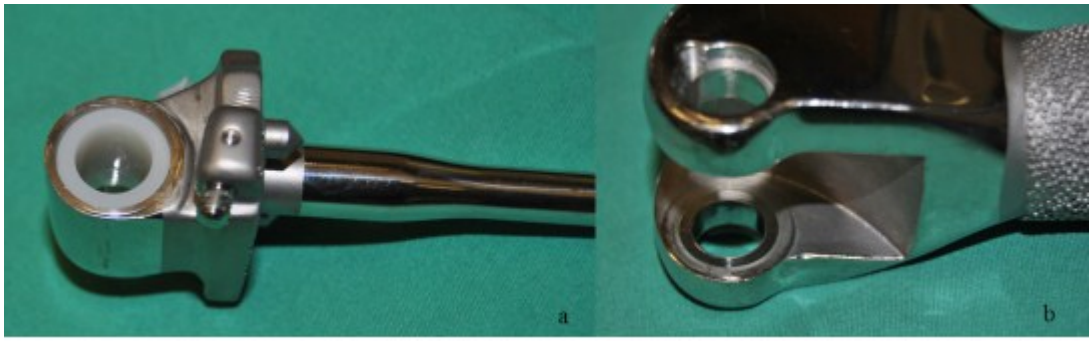

Figure 15 showing a) the femoral and b) the tibial component of an explanted HMRS® megaprosthesis. At the side of the hinge there was a direct metal-on-metal articulation with clearly signs of metal debris (scratches and striation) following abrasion of the PE bushings.

Romesburg et al. [149] related that titanium components of orthopaedic implants also seem to have an increased association with periarticular metallosis when compared with Co-Cr devices [150], while Willis-Owen et al. [151] related early metallosis after TKA in 15 Co-Cr knees needing implant revision combined with total synovectomy [60].

Referring to the published literature, it is not possible to state which type of alloy is better or worse to be used for the production of orthopaedic implants because it seems that complications associated with metallosis might occur in both titanium and Co-Cr devices.

Limitations:

One limitation of the study is the absence of pre-operative serum metal ion levels of Co and Cr of patients with fixed hinge and rotating hinge knee prostheses. A further limitation was that only a small number of patients was enrolled in the study, whereby it was not possible to include more due to the fact that the devices under investigation have been pulled from the market several years ago or are not used any more at our department.

Additionally, we have to point out, that there are differences between the follow-ups of the implant groups, whereas the fixed hinge megaprosthesis group had the longest follow-up with an average of 108 months. Nevertheless, we do not think that this is a confounding factor due to the fact that all patients have passed the reported "running-in period" of orthopaedic implants and therefore the metal ion levels must have stabilized.

On the other hand, it should be noted that this is the first study evaluating serum metal ion levels following fixed hinge total knee arthroplasty using megaprostheses in young patients. Further, these results were compared to the Co and Cr concentrations of patients with implanted rotating hinge prostheses.

All samples of each group were evaluated at the same laboratory using the same study protocol.

3.5 CONCLUSION

The current series is the first study reporting serum metal ion levels in young patients following limb salvage surgery using fixed hinge megaprostheses.

1.) Determination of serum metal ion concentrations revealed increments for Co and Cr in the fixed hinge megaprosthesis group, whereas these values were comparable to the results measured in patients treated with rotating hinge megaprostheses despite the different articulation mechanism. Nevertheless, we believe that there should be a concern due to long-term exposure to Co and Cr when using these types of megaprostheses.

2.) The authors believe that serum metal ion determination might also be used as an indicator for implant wear and periprosthetic metallosis in case of megaprosthetic reconstruction.

3.) Periprosthetic metallosis was observed at revision surgery which might cause additional complications like osteolysis and aseptic loosening of the implant.

4.) Upon the occurrence of ARMD or clinical symptoms of intoxication, the revision of the fixed hinge implant to a modern rotating hinge device or another reconstruction method should be considered.

5.) We recommend periodic surveillance of all patients with MoM devices, especially in case of elevated metal ion concentrations to preclude negative long-term effects. In addition, surgeons must consider implant design, size and position in order to reduce early failures and high implant wear.

4. APPENDIX

The systematic approach and usage of literature was accomplished with OvidSP and Pubmed. Statistical analysis was performed using the SPSS program.

5. REFERENCES

1. Jones RE, Barrack RL, Skedros J: Modular, mobile-bearing hinge total knee arthroplasty. Clin Orthop Relat Res 2001(392):306-314.

2. Charnley J: Anchorage of the femoral head prosthesis to the shaft of the femur. J Bone Joint Surg Br 1960, 42-B:28-30.

3. Charnley J: Arthroplasty of the hip. A new operation. Lancet 1961, 1(7187):1129-1132.

4. Evans BG, Salvati EA, Huo MH, Huk OL: The rationale for cemented total hip arthroplasty. Orthop Clin North Am 1993, 24(4):599-610.

5. Kolb A, Grubl A, Schneckener CD, Chiari C, Kaider A, Lass R, Windhager R: Cementless total hip arthroplasty with the rectangular titanium Zweymuller stem: a concise follow-up, at a minimum of twenty years, of previous reports. J Bone Joint Surg Am 2012, 94(18):1681-1684.

6. Shiers LG: Arthroplasty of the knee; preliminary report of new method. J Bone Joint Surg Br 1954, 36-B(4):553-560.

7. Watson JR, Wood H, Hill RC: The Shiers arthroplasty of the knee. J Bone Joint Surg Br 1976, 58(3):300-304.

8. Grimer RJ, Karpinski MR, Edwards AN: The long-term results of Stanmore total knee replacements. J Bone Joint Surg Br 1984, 66(1):55-62.

9. Lettin AW, Deliss LJ, Blackburne JS, Scales JT: The Stanmore hinged knee arthroplasty. J Bone Joint Surg Br 1978, 60-B(3):327-332.

10. Barrack RL, Lyons TR, Ingraham RQ, Johnson JC: The use of a modular rotating hinge component in salvage revision total knee arthroplasty. J Arthroplasty 2000, 15(7):858-866.

11. Sonstegard DA, Kaufer H, Matthews LS: The spherocentric knee: biomechanical testing and clinical trial. J Bone Joint Surg Am 1977, 59(5):602-616.

12. Manning DW, Chiang PP, Freiberg AA: Hinge Implants. In: Revision Total Knee Arthroplasty. edn. Edited by James V. Bono, Scott RD. New York: Springer Science+Business Media, Inc.; 2005: 219-236.

13. Bickels J, Wittig JC, Kollender Y, Henshaw RM, Kellar-Graney KL, Meller I, Malawer MM: Distal femur resection with endoprosthetic reconstruction: a long-term followup study. Clin Orthop Relat Res 2002(400):225-235.

14. Inglis AE, Walker PS: Revision of failed knee replacements using fixed-axis hinges. J Bone Joint Surg Br 1991, 73(5):757-761.

15. Capanna R, Morris HG, Campanacci D, Del Ben M, Campanacci M: Modular uncemented prosthetic reconstruction after resection of tumours of the distal femur. J Bone Joint Surg Br 1994, 76(2):178-186.

16. Kawai A, Muschler GF, Lane JM, Otis JC, Healey JH: Prosthetic knee replacement after resection of a malignant tumor of the distal part of the femur. Medium to long-term results. J Bone Joint Surg Am 1998, 80(5):636-647.

17. Engelbrecht E, Siegel A, Rottger J, Buchholz HW: Statistics of total knee replacement: partial and total knee replacement, design St. Georg: a review of a 4-year observation. Clin Orthop Relat Res 1976(120):54-64.

18. Attenborough CG: The Attenborough total knee replacement. J Bone Joint Surg Br 1978, 60-B(3):320-326.

19. Barrack RL: Evolution of the rotating hinge for complex total knee arthroplasty. Clin Orthop Relat Res 2001(392):292-299.

20. Kofoed H: The Attenborough total knee prosthesis. Results of 25 operations evaluated according to two different assessment systems. Acta Orthop Scand 1981, 52(5):561-568.

21. Rand JA, Chao EY, Stauffer RN: Kinematic rotating-hinge total knee arthroplasty. J Bone Joint Surg Am 1987, 69(4):489-497.

22. David HG, Bishay M, James ET: Problems with the Rotaflex: a 10 year review of a rotating hinge prosthesis. J Arthroplasty 1998, 13(4):402-408.

23. Jones RE, Barrack RL, Skedros J: Modular, mobile-bearing hinge total knee arthroplasty. Clin Orthop Relat Res 2001(392):306-314.

24. Heisel C, Kinkel S, Bernd L, Ewerbeck V: Megaprostheses for the treatment of malignant bone tumours of the lower limbs. Int Orthop 2006, 30(6):452-457.

25. Kabo JM, Yang RS, Dorey FJ, Eckardt JJ: In vivo rotational stability of the kinematic rotating hinge knee prosthesis. Clin Orthop Relat Res 1997(336):166-176.

26. Ilyas I, Kurar A, Moreau PG, Younge DA: Modular megaprosthesis for distal femoral tumors. Int Orthop 2001, 25(6):375-377.

27. Kotz R: [Megaprostheses: KMFTR to GMRS]. Orthopade 2010, 39(10):922-930.

28. Choong PF, Sim FH, Pritchard DJ, Rock MG, Chao EY: Megaprostheses after resection of distal femoral tumors. A rotating hinge design in 30 patients followed for 2-7 years. Acta Orthop Scand 1996, 67(4):345-351.

29. Walker PS, Emerson R, Potter T, Scott R, Thomas WH, Turner RH: The kinematic rotating hinge: biomechanics and clinical application. Orthop Clin North Am 1982, 13(1):187-199.

30. Shih LY, Sim FH, Pritchard DJ, Rock MG, Chao EY: Segmental total knee arthroplasty after distal femoral resection for tumor. Clin Orthop Relat Res 1993(292):269-281.

31. Berend KR, Lombardi AV, Jr.: Distal femoral replacement in nontumor cases with severe bone loss and instability. Clin Orthop Relat Res 2009, 467(2):485-492.

32. Deehan DJ, Murray J, Birdsall PD, Holland JP, Pinder IM: The role of the rotating hinge prosthesis in the salvage arthroplasty setting. J Arthroplasty 2008, 23(5):683-688.

33. Riaz S, Umar M: Revision knee arthroplasty. J Pak Med Assoc 2006, 56(10):456-460.

34. Westrich GH, Mollano AV, Sculco TP, Buly RL, Laskin RS, Windsor R: Rotating hinge total knee arthroplasty in severly affected knees. Clin Orthop Relat Res 2000(379):195-208.

35. Pradhan NR, Bale L, Kay P, Porter ML: Salvage revision total knee replacement using the Endo-Model rotating hinge prosthesis. Knee 2004, 11(6):469-473.

36. Kotz R, Ritschl P, Kropej D, Capanna R: Cementless modular prostheses. Basic concepts and evolution. Chir Organi Mov 1990, 75(1 Suppl):177-178.

37. Kotz R, Ritschl P, Trachtenbrodt J: A modular femur-tibia reconstruction system. Orthopedics 1986, 9(12):1639-1652.

38. Ritschl P, Capanna R, Helwig U, Campanacci M, Kotz R: [KMFTR (Kotz Modular Femur Tibia Reconstruction System) modular tumor endoprosthesis system for the lower extremity]. Z Orthop Ihre Grenzgeb 1992, 130(4):290-293.

39. Ilyas I, Kurar A, Moreau PG, Younge DA: Modular megaprosthesis for distal femoral tumors. Int Orthop 2001, 25(6):375-377.

40. Zeegen EN, Aponte-Tinao LA, Hornicek FJ, Gebhardt MC, Mankin HJ: Survivorship analysis of 141 modular metallic endoprostheses at early followup. Clin Orthop Relat Res 2004(420):239-250.

41. Paxton EW, Inacio MC, Namba RS, Love R, Kurtz SM: Metal-on-conventional polyethylene total hip arthroplasty bearing surfaces have a higher risk of revision than metal-on-highly crosslinked polyethylene: results from a US registry. Clin Orthop Relat Res 2015, 473(3):1011-1021.

42. Hu D, Tie K, Yang X, Tan Y, Alaidaros M, Chen L: Comparison of ceramic-on-ceramic to metal-on-polyethylene bearing surfaces in total hip arthroplasty: a meta-analysis of randomized controlled trials. J Orthop Surg Res 2015, 10(1):22.

43. Varnum C, Pedersen AB, Kjaersgaard-Andersen P, Overgaard S: Comparison of the risk of revision in cementless total hip arthroplasty with ceramic-on-ceramic and metal-on-polyethylene bearings. Acta Orthop 2015:1-8.

44. Dong YL, Li T, Xiao K, Bian YY, Weng XS: Ceramic on Ceramic or Ceramic-on-polyethylene for Total Hip Arthroplasty: A Systemic Review and Meta-analysis of Prospective Randomized Studies. Chin Med J (Engl) 2015, 128(9):1223-1231.

45. Si HB, Zeng Y, Cao F, Pei FX, Shen B: Is a ceramic-on-ceramic bearing really superior to ceramic-on-polyethylene for primary total hip arthroplasty? A systematic review and meta-analysis of randomised controlled trials. Hip Int 2015:0.

46. August AC, Aldam CH, Pynsent PB: The McKee-Farrar hip arthroplasty. A long-term study. J Bone Joint Surg Br 1986, 68(4):520-527.

47. Randelli F, Banci L, D'Anna A, Visentin O, Randelli G: Cementless Metasul metal-on-metal total hip arthroplasties at 13 years. J Arthroplasty 2012, 27(2):186-192.

48. Bjorgul K, Novicoff WN, Andersen ST, Ahlund OR, Bunes A, Wiig M, Brevig K: High rate of revision and a high incidence of radiolucent lines around Metasul

metal-on-metal total hip replacements: results from a randomised controlled trial of three bearings after seven years. Bone Joint J 2013, 95-B(7):881-886.

49. Saito S, Ishii T, Mori S, Hosaka K, Ootaki M, Tokuhashi Y: Long-term results of metasul metal-on-metal total hip arthroplasty. Orthopedics 2010, 33(8).

50. Maurer-Ertl W, Friesenbichler J, Sadoghi P, Pechmann M, Trennheuser M, Leithner A: Metal ion levels in large-diameter total hip and resurfacing hip arthroplasty--preliminary results of a prospective five year study after two years of follow-up. BMC Musculoskelet Disord 2012, 13:56.

51. van Raay JJ: Metal-on-metal total hip arthroplasty: known and unknown side effects. Orthopedics 2012, 35(6):447-449.

52. Fary C, Thomas GE, Taylor A, Beard D, Carr A, Glyn-Jones S: Diagnosing and investigating adverse reactions in metal on metal hip implants. BMJ 2011, 343:d7441.

53. Jacobs JJ, Urban RM, Hallab NJ, Skipor AK, Fischer A, Wimmer MA: Metal-on-metal bearing surfaces. J Am Acad Orthop Surg 2009, 17(2):69-76.

54. Fabi D, Levine B, Paprosky W, Della Valle C, Sporer S, Klein G, Levine H, Hartzband M: Metal-on-Metal Total Hip Arthroplasty: Causes and High Incidence of Early Failure. Orthopedics 2012, 35(7):e1009-1016.

55. Australian National Joint Replacement Registry: Australian National Joint Replacement Registry annual report 2009. 2010 [http://www.dmac.adelaide.edu.au/aoanjrr/publications.jsp]

56. Whitwell GS, Shine A, Young SK: The articular surface replacement implant recall: a United Kingdom district hospital experience. Hip Int 2012, 22(4):362-370.

57. Fox CM, Bergin KM, Kelly GE, McCoy GF, Ryan AG, Quinlan JF: MRI findings following metal on metal hip arthroplasty and their relationship with metal ion levels and acetabular inclination angles. J Arthroplasty 2014, 29(8):1647-1652.

58. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV: Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. J Bone Joint Surg Br 2010, 92(1):38-46.

59. Aroukatos P, Repanti M, Repantis T, Bravou V, Korovessis P: Immunologic adverse reaction associated with low-carbide metal-on-metal bearings in total hip arthroplasty. Clin Orthop Relat Res 2010, 468(8):2135-2142.

60. Friesenbichler J, Sadoghi P, Maurer-Ertl W, Szkandera J, Glehr M, Ogris K, Wolf M, Weger C, Leithner A: Serum metal ion concentrations in paediatric patients following total knee arthroplasty using megaprostheses. Biomed Res Int 2014, 2014:817257.

61. Maurer-Ertl W, Friesenbichler J, Sadoghi P, Pechmann M, Trennheuser M, Leithner A: Metal ion levels in large-diameter total hip and resurfacing hip arthroplasty - Preliminary results of a prospective five year study after two years of follow-up. BMC Musculoskelet Disord 2012, 13(1):56.

62. Friesenbichler J, Maurer-Ertl W, Sadoghi P, Lovse T, Windhager R, Leithner A: Serum metal ion levels after rotating-hinge knee arthroplasty: comparison between a standard device and a megaprosthesis. Int Orthop 2012, 36(3):539-544.

63. Daniel J, Ziaee H, Pradhan C, Pynsent PB, McMinn DJ: Blood and urine metal ion levels in young and active patients after Birmingham hip resurfacing arthroplasty: four-year results of a prospective longitudinal study. J Bone Joint Surg Br 2007, 89(2):169-173.

64. De Haan R, Campbell PA, Su EP, De Smet KA: Revision of metal-on-metal resurfacing arthroplasty of the hip: the influence of malpositioning of the components. J Bone Joint Surg Br 2008, 90(9):1158-1163.

65. deSouza RM, Parsons NR, Oni T, Dalton P, Costa M, Krikler S: Metal ion levels following resurfacing arthroplasty of the hip: serial results over a ten-year period. J Bone Joint Surg Br 2010, 92(12):1642-1647.

66. Garbuz DS, Tanzer M, Greidanus NV, Masri BA, Duncan CP: The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: a randomized clinical trial. Clin Orthop Relat Res 2010, 468(2):318-325.

67. Hart AJ, Hester T, Sinclair K, Powell JJ, Goodship AE, Pele L, Fersht NL, Skinner J: The association between metal ions from hip resurfacing and reduced T-cell counts. J Bone Joint Surg Br 2006, 88(4):449-454.

68. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, Nargol AV, De Smet KA: Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. J Bone Joint Surg Br 2011, 93(2):164-171.

69. Matthies A, Underwood R, Cann P, Ilo K, Nawaz Z, Skinner J, Hart AJ: Retrieval analysis of 240 metal-on-metal hip components, comparing modular total hip replacement with hip resurfacing. J Bone Joint Surg Br 2011, 93(3):307-314.

70. Oldenburg M, Wegner R, Baur X: Severe cobalt intoxication due to prosthesis wear in repeated total hip arthroplasty. J Arthroplasty 2009, 24(5):825 e815-820.

71. Pazzaglia UE, Apostoli P, Congiu T, Catalani S, Marchese M, Zarattini G: Cobalt, chromium and molybdenum ions kinetics in the human body: data gained from a total hip replacement with massive third body wear of the head and neuropathy by cobalt intoxication. Arch Orthop Trauma Surg 2011, 131(9):1299-1308.

72. Savarino L, Granchi D, Ciapetti G, Cenni E, Greco M, Rotini R, Veronesi CA, Baldini N, Giunti A: Ion release in stable hip arthroplasties using metal-on-metal articulating surfaces: a comparison between short- and medium-term results. J Biomed Mater Res A 2003, 66(3):450-456.

73. Steens W, Loehr JF, von Foerster G, Katzer A: [Chronic cobalt poisoning in endoprosthetic replacement]. Orthopade 2006, 35(8):860-864.

74. Engh CA, Jr., MacDonald SJ, Sritulanondha S, Thompson A, Naudie D, Engh CA: 2008 John Charnley award: metal ion levels after metal-on-metal total hip arthroplasty: a randomized trial. Clin Orthop Relat Res 2009, 467(1):101-111.

75. Langton DJ, Sprowson AP, Joyce TJ, Reed M, Carluke I, Partington P, Nargol AV: Blood metal ion concentrations after hip resurfacing arthroplasty: a comparative study of articular surface replacement and Birmingham Hip Resurfacing arthroplasties. J Bone Joint Surg Br 2009, 91(10):1287-1295.

76. Sauve P, Mountney J, Khan T, De Beer J, Higgins B, Grover M: Metal ion levels after metal-on-metal Ring total hip replacement: a 30-year follow-up study. J Bone Joint Surg Br 2007, 89(5):586-590.

77. Natu S, Sidaginamale RP, Gandhi J, Langton DJ, Nargol AV: Adverse reactions to metal debris: histopathological features of periprosthetic soft tissue reactions seen in association with failed metal on metal hip arthroplasties. J Clin Pathol 2012, 65(5):409-418.

78. Hug KT, Watters TS, Vail TP, Bolognesi MP: The withdrawn ASR THA and hip resurfacing systems: how have our patients fared over 1 to 6 years? Clin Orthop Relat Res 2013, 471(2):430-438.

79. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV: Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. J Bone Joint Surg Br 2010, 92(1):38-46.

80. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, Nargol AV, De Smet KA: Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. J Bone Joint Surg Br 2011, 93(2):164-171.

81. Chang EY, McAnally JL, Van Horne JR, Van Horne JG, Wolfson T, Gamst A, Chung CB: Relationship of plasma metal ions and clinical and imaging findings in patients with ASR XL metal-on-metal total hip replacements. J Bone Joint Surg Am 2013, 95(22):2015-2020.

82. Fernandez-Valencia J, Gallart X, Bori G, Ramiro SG, Combalia A, Riba J: Assessment of Patients with a DePuy ASR Metal-on-Metal Hip Replacement: Results of Applying the Guidelines of the Spanish Society of Hip Surgery in a Tertiary Referral Hospital. Adv Orthop 2014, 2014:982523.

83. Cip J, von Strempel A, Bach C, Luegmair M, Benesch T, Martin A: Implication of femoral stem on performance of articular surface replacement (ASR) XL total hip arthroplasty. J Arthroplasty 2014, 29(11):2127-2135.

84. Antoniou J, Zukor DJ, Mwale F, Minarik W, Petit A, Huk OL: Metal ion levels in the blood of patients after hip resurfacing: a comparison between twenty-eight and thirty-six-millimeter-head metal-on-metal prostheses. J Bone Joint Surg Am 2008, 90 Suppl 3:142-148.

85. Grubl A, Marker M, Brodner W, Giurea A, Heinze G, Meisinger V, Zehetgruber H, Kotz R: Long-term follow-up of metal-on-metal total hip replacement. J Orthop Res 2007, 25(7):841-848.

86. Makela KT, Visuri T, Pulkkinen P, Eskelinen A, Remes V, Virolainen P, Junnila M, Pukkala E: Cancer incidence and cause-specific mortality in patients with metal-on-metal hip replacements in Finland. Acta Orthop 2014, 85(1):32-38.

87. De Smet K, De Haan R, Calistri A, Campbell PA, Ebramzadeh E, Pattyn C, Gill HS: Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. J Bone Joint Surg Am 2008, 90 Suppl 4:202-208.

88. Nicolli A, Bisinella G, Padovani G, Vitella A, Chiara F, Trevisan A: Predictivity and fate of metal ion release from metal-on-metal total hip prostheses. J Arthroplasty 2014, 29(9):1763-1767.

89. Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, J AS: Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br 2011, 93(10):1308-1313.

90. Macnair RD, Wynn-Jones H, Wimhurst JA, Toms A, Cahir J: Metal ion levels not sufficient as a screening measure for adverse reactions in metal-on-metal hip arthroplasties. J Arthroplasty 2013, 28(1):78-83.

91. Kolatat K, Perino G, Wilner G, Kaplowitz E, Ricciardi BF, Boettner F, Westrich GH, Jerabek SA, Goldring SR, Purdue PE: Adverse local tissue reaction (ALTR) associated with corrosion products in metal-on-metal and dual modular neck total hip replacements is associated with upregulation of interferon gamma-mediated chemokine signaling. J Orthop Res 2015.

92. Smolders JM, Hol A, Rijnberg WJ, van Susante JL: Metal ion levels and functional results after either resurfacing hip arthroplasty or conventional metal-on-metal hip arthroplasty. Acta Orthop 2011, 82(5):559-566.

93. Pazzaglia UE, Apostoli P, Congiu T, Catalani S, Marchese M, Zarattini G: Cobalt, chromium and molybdenum ions kinetics in the human body: data gained from a total hip replacement with massive third body wear of the head and neuropathy by cobalt intoxication. Arch Orthop Trauma Surg 2011.

94. Maurer-Ertl W, Friesenbichler J, Liegl-Atzwanger B, Kuerzl G, Windhager R, Leithner A: Noninflammatory pseudotumor simulating venous thrombosis after metal-on-metal hip resurfacing. Orthopedics 2011, 34(10):e678-681.

95. Friesenbichler J, Maurer-Ertl W, Sadoghi P, Lovse T, Windhager R, Leithner A: Serum metal ion levels after rotating-hinge knee arthroplasty: comparison between a standard device and a megaprosthesis. Int Orthop 2011.

96. Garrett S, Jacobs N, Yates P, Smith A, Wood D: Differences in metal ion release following cobalt-chromium and oxidized zirconium total knee arthroplasty. Acta Orthop Belg 2010, 76(4):513-520.

97. Zeh A, Planert M, Siegert G, Lattke P, Held A, Hein W: Release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick-type artificial lumbar disc (Medtronic Sofamor Danek). Spine (Phila Pa 1976) 2007, 32(3):348-352.

98. Zeh A, Becker C, Planert M, Lattke P, Wohlrab D: Time-dependent release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick type artificial lumbar disc (Medtronic Sofamor Danek). Arch Orthop Trauma Surg 2009, 129(6):741-746.

99. Bisseling P, Zeilstra DJ, Hol AM, van Susante JL: Metal ion levels in patients with a lumbar metal-on-metal total disc replacement: should we be concerned? J Bone Joint Surg Br 2011, 93(7):949-954.

100. European Federation of National Associations of Orthopaedics and Traumatology (EFORT): Consensus statement “Current Evidence on the Management of Metal-on-Metal Bearings”. 2012, [https://www.efort.org/wp-content/uploads/2013/10/2012_05_10_MoM_Consensus_statement1.pdf]

101. Current Concerns with Metal-on-Metal Hip Arthroplasty [http://www.aaos.org/about/papers/advistmt/1035.asp]

102. Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AV: The effect of component size and orientation on the concentrations of metal ions after resurfacing arthroplasty of the hip. J Bone Joint Surg Br 2008, 90(9):1143-1151.

103. Imanishi T, Hasegawa M, Sudo A: Serum metal ion levels after second-generation metal-on-metal total hip arthroplasty. Arch Orthop Trauma Surg 2010, 130(12):1447-1450.

104. Garrett S, Jacobs N, Yates P, Smith A, Wood D: Differences in metal ion release following cobalt-chromium and oxidized zirconium total knee arthroplasty. Acta Orthop Belg 2010, 76(4):513-520.

105. Dieckmann R, Liem D, Gosheger G, Henrichs MP, Holl S, Hardes J, Streitburger A: Evaluation of a reconstruction reverse shoulder for tumour surgery and tribological comparision with an anatomical shoulder arthroplasty. Int Orthop 2013, 37(3):451-456.

106. Galetz MC, Fleischmann EW, Konrad CH, Schuetz A, Glatzel U: Abrasion resistance of oxidized zirconium in comparison with CoCrMo and titanium nitride coatings for artificial knee joints. J Biomed Mater Res B Appl Biomater 2010, 93(1):244-251.

107. van Hove RP, Nolte PA, Semeins CM, Klein-Nulend J: Differences in proliferation, differentiation, and cytokine production by bone cells seeded on titanium-nitride and cobalt-chromium-molybdenum surfaces. J Biomater Appl 2013, 28(2):278-287.

108. van Hove RP, Brohet RM, van Royen BJ, Nolte PA: No clinical benefit of titanium nitride coating in cementless mobile-bearing total knee arthroplasty. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 2015, 23(6):1833-1840.

109. Mohammed A, Metcalfe A, Woodnutt D: Medium-term outcome of titanium nitride, mobile bearing total knee replacement. Acta Orthop Belg 2014, 80(2):269-275.

110. Park SW, Kim H, In Y: Fracture of titanium nitride-coated femoral component after total knee arthroplasty. Knee 2014, 21(4):871-874.

111. Gosheger G, Gebert C, Ahrens H, Streitbuerger A, Winkelmann W, Hardes J: Endoprosthetic reconstruction in 250 patients with sarcoma. Clin Orthop Relat Res 2006, 450:164-171.

112. Raiss P, Kinkel S, Sauter U, Bruckner T, Lehner B: Replacement of the proximal humerus with MUTARS tumor endoprostheses. Eur J Surg Oncol 2010, 36(4):371-377.

113. Gosheger G, Hardes J, Ahrens H, Streitburger A, Buerger H, Erren M, Gunsel A, Kemper FH, Winkelmann W, Von Eiff C: Silver-coated megaendoprostheses in a rabbit model--an analysis of the infection rate and toxicological side effects. Biomaterials 2004, 25(24):5547-5556.

114. Glehr M, Leithner A, Friesenbichler J, Goessler W, Avian A, Andreou D, Maurer-Ertl W, Windhager R, Tunn PU: Argyria following the use of silver-coated megaprostheses: no association between the development of local argyria and elevated silver levels. Bone Joint J 2013, 95-B(7):988-992.

115. Bozic KJ, Browne J, Dangles CJ, Manner PA, Yates AJ, Jr., Weber KL, Boyer KM, Zemaitis P, Woznica A, Turkelson CM et al: Modern metal-on-metal hip implants. J Am Acad Orthop Surg 2012, 20(6):402-406.

116. Back DL, Young DA, Shimmin AJ: How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? Clin Orthop Relat Res 2005, 438:177-181.

117. Savarino L, Granchi D, Ciapetti G, Cenni E, Nardi Pantoli A, Rotini R, Veronesi CA, Baldini N, Giunti A: Ion release in patients with metal-on-metal hip bearings

in total joint replacement: a comparison with metal-on-polyethylene bearings. J Biomed Mater Res 2002, 63(5):467-474.

118. Witzleb WC, Ziegler J, Krummenauer F, Neumeister V, Guenther KP: Exposure to chromium, cobalt and molybdenum from metal-on-metal total hip replacement and hip resurfacing arthroplasty. Acta Orthop 2006, 77(5):697-705.

119. Daniel J, Ziaee H, Pradhan C, McMinn DJ: Six-year results of a prospective study of metal ion levels in young patients with metal-on-metal hip resurfacings. J Bone Joint Surg Br 2009, 91(2):176-179.

120. Keel SB, Jaffe KA, Petur Nielsen G, Rosenberg AE: Orthopaedic implant-related sarcoma: a study of twelve cases. Mod Pathol 2001, 14(10):969-977.

121. Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M: Polyneuropathy caused by cobalt-chromium metallosis after total hip replacement. Muscle Nerve 2010, 42(1):140-143.

122. Pelclova D, Sklensky M, Janicek P, Lach K: Severe cobalt intoxication following hip replacement revision: clinical features and outcome. Clin Toxicol (Phila) 2012, 50(4):262-265.

123. Matziolis G, Perka C, Disch A: Massive metallosis after revision of a fractured ceramic head onto a metal head. Arch Orthop Trauma Surg 2003, 123(1):48-50.

124. Boardman DR, Middleton FR, Kavanagh TG: A benign psoas mass following metal-on-metal resurfacing of the hip. J Bone Joint Surg Br 2006, 88(3):402-404.

125. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, Ostlere S, Athanasou N, Gill HS, Murray DW: Pseudotumours associated with metal-on-metal hip resurfacings. J Bone Joint Surg Br 2008, 90(7):847-851.

126. Toms AP, Marshall TJ, Cahir J, Darrah C, Nolan J, Donell ST, Barker T, Tucker JK: MRI of early symptomatic metal-on-metal total hip arthroplasty: a retrospective review of radiological findings in 20 hips. Clin Radiol 2008, 63(1):49-58.

127. Clayton RA, Beggs I, Salter DM, Grant MH, Patton JT, Porter DE: Inflammatory pseudotumor associated with femoral nerve palsy following metal-on-metal resurfacing of the hip. A case report. J Bone Joint Surg Am 2008, 90(9):1988-1993.

128. Glyn-Jones S, Pandit H, Kwon YM, Doll H, Gill HS, Murray DW: Risk factors for inflammatory pseudotumour formation following hip resurfacing. J Bone Joint Surg Br 2009, 91(12):1566-1574.

129. Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS, Murray DW: "Asymptomatic" pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. J Arthroplasty 2011, 26(4):511-518.

130. Mahendra G, Pandit H, Kliskey K, Murray D, Gill HS, Athanasou N: Necrotic and inflammatory changes in metal-on-metal resurfacing hip arthroplasties. Acta Orthop 2009, 80(6):653-659.

131. Shahrdar C: Pseudotumor in large-diameter metal-on-metal total hip articulation. J Arthroplasty 2011, 26(4):665 e621-663.

132. Toms AP, Nolan J, Barker T, Darrah C, Malcolm P: Early failure of a Birmingham resurfacing hip replacement with lymphoreticular spread of metal debris: pre-operative diagnosis with MR. Br J Radiol 2009, 82(977):e87-91.

133. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, Lohmann CH: Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 2005, 87(1):28-36.

134. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K: Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. J Bone Joint Surg Br 2008, 90(10):1291-1297.

135. Wiley KF, Ding K, Stoner JA, Teague DC, Yousuf KM: Incidence of pseudotumor and acute lymphocytic vasculitis associated lesion (ALVAL) reactions in metal-on-metal hip articulations: a meta-analysis. J Arthroplasty 2013, 28(7):1238-1245.

136. Bayley N, Khan H, Grosso P, Hupel T, Stevens D, Snider M, Schemitsch E, Kuzyk P: What are the predictors and prevalence of pseudotumor and elevated metal ions after large-diameter metal-on-metal THA? Clin Orthop Relat Res 2015, 473(2):477-484.

137. Wynn-Jones H, Macnair R, Wimhurst J, Chirodian N, Derbyshire B, Toms A, Cahir J: Silent soft tissue pathology is common with a modern metal-on-metal hip arthroplasty. Acta Orthop 2011, 82(3):301-307.

138. Plitz W, Veihelmann A, Pellengahr C: [Metal-on-metal pairs for hip prostheses]. Orthopade 2003, 32(1):17-22.

139. Hart AJ, Sabah S, Henckel J, Lewis A, Cobb J, Sampson B, Mitchell A, Skinner JA: The painful metal-on-metal hip resurfacing. J Bone Joint Surg Br 2009, 91(6):738-744.

140. Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF: Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. Skeletal Radiol 2011, 40(3):303-307.

141. Mavrogenis AF, Nomikos GN, Sakellariou VI, Karaliotas GI, Kontovazenitis P, Papagelopoulos PJ: Wear debris pseudotumor following total knee arthroplasty: a case report. J Med Case Rep 2009, 3:9304.

142. Berry MR, Peterson BG, Alander DH: A granulomatous mass surrounding a Maverick total disc replacement causing iliac vein occlusion and spinal stenosis: a case report. J Bone Joint Surg Am 2010, 92(5):1242-1245.

143. Ottaviani G, Catagni MA, Matturri L: Massive metallosis due to metal-on-metal impingement in substitutive long-stemmed knee prosthesis. Histopathology 2005, 46(2):237-238.

144. Jacobs JJ, Shanbhag A, Glant TT, Black J, Galante JO: Wear Debris in Total Joint Replacements. J Am Acad Orthop Surg 1994, 2(4):212-220.

145. Cavanaugh DA, Nunley PD, Kerr EJ, 3rd, Werner DJ, Jawahar A: Delayed hyper-reactivity to metal ions after cervical disc arthroplasty: a case report and literature review. Spine (Phila Pa 1976) 2009, 34(7):E262-265.

146. Berry MR, Peterson BG, Alander DH: A granulomatous mass surrounding a Maverick total disc replacement causing iliac vein occlusion and spinal stenosis: a case report. J Bone Joint Surg Am 2010, 92(5):1242-1245.

147. Cavanaugh DA, Nunley PD, Kerr EJ, 3rd, Werner DJ, Jawahar A: Delayed hyper-reactivity to metal ions after cervical disc arthroplasty: a case report and literature review. Spine (Phila Pa 1976) 2009, 34(7):E262-265.

148. Sanchis-Alfonso V: Severe metallosis after unicompartmental knee arthroplasty. Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA 2007, 15(4):361-364.

149. Romesburg JW, Wasserman PL, Schoppe CH: Metallosis and Metal-Induced Synovitis Following Total Knee Arthroplasty: Review of Radiographic and CT Findings. J Radiol Case Rep 2010, 4(9):7-17.

150. Weissman BN, Scott RD, Brick GW, Corson JM: Radiographic detection of metal-induced synovitis as a complication of arthroplasty of the knee. The Journal of bone and joint surgery American volume 1991, 73(7):1002-1007.

151. Willis-Owen CA, Keene GC, Oakeshott RD: Early metallosis-related failure after total knee replacement: a report of 15 cases. The Journal of bone and joint surgery British volume 2011, 93(2):205-209.

6. QUESTIONNAIRES

6.1 KNEE SOCIETY SCORE-PART 1

Part 1 - Knee Score (max. 100)

Pain	**Points**	Mild (Walking and Stairs)	30
None	50	Moderate – Occasional	20
Mild / Occasional	45	Moderate – Continual	10
Mild (Stairs only)	40	Severe	0

Total Range of Flexion	**Points**	61-65	13
0-5	1	66-70	14
6-10	2	71-75	15
11-15	3	76-80	16
16-20	4	81-85	17
21-25	5	86-90	18
26-30	6	91-95	19
31-35	7	96-100	20
36-40	8	101-105	21
41-45	9	106-110	22
46-50	10	111-115	23
51-55	11	116-120	24
56-60	12	121-125	25

Stability (Maximum movement in any position)	**Points**	**Mediolateral**	
Antero-posterior		<5°	15
<5mm	10	6-9°	10
5-10mm	5	10-14°	5
>10mm	0	15°	0

Flexion Contracture (deduction)	**Points**	**Extension Lag (deduction)**	**Points**
5°-10°	2	<10°	5
10°-15°	5	10°-20°	10
16°-20°	10	>20°	20
>20°	15		

Tibiofemoral Angle (deduction)	**Points**
5°-10° (valgus)	0
0°-4° (varus, max.15 pts [3 pts/°])	
11°-15° (valgus, max.15 pts [3 pts/°])	

Total	

6.2 KNEE SOCIETY SCORE-PART 2

Part 2 - Function Score (max. 100)

Walking	Points	Staires	Points
Unlimited	50	Normal up and down	50
> 2 km	40	Normal up and down with rail	40
1-2 km	30	Up and down with rail	30
< 1 km	20	Up with rail, down unable	15
Household	10	Unable	0
Unable	0		

Walking aids used (deduction)	Points
None used	0
Use of cane/Walking stick deduct	5
Two canes/sticks	10
Crutches or frame	20

Total	

Grading for the Knee Society Score	
100-80	Excellent
70-79	Good
69-60	Fair
below 60	Poor

WOMAC SCORE (Western Ontario and McMaster Universities Osteoarthrithis Index)

Schmerzfragen (Schmerzen in den letzten 2 Tagen verspürt)

Wie starke Schmerzen haben Sie beim...	keine	leicht	moderat	stark	extrem
Gehen auf ebenen Boden?	0	1	2	3	4
Treppensteigen (hinauf/hinunter)?	0	1	2	3	4
Nachts im Bett?	0	1	2	3	4
Sitzen oder Liegen?	0	1	2	3	4
Aufrecht stehen?	0	1	2	3	4

Fragen zur Steifigkeit (verspürte Steifigkeit in den letzten 2 Tagen)

Wie stark ist die Steifigkeit nach dem Erwachen am Morgen?	0	1	2	3	4
Wie stark ist Ihre Steifigkeit nach Sitzen, Liegen oder Ausruhen im späteren Tagesverlauf?	0	1	2	3	4

Fragen zur körperlichen Tätigkeit (Fähigkeiten im Alltag/Selbstversorgung in den letzten 2 Tagen)

Wie groß sind Ihre Schwierigkeite beim Treppen hinuntersteigen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Treppen hinaufsteigen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Aufstehen vom Sitzen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Stehen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim sich zum Boden bücken?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Gehen auf ebenem Boden?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Ein- und Aussteigen in ein Auto?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Einkaufen gehen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Socken/Strümpfe anziehen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Aufstehen aus dem Bett?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Socken/Strümpfe ausziehen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Liegen im Bett?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim ins Bad/aus dem Bad steigen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim Sitzen?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite beim sich auf die Toilette setzen/aufstehen von der Toilette?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite bei anstrengenden Hausarbeiten?	0	1	2	3	4
Wie groß sind Ihre Schwierigkeite bei leichten Hausarbeiten?	0	1	2	3	4

6.4 MSTS-SCORE

	PAIN	FUNCTION	EMOTIONAL ACCEPTANCE	SUPPORTS	WALKING	GAIT
L O W E R L I M B	5 none	no restriction	enthused	none	unlimited	normal
	4 ____	____	intermediate	____	____	____
	3 modest	recreational restriction	satisfied	brace	limited	minor cosmetic
	2 ____	____	intermediate	____	____	____
	1 moderate	partial disability	accepts	1 cane/1 crutch	inside only	major cosmetic, minor HCAP
	0 severe	total disability	dislikes	2 canes/2 crutches	unable unaided	major HCAP

Total Score _____

Maximum Score _____

% Rating _____

7. CURRICULUM VITAE

Name: Dr. med. univ. Jörg Friesenbichler

Date of birth: 9th June 1984

Nationality: Austrian

Current Address: Heinrichstr. 33, 8010 Graz

e-mail: joerg.friesenbichler@medunigraz.at

EDUCATION:

2003-2010: Medical study at the Medical University of Graz, Austria

March 2010: Doctor of Medicine (MD) at the Medical University of Graz, Austria

August-December 2010: Trauma Hospital Klagenfurt

February 2011-till now: Residency in Orthopaedic Surgery, Medical University of Graz

LANGUAGES:

Native language: German

Basics in medical English (spoken and written).

Some knowledge in Italian. No medical Italian.

AWARDS:

2011 Leistungsstipendium der Meduni Graz

2010 Förderungsstipendium der Meduni Graz

REVIEWER FOR SCIENTIFIC JOURNALS:

2012-2013 Sarcoma

2013 World Journal of Orthopedics

2015 Case Reports in Orthopedics

8. PRESENTATIONS

8.1 PAPERS (First- and Co-authorship)

Friesenbichler, J; Leithner, A; Maurer-Ertl, W; Szkandera, J; Sadoghi, P; Frings, A; Maier, A; Andreou, D; Windhager, R; Tunn, PU Surgical therapy of primary malignant bone tumours and soft tissue sarcomas of the chest wall: a two-institutional experience.
Int Orthop. 2014; 38(6):1235-1240

Friesenbichler, J; Maurer-Ertl, W; Sadoghi, P; Pirker-Fruehauf, U; Bodo, K; Leithner, A Adverse reactions of artificial bone graft substitutes: lessons learned from using tricalcium phosphate geneX®.
Clin Orthop Relat Res. 2014; 472(3):976-982

Friesenbichler, J; Sadoghi, P; Maurer-Ertl, W; Szkandera, J; Glehr, M; Ogris, K; Wolf, M; Weger, C; Leithner, A Serum Metal Ion Concentrations in Paediatric Patients following Total Knee Arthroplasty Using Megaprostheses.
Biomed Res Int. 2014; 2014: 817257-817257.

Friesenbichler, J; Maurer-Ertl, W; Sadoghi, P; Pirker-Fruehauf, U; Bodo, K; Leithner, A Reply to the Letter to the Editor: Adverse reactions of artificial bone graft substitutes: lessons learned from using tricalcium phosphate geneX ®.
Clin Orthop Relat Res. 2014; 472(2):767-768

Friesenbichler, J; Leithner, A; Glehr, M; Sadoghi, P; Maurer-Ertl, W; Avian, A; Windhager, R Evaluation of stability of rotating hinge knee prostheses: a biomechanical study.
ISRN Orthop. 2013; 2013:701693-701693

Friesenbichler, J; Glehr, M; Sadoghi, P; Maurer-Ertl, W; Ott, F; Leithner, A In vivo testing of knee stability after rotating-hinge total knee arthroplasty: a comparison of 2 knee systems.
Orthopedics. 2012; 35(3):e335-e342

Friesenbichler, J; Maurer-Ertl, W; Pirker-Fruhauf, U; Wolf, M; Leithner, A; Weger, C; Pechmann, M; Sadoghi, P; Adverse effects after metal-on-metal bearings in total hip arthroplasty.
MINERVA ORTOP TRAUMATOL. 2012; 63(5): 379-385

Friesenbichler, J; Maurer-Ertl, W; Sadoghi, P; Lovse, T; Windhager, R; Leithner, A Serum metal ion levels after rotating-hinge knee arthroplasty: comparison between a standard device and a megaprosthesis.
Int Orthop. 2012; 36(3):539-544

Friesenbichler, J; Molcan, A; Aigner, R; Sadoghi, P; Liegl-Atzwanger, B; Maurer-Ertl, W; Weger, C; Leithner, A The role of somatostatin receptor scintigraphy on the diagnosis of desmoid tumors.
ISRN Oncol. 2012; 2012(3):167545-167545

Friesenbichler, J; Schwarzkopf, R; Sadoghi, P; Marwin, SE; Glehr, M; Maurer-Ertl, W; Leithner, A Failure rate of a rotating hinge knee design due to yoke fracture of the hinged tibial insert: a retrospective data analysis and review of the literature.
Int Orthop. 2012; 36(5):993-998

Friesenbichler, J; Maurer-Ertl, W; Sadoghi, P; Wolf, E; Leithner, A Auto-aggressive metallic mercury injection around the knee joint: a case report.
BMC Surg. 2011; 11: 31-31.

Glehr, M; Breisach, M; Walzer, S; Lohberger, B; Fürst, F; Friesenbichler, J; Rinner, B; Avian, A; Windhager, R; Leithner, A The influence of resveratrol on the synovial expression of matrix metalloproteinases and receptor activator of NF-kappaB ligand in rheumatoid arthritis fibroblast-like synoviocytes.
Z Naturforsch C. 2013; 68(7-8): 336-342.

Glehr, M; Friesenbichler, J; Hofmann, G; Bernhardt, GA; Zacherl, M; Avian, A; Windhager, R; Leithner, A Novel Biomarkers to Detect Infection in Revision Hip and Knee Arthroplasties.
Clin Orthop Relat Res. 2013; 471(8):2621-2628

Glehr, M; Leithner, A; Friesenbichler, J; Goessler, W; Avian, A; Andreou, D; Maurer-Ertl, W; Windhager, R; Tunn, PU; Argyria following the use of silver-coated megaprostheses NO ASSOCIATION BETWEEN THE DEVELOPMENT OF LOCAL ARGYRIA AND ELEVATED SILVER LEVELS.
BONE JOINT J. 2013; 95B(7): 988-992.

Kastner, N; Aigner, BA; Meikl, T; Friesenbichler, J; Wolf, M; Glehr, M; Gruber, G; Leithner, A; Sadoghi, P Gender-specific outcome after implantation of low-contact-stress mobile-bearing total knee arthroplasty with a minimum follow-up of ten years.
Int Orthop. 2014; 38(12):2489-2493

Kastner, N; Sternbauer, S; Friesenbichler, J; Vielgut, I; Wolf, M; Glehr, M; Leithner, A; Sadoghi, P Impact of the tibial slope on range of motion after low-contact-stress, mobile-bearing, total knee arthroplasty.
Int Orthop. 2014; 38(2):291-295

Kastner, N; Gruber, G; Aigner, BA; Friesenbichler, J; Pechmann, M; Fürst, F; Vavken, P; Leithner, A; Sadoghi, P Sex-related outcome differences after implantation of low-contact-stress mobile-bearing total knee arthroplasty.
Int Orthop. 2012; 36(7):1393-1397

Leithner, A; Friesenbichler, J; Andreou, D; Maurer-Ertl, W; Tunn, PU [Bone metastases treatment strategies].
Orthopade. 2012; 41(10):863-871

Leithner, A; Maurer-Ertl, W; Glehr, M; Friesenbichler, J; Leithner, K; Windhager, R Wikipedia and osteosarcoma: a trustworthy patients' information?
J Am Med Inform Assoc. 2010; 17(4): 373-374

Maurer-Ertl, W; Friesenbichler, J; Sadoghi, P; Pechmann, M; Trennheuser, M; Leithner, A Metal ion levels in large-diameter total hip and resurfacing hip arthroplasty--preliminary results of a prospective five year study after two years of follow-up.
BMC Musculoskelet Disord. 2012; 13(11):56-56

Maurer-Ertl, W; Glehr, M; Friesenbichler, J; Sadoghi, P; Wiedner, M; Haas, F; Leithner, A; Windhager, R; Zwick, EB No adverse affect after harvesting of free fibula osteoseptocutaneous flaps on gait function.
Microsurgery. 2012; 32(5):364-369

Maurer-Ertl, W; Friesenbichler, J; Liegl-Atzwanger, B; Kuerzl, G; Windhager, R; Leithner, A Noninflammatory pseudotumor simulating venous thrombosis after metal-on-metal hip resurfacing.
ORTHOPEDICS. 2011; 34(10): e678-e681

Pirker-Frühauf, UM; Friesenbichler, J; Rabitsch, K; Liegl-Atzwanger, B; Bauernhofer, T; Windhager, R; Leithner, A Three Metachronous Osteosarcomas within 22 Years without Pulmonary Metastases: A Case Report and Review of the Literature.
Case Rep Orthop. 2013; 2013(4):197287-197287

Pirker-Frühauf, UM; Friesenbichler, J; Urban, EC; Obermayer-Pietsch, B; Leithner, A Osteoporosis in Children and Young Adults: A Late Effect After Chemotherapy for Bone Sarcoma.
Clin Orthop Relat Res. 2012; 470(10):2874-2885

Sadoghi, P; Lohberger, B; Aigner, B; Kaltenegger, H; Friesenbichler, J; Wolf, M; Sununu, T; Leithner, A; Vavken, P Effect of platelet-rich plasma on the biologic activity of the human rotator-cuff fibroblasts: A controlled in vitro study.
J Orthop Res. 2013; 31(8):1249-1253

Sadoghi, P; Borbas, P; Friesenbichler, J; Scheipl, S; Kastner, N; Eberl, R; Leithner, A; Gruber, G Evaluating the tibial and femoral insertion site of the anterior cruciate ligament using an objective coordinate system: A cadaver study.

Injury. 2012; 43(10):1771-1775

Sadoghi, P; Leithner, A; Weber, P; Friesenbichler, J; Gruber, G; Kastner, N; Pohlmann, K; Jansson, V; Wegener, B Radiolucent lines in low-contact-stress mobile-bearing total knee arthroplasty: a blinded and matched case control study.
BMC Musculoskelet Disord. 2011; 12(13-14):142-142

Schippinger, M; Ruckenstuhl, P; Friesenbichler, J; Leithner, A [Osteosarcoma: reliability and quality of the information in the internet].
Wien Med Wochenschr. 2014; 164(17-18):353-357

Szkandera, J; Gerger, A; Liegl-Atzwanger, B; Absenger, G; Stotz, M; Friesenbichler, J; Trajanoski, S; Stojakovic, T; Eberhard, K; Leithner, A; Pichler, M The lymphocyte/monocyte ratio predicts poor clinical outcome and improves the predictive accuracy in patients with soft tissue sarcomas.
Int J Cancer. 2014; 135(2): 362-370.

Szkandera, J; Gerger, A; Liegl-Atzwanger, B; Stotz, M; Samonigg, H; Friesenbichler, J; Stojakovic, T; Leithner, A; Pichler, M The derived neutrophil/lymphocyte ratio predicts poor clinical outcome in soft tissue sarcoma patients.
Am J Surg. 2014;

Weger, C; Frings, A; Friesenbichler, J; Grimer, R; Andreou, D; Machacek, F; Pfeiffenberger, K; Liegl-Atzwanger, B; Tunn, PU; Leithner, A Osteolytic lesions of the calcaneus: results from a multicentre study.
Int Orthop. 2013; 37(9):1851-1856

Wolf, M; Clar, H; Friesenbichler, J; Schwantzer, G; Bernhardt, G; Gruber, G; Glehr, M; Leithner, A; Sadoghi, P Prosthetic joint infection following total hip replacement: results of one-stage versus two-stage exchange.
Int Orthop. 2014; 38(7):1363-1368