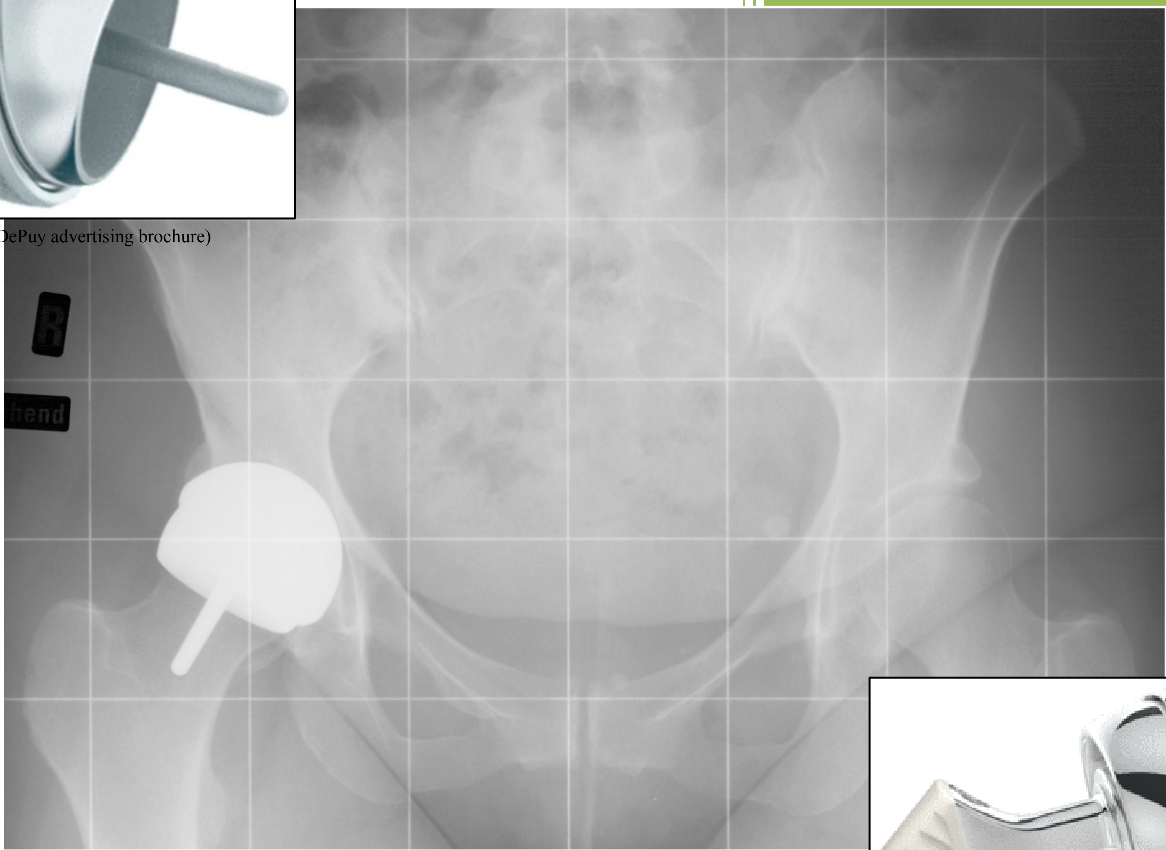
Metal ion levels in patients before and after total hip arthroplasty with metal-on-metal large-head bearing

Intermediate data at one year follow-up


(Picture from a DePuy advertising brochure)




(Picture from a DePuy advertising brochure)

Matthias Trennheuser

Diplomarbeit

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Intermediate data at one year follow-up

eingereicht von

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Mat.Nr.: 0533400

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Doktor der gesamten Heilkunde

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Universitätsklinik für Orthopädie und orthopädische Chirurgie

unter der Anleitung von

Dr. Werner Maurer-Ertl

Graz, der 12.08.2011 (Unterschrift)

Affidavit

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

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I declare that the work in this assignment is completely my own work. No part of this assignment is taken from other people's work without giving them credit. All references have been clearly cited.

Graz, 12th August *Signature*

Danksagung

An dieser Stelle möchte ich mich bei allen Personen bedanken, die mich bei der Erstellung dieser Diplomarbeit unterstützt haben.

Zunächst möchte ich mich bei OA Dr.med.univ. Werner Maurer-Ertl bedanken für die Themenstellung, die zahlreichen Stunden der Besprechung und Diskussion, sowie seine Geduld und gute Betreuung.

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Abstract

Background: Elevated metal ion levels are one of the main concerns about metal-on-metal THAs because of their possible side effects like neuropathy following cobalt intoxication, higher revision rates, pseudotumours, or chromosomal aberrations in peripheral blood. In this context, former studies revealed a correlation between the inclination or rather the arc of cover of the acetabular cup and metal ion levels in the serum. In our study we tried to figure out if this correlation can also be found in patients treated at our hospital with the DePuy ASR Resurfacing System and DePuy ASR XL Head System.

Methods: In this prospective, non-randomised monocentre study we determined metal ion levels in the serum of cobalt and chromium in 36 patients (40 THAs; eight DePuy ASR System and 32 DePuy ASR XL Head System) four times: preoperatively, one week, three months and one year post-operatively. Additional radiographs of the pelvis and the affected hip in two planes were taken at the same follow-up points of time. The cup inclination was measured by two independent observers and the arc of cover was calculated referring to the publication of De Haan *et al*. Finally, we did a correlation analysis following Pearson and Spearman.

Results: Mean concentrations of metal ions in serum one year post-operatively were 0.51 µg/dl for cobalt and 0.53 µg/dl for chromium. We found no significant correlation between the cup inclination or rather the arc of cover and metal ion level in the serum within our study group.

Conclusion: Within our study group we could neither confirm nor refute a statistical significant correlation between the cup inclination or the arc of cover and metal ion levels in the serum at one year follow-up. These findings may be due to the small amount of THAs in the steep group with a cup inclination of more than 55° or rather the group with an arc of cover less than 10 mm. Nevertheless, based on these findings further research will take place about this issue at our department to identify further influences on metal ion levels in serum and to learn more about these.

Zusammenfassung

Hintergrund: Erhöhte Metallionenspiegel sind eines der Hauptbedenken bezüglich Totalhüftendoprothesen mit Metall-Metall-Gleitpaarung aufgrund möglicher Nebenwirkungen wie Neuropathien durch Kobaltintoxikation, höherer Revisionsraten, Pseudotumoren und Chromosomenänderungen im peripheren Blut. In diesem Zusammenhang haben frühere Studien eine Korrelation zwischen Schaleninklination/Deckungsbogen („arc of cover“) der Hüftpfanne und dem Metallionenspiegel im Serum nachgewiesen. In unserer Studie versuchten wir herauszufinden, ob diese Korrelation auch in Patienten, die an unserem Krankenhaus mit dem DePuy ASR System oder dem DePuy ASR Großkopf System behandelt wurden, nachzuweisen ist.

Methoden: In dieser prospektiven, nicht-randomisierten Monocenter-Studie bestimmten wir viermal die Metallionenspiegel von Kobalt und Chrom in 36 Patienten (40 Totalhüftendoprothesen; acht DePuy ASR System und 32 DePuy ASR Großkopfsystem): Präoperativ und eine Woche, drei Monate und ein Jahr postoperativ. Zusätzlich wurden zu denselben Terminen Röntgenbilder des Beckens und der betroffenen Hüfte in zwei Ebenen angefertigt. Die Schaleninklination wurde von zwei unabhängigen Personen gemessen und der Deckungsbogen gemäß der Publikation von DeHaan *et al*. berechnet. Anschließend führten wir eine Korrelationsanalyse nach Pearson und Spearman durch.

Ergebnisse: Die durchschnittliche Metallionenkonzentration im Serum ein Jahr postoperativ war 0,51 µg/dl für Kobalt und 0,53 µg/dl für Chrom. Wir fanden keine signifikante Korrelation zwischen der Schaleninklination oder dem Deckungsbogen und dem Metallionenspiegel im Serum.

Schlussfolgerung: Wir konnten eine statistisch signifikante Korrelation zwischen Schaleninklination/Deckungsbogen und dem Metallionenspiegel im Serum nach einem Jahr in unserer Versuchsgruppe weder bekräftigen noch widerlegen. Dieses Ergebnis könnte aufgrund der geringen Anzahl an Totalendoprothesen in der Gruppe mit einer Schaleninklination von mehr als 55° oder in der Gruppe mit einem Deckungsbogen von weniger als 10 mm zustande gekommen sein. Nichtsdestotrotz werden wir aufgrund dieser Ergebnisse genauere Untersuchungen zu diesem Thema an unserer Klinik anstellen, um weitere Einflüsse auf Metallionenspiegel im Serum zu identifizieren und mehr über diese in Erfahrung zu bringen.

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Glossary and abbreviations

Acetabulum	The medical term for the socket of the hip joint
Albumin	The most abundant protein in human blood plasma, which is produced in the liver. It comprises about half of the blood serum protein
Amlodipin	A calcium channel antagonist – A type of medication that hinders calcium from passing through calcium channels. This especially has a tonus lowering effect on smooth muscle cells and heart cells and is therefore used in hypertension treatment
Arc of cover	The arc of cover is the product of the component radius (r) and angle (in radians) subtended between the vertical and the lateral acetabular component edge (γ) as follows: $a=r\alpha$
ASR Resurfacing System	Articular surface replacement; metal-on-metal total hip arthroplasty of the modern generation produced by DePuy, a Johnson & Johnson company. It consists of a socket and a fitting resurfacing cap on the femoral side
ASR XL Head System	Articular surface replacement with a large head in place of the resurfacing cap in the ASR Resurfacing System
Avascular necrosis	A disease where an interruption of the blood supply leads to cellular death of bone components

Bisoprolol	A selective β1-blocker – A medication used as treatment for cardiac arrhythmias, cardioprotection and hypertension by antagonizing endogenous catecholamines and norepinephrine selectively on β1-adrenergic receptors
BMI	Body mass index – Calculated with the formula BMI = m/l² (m in kilogram, l in metre)
CA	Carcinoma; a malignant tumour
CRP	C-reactive protein – An acute phase protein that is produced in the liver. It is used as a serum parameter for infections
Clearance	A measurement of the renal excretion ability
Corail®	Name of a type of stem by DePuy
Creatinine	An indicator in plasma of renal function: Elevated levels indicate an impairment of the kidneys
Diclofenac	A non-steroidal anti-inflammatory drug – A medication with analgesic, antipyretic (fever-reducing) and anti-inflammatory effects
Enoxaparin sodium	A low molecular weight heparin – A medication used as an anticoagulant in diseases that feature thrombosis, as well as for prophylaxis in situations that lead to a high risk of thrombosis
Femur	Medical term for the thigh bone

Future®	Name of a type of stem by DePuy
IL-1α	Interleukin-1α; a cytokine expressed by white blood cells, which functions as an important messenger of the immune system
Cup inclination	The inclination of the acetabular cup is given by the angle between the straight line running parallel to the opening edges of the acetabular component and a straight line running through both tear drop signs
Latanoprost	A prostaglandin analogue – An ophthalmic solution that reduces the intraocular pressure by increasing the outflow of aqueous fluid from the eyes
Levothyroxine sodium	A synthetic form of thyroxine, a hormone of the thyroid gland
Metasul	A special cobalt/chromium/molybdenum alloy with excellent wear characteristics in THAs
MRI	Magnetic resonance imaging
Naftidrofurylhydrogenoxalate	A peripheral vasodilator
Outlier	A metal ion value above the limit of 1.00 µg/dl
Outlier patient	A patient whose metal ion levels increase above the limit of 1.00 µg/dl at least one time
Normal range (metal ion level)	Ranges from 0.00 µg/dl to 1.00 µg/dl

Phagozitation	Intake of nutrition particles up to small cells in a single eukaryote cell
Pantoprazole	A proton pump inhibitor – A medication that reduces the production of gastric acid
Polyethylene	The most widely used plastic, especially as a bearing component in THA
Raloxifene	A selective oestrogen receptor modulator – A medication used in the prevention of osteoporosis in postmenopausal women by stimulating the oestrogen receptors in the bone and by blocking the oestrogen receptors in the uterus and breast
Rpm	Rounds per minute
Running-in phase	Describes the phase after a metal-on-metal total hip arthroplasty while there is an increased release of metal ions from the arthroplasty due to adaption processes between the femoral and the acetabular component
SD	Standard deviation
Steady-state phase	Describes the phase after the running-in phase when there is no further increase of metal ion levels due to adaption processes between the femoral and the acetabular component
T-cell	A special type of blood cells responsible for immune defences

Tear drop sign	A radiological sign in hip radiographs that originates from overlapping bone structures at the medio-caudal base of the acetabulum
Tetrazepam	A benzodiazepine – A calmative with anticonvulsant, anxiolytic, hypnotic and muscle relaxant effects
THA	Total hip arthroplasty – Hip joint prosthesis that replaces the total hip joint with an implant that includes the acetabulum and the femoral head
Trazodone	An antidepressant in the serotonin antagonist and reuptake inhibitor class
Tribology/tribological	Science and engineering of interacting surfaces in relative motion. It includes the study and application of the principles of friction, lubrication and wear
Urea	An important end-product of the protein metabolism; also used for the diagnosis of and to follow-up renal failure
Uric acid	End-product of the purine metabolism

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1 Introduction and clinical theory

1.1 *History of hip resurfacing and metal-on-metal THA with large head diameter*

1.1.1 First generation

The history of the artificial reconstruction of the hip joint already began in 1928 when Smith-Petersen implanted femoral glass caps in arthritic hips. Although it reduced the patients' pain, the clinical outcome of this procedure was poor and many of this glass caps broke. (1)

The next promising development Charnley invented only in the early 1950s. It was a total surface replacement made of two Teflon cups. But this intent also failed because of the massive wear rates causing early loosening and necrosis of the femoral head (2). This was the beginning of testing various bearing combinations in articular surface replacement.

However, until the mid1980s the idea of articular surface replacement was abandoned.

Reasons for this abandonment were the use of improper materials, inappropriate implant design and instruments and Charnley's development and success in conventional THA in the 1960s (2).

As an example for a common hip resurfacing system in Europe in the 1970s serves the "Wagner's Cup": It consisted of a 4 mm thick Polyethylene acetabulum paired with a femoral Co/Cr- or ceramic component (2). However, in this case the preparation of the femur was imprecise and there were plenty cases of aseptic loosening.

1.1.2 New generation

In 1991 the idea of resurfacing was revived. Metal-on-metal bearing surfaces were reintroduced because Weber developed the so-called "Metasul" alloy (Co/Cr) in 1988 for tribological metal-on-metal bearing surfaces in THAs (2). With that technical innovation the problem of the polyethylene wall thickness was avoided. Also the fact that some metal-on-metal arthroplasties of the first generation survived for a long time (3,4) renewed the interest in this bearing combination. So Wagner and McMinn started to develop new designs, which should have produced less debris.

And up to now there is a steady effort to optimize the design. Since 2004 several implantation designs have been provided. An offshoot of this development is the ASR XL Head System used in THAs, trying to create the advantage of a large joint surface also in cases when the implantation of a resurfacing system is not possible. The DePuy ASR Resurfacing System and the DePuy ASR XL Head System we examined are two results of this ongoing development in optimizing the metal-on-metal bearing surface.

1.2 Background of the study

The reason why especially resurfacing systems were revived was because the common THAs using Polyethylene had some unsolved problems like high wear rates associated with periprosthetic osteolysis and therefore a relative short survival time (2). As the benefits of resurfacing were promising, researchers tried to avoid failures of the first generation by developing new designs. This new design was considered a bone saving procedure and a reconstruction of the individual original anatomy of the hip. During resurfacing surgery, only few bone of the femoral articular surface has to be resected and replaced with a metal cap. Soon first studies analysing the clinical results of the new resurfacing systems appeared (5-24).

The primary results have been encouraging. They attested good short-term and mid-term outcome especially in young patients (5-8), while long-term results are still not available. With the new design a 60-fold decreased volumetric wear in large metal-on-metal bearings was achieved compared to metal-on-polyethylene arthroplasties. Sieber *et al*. concluded in their study that this could lead to reduced osteolysis, although the nanometre particles rose up to 500 times more in this design (9). Also recent studies confirmed lower wearing rates in metal-on-metal total hip arthroplasties (10) and attested a higher range of motion, a smaller rate of dislocations and less impingement of the femoral neck (10,11). In a further study, comparing metal-on-metal hip arthroplasties with conventional THAs using smaller heads of Mont *et al*., metal-on-metal hip arthroplasties showed a “more normal hip kinematics and functionality” (12) than conventional THAs.

On the other hand there are also concerns associated with metal-on-metal bearings. Some reports stated that there is a higher revision rate (13) and a higher count of neck fractures (13,14) after hip resurfacing but the authors traced it back to required learning curve for correct implantation of these devices (13,14).

Some studies also mentioned local soft-tissue reactions after metal-on-metal THAs. For example Pandit *et al.* published a case series of 17 patients with a periprosthetic pseudotumour after metal-on-metal resurfacing (15). He estimated that approximately 1% of patients who have got a metal-on-metal resurfacing develop a pseudotumour within five years.

Other studies focus on the effect of systemic exposure to metal ions, because metal ions from arthroplasty devices enter the blood circulation (16-20). Chromosomal aberrations in peripheral blood, reduced T-cell counts, and increasing lymphocyte metal induced reactivity associated with high metal ion levels have been reported (21-24). There are also case reports of cobalt intoxication after THA surgery including loss of sight, hearing, muscle weakness, paraesthesia, diffused anaesthesia and exanthemas although these sensations appeared in THAs using metal-on-ceramic couplings (25,26).

The latest negative development of metal-on-metal bearings has been the voluntary international recall of the ASR Resurfacing System and the ASR XL Head System by DePuy in October 2010. The reason was the seventh annual report of the National Joint Registry for England and Wales that caused the Medicines and Healthcare products Regulatory Agency to publish a warning on 22nd April (MDA/2010/033) and 25th May (MDA/2010/044) concerning metal-on-metal hip replacements in general and especially the ASR XL Head System and the Resurfacing System. The National Joint Registry registered elevated revision rates five years after implantation especially in both devices of DePuy. If elevated metal ion levels in serum were a factor causing these elevated revision rates is still under investigation.

As a consequence of these findings, further research focuses on characteristics that affect the level of metal ions in serum, with the goal of keeping metal ion levels as low as possible.

1.3 Common indications of THA

The common indications for THA are as follows:

- Rheumatoid arthritis
- Osteoarthritis
- Posttraumatic arthritis
- Collagen disease
- Avascular necrosis
- Congenital dysplasia of the hip
- Acetabular protrusion
- Epiphyseal coxa vara
- Disability because of earlier arthrodesis

In case of hip resurfacing, indications are primary or secondary osteoarthritis of the hip. In contrast to common THAs, Posttraumatic arthritis, severe acetabulum or femoral head deformity are contraindications. Also the epiphyseolysis capitis femoris, the arthritis of the hip after osteotomy, and an allergy to metal are contraindications for metal-on-metal hip resurfacing.

1.4 Investigated characteristics of metal ions and serum metal ion levels

Up to now there have been many studies investigating the characteristics of metal ions in the human body after total hip arthroplasty with metal-on-metal bearings.

Some of them described different phases of metal ion release into the systemic blood circulation after implantation (27-29). They differentiated between an early running-in phase of wear with an explicit increase of metal ions in the blood and a late steady-state phase of wear, during which metal ions in the blood are levelling out or are decreasing to a slightly lower level.

This wear during the steady-state phase is much lower than the wear in conventional metal-on-polyethylene or ceramic-on-polyethylene arthroplasties (27).

For example, during a six-year study Daniel *et al.* (30) revealed an initial peak of cobalt ions after six months and chromium ions after one year in serum and 24-hour urinary excretion. After these peaks there was also a slightly but steady decrease of these values.

Contrary to this, Iminashi *et al.* (31) reports in his current study that a steady-state of cobalt and chromium is already reached after three months without any further increase up to one year.

The fact that published studies had different findings concerning metal ion levels over time implies that there have to be additional factors other than time that influence the release of metal ions. Research about the relationship between the activity of the patients and the metal ions in serum revealed no correlation (32,33). Furthermore, one study showed that increasing the diameter of the head shortens the running-in phase (34) and Clarke *et al.* (35) reported of higher systemic metal ion levels in large-head arthroplasties compared to small heads.

Garbuz *et al.* (36) reported that patients with large-head metal-on-metal total hip arthroplasty had significantly higher metal ion levels, than patients with the resurfacing system. He ascribed this to a possible additional ion release from the connection device between the head and the stem.

Factors that seem to be very important are the design as well as the tribological characteristics of the device, the component size, and the adjustment of the arthroplasty (37,38). A fluid elastohydrodynamic film in the lubrication is the key for low wear characteristics.

To achieve that, the largest possible head diameter, a defined clearance, fine surface finishes, good sphericity, and only a minimal structural elastic deformation of the cup during the implantation have to be used in comparison to the standard THAs (39). Hart *et al.* (40) showed that a cup inclination of more than 50° in metal-on-metal bearings significantly increases whole blood metal ion levels. Further, Langton *et al.* (41) stated in their study, interestingly in contrary to the study of Clarke *et al.* (35), that the component size is negatively correlated with metal ion levels and cup anteversion and cup inclination only have an effect on arthroplasties with smaller component sizes. Also, De Haan *et al.* (42) found a correlation between the inclination of the acetabular cup and metal ion levels. He established as new term the arc of cover, which also correlates with the metal ion level, to take account of cup inclination and cup size in one parameter.

1.5 Aim of the study

Former studies (42) revealed a correlation between the inclination or rather the arc of cover of the acetabular cup and metal ion levels in the serum. In our study we tried to figure out if this correlation can also be found in patients treated at our hospital with the metal-on-metal ASR Resurfacing System and large-head metal-on-metal ASR XL Head System produced by DePuy Johnson & Johnson Company.

2 Material and methods

2.1 Design of the study

This study is a prospective, non-randomised monocentre study within a company sponsored prospective multicentre post marketing surveillance study, which analyses prosthesis outcome and patients satisfaction under the management of Univ. Prof. Dr. Reinhard Windhager. After consulting the sponsor company DePuy we got the permission to perform a local additional investigation to take blood samples of the 36 participating patients at our department and analyse the serum metal ion levels. The study was approved by the local ethics committee. As the end point we defined the last measurement five years post-operatively. This dissertation presents intermediate data of the study at one year follow-up.

2.2 Privacy

All people entrusted with this study committed themselves to handle patient data and results of documentation strictly confidentially. All published data of this study are handled anonymously.

2.3 Inclusion criteria and exclusion criteria of probands

2.3.1 General inclusion criteria

Men and women between the age of 18 and 65 participated in the study. They were able and willing to understand the conditions in the study and to cooperate. They also had to sign a consent form in their own will.

2.3.2 Inclusion criteria for DePuy ASR Resurfacing System

Participants with primary osteoarthritis who have the indication for a standard metal-on-metal hip resurfacing with cementless acetabuloplasty are included in the study.

2.3.3 Inclusion criteria for the DePuy ASR XL Head System

Participants whose bone morphology and quality is not suitable for a standard metal-on-metal hip resurfacing but for a cementless acetabulum and a large-head metal-on-metal total hip arthroplasty are included in the study.

2.3.4 General exclusion criteria

Participants who are not in the condition for joining the study and the follow-up are excluded from the study. Excluded are also people with:

- Impaired renal function
- Metal sensitivity
- Infectious diseases
- Pregnancy or planned pregnancy within two years after surgery
- Drug and alcohol abusing behaviour
- Psychological diseases
- Participation to another clinical study while the last twelve months
- Corticosteroid treatment
- Active or recent joint sepsis

2.3.5 Additional exclusion criteria for DePuy ASR Resurfacing System

People with following conditions are excluded from the study:

- Significant osteoporosis and bad bone quality
- Marked atrophy and deformities of the proximal femur
- Premature skeleton
- Loss of muscles or neuromuscular diseases
- Anatomic stem-shaft-angle below 120°
- Radiation treatment of the concerned hip

2.4 Blood sample system and procedure

We used the blood samples to determine serum levels of CRP, renal function parameters, and levels of cobalt and chromium ions.

The CRP was of interest because it correlates with the grade of inflammation. A short time after surgery, CRP levels are normally elevated, but decrease after a while. If they stay high, something could be wrong with regeneration, or the hip joint could be inflamed. This could also affect serum metal ion levels and therefore we had to observe the CRP level.

Renal function parameters were creatinine, urea and uric acid. It was important to measure these serum levels because if they are elevated renal function is restricted. Also because metal ions are eliminated through renal clearance, a restricted renal function could lead to an artificial elevation of metal ion levels in serum (43).

We focused on the metal ions cobalt and chromium. Almost all modern hip resurfacing systems are made of a cobalt/chromium cast alloy, as well as the DePuy ASR Resurfacing System and the DePuy ASR XL Head System.

2.4.1 Instruments

For the blood samples we used the Vacuette® multi extraction cannula model 21 G x 1½´´; 0.8 mm x 38 mm (LOT: 06G29B). Further we used two different tubes. For renal function parameters and CRP we used Vacuette® 4 ml LH lithium heparin tubes (LOT: A010901) and for serum metal ion levels we used Vacuette® 6 ml Z No additive tubes (LOT: L090609). We used these "no additive" tubes to get exact results of metal ion levels, because additives like EDTA could adulterate them. The contamination level specification is mapped in figure 1.

2.4.2 Procedure

We took blood samples at following points of time:

Pre-operatively:

- 1 x Lithium heparin tube
- 2 x No additive tubes

One week post-operatively (five to seven days after surgery):

- 1 x Lithium heparin tube

Six weeks, three months, six months and one year post-operatively:

- 1 x Lithium heparin tube
- 2 x No additive tubes

If there was a clinical suspicion of early increased debris, additional blood samples were planned.

We sent the lithium heparin tube directly to the laboratory, where CRP and renal function parameter were determined.

greiner bio-one

Greiner Bio-One Ges.m.b.H.
Bad Haller Straße 32
A-4550 Kremsmünster

Contamination Level Specification

Product description: VACUETTE® 6 ml Z No additive tube

Greiner item no.: 456085

Element	Normal range in whole blood [ppb] [*1]	Typical contamination level in empty tubes [ppb]
Aluminium **Al**	< 7,5	2-6
Manganese **Mn**	6- 11	< 1,0 [*3]
Cadmium **Cd**	<1,7	< 0,2[*3]
Lead **Pb**	< 100	< 1,0[*3]
Mercury **Hg**	< 5	< 0,2[*3]
Thallium **Tl**	< 2	< 0,2[*3]
Uranium **U**	< 1	< 0,2[*3]
Silver **Ag**	< 0,6	< 1,0[*3]
Chrome **Cr**	0,5 - 4	< 1,0[*3]
Beryllium **Be**	<1	< 1,0[*3]
Arsenic **As**	<12	< 1,0[*3]
Cobalt **Co**	0,5 – 3,9	< 1,0[*3]

8th May 2009
date

greiner QM bio-one

Gabriele Rose
Gabriele Rose
QM / Regulatory Affairs

[*1] *References*:
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Thomas L.; Labor und Diagnose ; 6. Edition 2005 Frankfurt/Main: TH-Books Verlags Gesellschaft
[*3] *These are the detection limits measured by ICP-MS. The actual levels may be lower that the detection limits shown*

Figure 1: Contamination level specification of the no additive tube from greiner bio-one

The No additive tubes were centrifuged approximately two hours after blood extraction for ten minutes at 4300 rpm. The supernatant was filled into 5 ml cryo tubes and one tube was stored until the metal ion measurement at Medical and Chemical Laboratory Diagnostic Lorenz & Petek GmbH at 4° Celsius. The second tube is still stored at the department at -20° Celsius for possible further questions or a repetition of the metal ion measurement.

2.4.3 Metal ion measurement

The serum metal ion levels that we determined were cobalt, chromium, and molybdenum. Later we focused only on cobalt and chromium, because we expected no differences in pre-operative and post-operative molybdenum levels like described in other studies (44,45). For the determination of serum levels of cobalt, chromium, and molybdenum, the samples were measured by graphite furnace atomic absorption spectrometry. This method has been established as a standard in hospitals. Although inductively-coupled plasma mass spectrometry is a more sensitive method to determine metal ion levels, the graphite furnace absorption spectrometry is sufficient as the focus of interest were the high concentrations of metal ions not the low ones.

Chemicals

- Triton X 100 (Serva)
- Cobalt Standard 1000 µg/ml (Perking Elmer)
- Molybdenum Standard 1000 µg/ml (Perking Elmer)
- Tritisol Chrome-Standard 1000 µg/ml (Merck)
- Magnesium nitrate hexa hydrate (Roth)
- Aqua dist. Rotipuran (Roth)

Preparation

300 µl of the sample were drugged with 50 µl modifier and 550 µl aqua dist. (Rotipuran) and well mixed. Control samples as well as standard samples were mixed in the same way. As blank value of the reagents, 50 µl modifier and 850 µl aqua dist. (Rotipuran) were used. Two parallel determinations of each sample were done.

Measurement

The sample to be examined was evaporated in an atomization apparatus and transformed into atomic condition. With graphite furnace atomic absorption spectrometry, solved samples were charged in a graphite tube with a micro pipette and liberated from the solvent and other concomitant agents by stepwise heating. After that they were atomized. This produced a signal whose area is proportional to the element we want to determine. The concentration of the dilution can be calculated by using the dosed volume of the sample.

2.5 The DePuy ASR Resurfacing System and ASR XL Head System

Two types of bearing components were used in this study. First the DePuy ASR Resurfacing System and second the DePuy ASR XL Head System. As a stem within the ASR XL Head System we used the Corail® stem or the Future® stem, both out of the portfolio by DePuy. The following two chapters introduce both ASR devices.

2.5.1 ASR Resurfacing System

The ASR Resurfacing System we used in our study is a metal-on-metal hip resurfacing system of the modern generation produced by DePuy, a Johnson & Johnson company. It has been used at our department since 2004. It is a cast Co-Cr alloy. For details of the alloy see table 1. In Europe it has been approved and established in 2003 and by the beginning of this study approximately 4000 pieces have been implanted. In October 2010 the system has been removed from the market due to an increased revision rate at five year follow-up in comparison to other resurfacing systems on the market. This higher failure rate was detected by the UK Medicines and Healthcare products Regulatory Agency (MHRA). Therefore a Medical Device Alert was published (Ref: MDA/2010/044 Issued: 25 May 2010) and as a consequence of this the ASR Resurfacing System was withdrawn from the market by DePuy Johnson & Johnson company.

Figure 2: ASR Resurfacing System (picture from a DePuy advertising brochure)

Table 1: Chemical composition of the Co-Cr-alloy of DePuy's metal THA devices. Main contents are cobalt, chromium and molybdenum.

Component	Chemical composition (weight %) after ASTM F75
C	0.28%
Si	< 1.0%
Mn	0.6%
S	0.01%
P	0.02%
Al	0.1%
B	0.01%
Cr	29%
Fe	0.5%
Mo	5.7%
N (ppm)	200 ppm
Ni	0.7%
O (ppm)	< 30 ppm
Ti	< 0.05%
W	0.10%
Co	Balance

DePuy expected following improvements from this system:

Bone saving profile

Additional to the principal of hip resurfacing which can already be considered bone saving on its own, the inside of the femoral component is for 3° conic. This should allow a smaller diameter of the head without the risk of neck notching.

Figure 3: Conic shape (picture from a DePuy advertising brochure)

Optimized clearance

With a combination of a larger head diameter and a lower clearance, DePuy expected better lubrication and as a result a lower wearing rate. The clearance of the ASR Resurfacing System is up to three times lower than in competitors' systems.

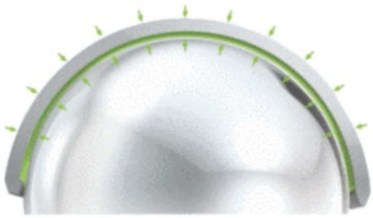

Figure 4: Clearance of the ASR Resurfacing System
(picture from a DePuy advertising brochure)

Relation between clearance and cup deformation

The DePuy ASR Resurfacing System should take the deformation which occurs during the implantation into consideration. The clearance is always higher than the measured deformation, so that the optimal lubrication should be saved.

2.5.2 ASR XL Head System

The ASR XL Head System is an alternative to use a large-head metal-on-metal bearing system in patients who do not fulfil the conditions for the ASR Resurfacing System. The bone saving advantage of the ASR Resurfacing System gets lost but it still provides the benefits of a large-head diameter equal to the ASR Resurfacing System. The ASR XL Head System can be combined with a common DePuy THA stem. In our case the stem was either a Corail® stem or a Future® stem. The chemical composition of both stems is listed in table 2.

Figure 5: ASR XL Head System
(picture from a DePuy advertising brochure)

Table 2: Material composition Future® stem and Corail® stem

Titan – aluminium 6 – vanadium 4 – forge alloy				
Component	Chemical composition (weight %)			
	by ISO 5832/III		by ASTM F-138	
	min.	max.	min.	max.
Aluminium	5,50	6,75	5,50	8,50
Vanadium	3,50	4,50	3,50	4,50
Iron		0,30		0,25
Oxygen		0,20		0,13
Carbon		0,08		0,08
Nitrogen		0,05		0,05
Hydrogen		0,015		0,012
Titan	rest	rest	rest	rest

2.6 *Radiological Analysis*

2.6.1 Radiographs

We took standard radiographs anteroposterior view of the pelvis and anteroposterior and lateral view of the affected hip, from every patient four times: preoperatively, one week, three months and one year post-operatively.

2.6.2 Measured parameters

To describe the implantation adjustment we measured the inclination of the acetabulum component and calculated the arc of cover after the implantation, using the synedra View Personal version 1.0.12.3 (© Synedra information technologies GmbH) software. All measurements were performed by two independent observers.

Cup inclination

The cup inclination is given by the angle between the straight line running parallel to the opening edges of the acetabular component and a straight line running through both tear drop signs at the anteroposterior pelvis x-ray (figure 6). Referring to the study of De Haan *et al.* (42) the cup inclination was considered steep if the angle was steeper than 55° and we expected elevated metal ion levels in the serum.

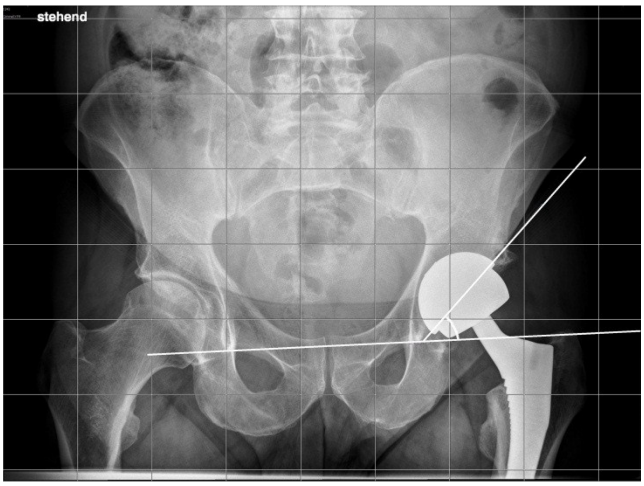

Figure 6: Cup inclination measured in a 57-year-old man with an ASR XL Head System one year after implantation

Arc of cover

The arc of cover (42) is given by the product of the component radius (r) and angle (in radians) subtended between the vertical and the lateral acetabular component edge (γ) as follows (Figure 7):

$$a=r\alpha$$

It is supposed to quantify the edge loading because it determines the surface of the proximal pole and the lateral edge of the acetabular component. If the arc of cover was less than 10 mm we expected elevated metal ion levels in serum.

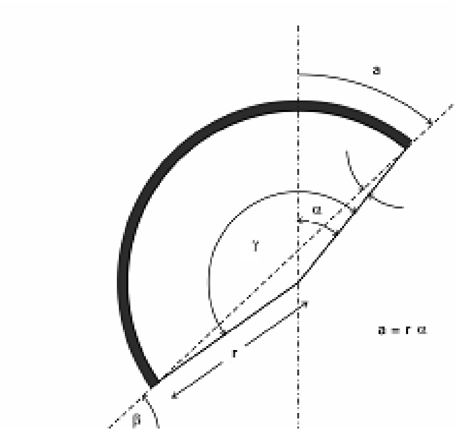

Figure 7: Arc of cover (42)

2.7 Statistics

We performed a descriptive statistical analysis by gender. Then we did a correlation analysis following Pearson and Spearman between metal ion levels at different points of time as well as between metal ion levels and the implantation adjustment.

We defined two groups like it was done in the study of De Haan *et al.* (42). One group consisted of hips with a cup inclination of ≥ 55° which was considered to be steep. The other group consisted hips with a cup inclination of < 55° which was considered to be the non-steep group. We used the Mann-Whitney U test to see if there was a significant difference between the steep component implantation and the non-steep component implantation.

We did the same with two additional groups regarding the arc of cover: One group with an arc of cover of < 10 mm and second group with an arc of cover of ≥ 10 mm. The threshold of 10 mm we chose also according to the study of De Haan *et al*. (42).

To go more into detail, we additionally performed a subgroup analysis between the ASR Resurfacing System and the ASR XL Head System by performing a correlation analysis following Pearson and Spearman of metal ion levels at different points of time and metal ion levels and implantation adjustment separately for both systems.

A p value of ≤ 0.05 was considered significant in all analyses.

3 Results

3.1 General results

All 36 patients completed follow-up one year post-operatively. One patient (hip 102) was excluded from the analysis due to poor radiographs. Among the remaining 35 patients there were 20 male and 15 female with a mean BMI of 27.2 (21.3 to 37.6) and an average age of 51.0 (33.0 to 60.8). Four patients had been treated bilaterally with an ASR XL Head System. So there was a total count of 39 hips, 31 ASR XL Head Systems (14 female, 17 male) and eight ASR Resurfacing Systems (three female, five male). The average diameter of the implanted femoral head was 46.4 mm (41.0 to 51.0 mm) and of the implanted acetabular cup 53.0 mm (46.0-58.0 mm). All operations were performed by six well experienced senior surgeons at the Department of Orthopaedic and Orthopaedic Surgery, Medical University of Graz.

The total number of available hip data and the number of acetabular cup measurement parameters were variable at different points of follow-up, e.g. due to missing radiographs or other reasons. The variation of number of the acetabular cups in the steep group and the non-steep group was caused by slight differences between the radiographs taken at different points of time, for example because of rotation differences and inter-observer variability. For this reason, the hips with a cup inclination or an arc of cover near the threshold value of 55° cup inclination or an arc of cover with 10 mm could change the group from one point of time to another. Table 3 shows the summary of a descriptive statistic of the categorical variables.

Table 3: Descriptive statistic of categorical variables

Patient characteristics/ single measurement		Total	ASR XL Head System	ASR Resurfacing System
Total patients		**36**	**28**	**8**
Patients (sex)	m	20	15	5
	f	16	13	3
Number hips / patient	1	32	24	8
	2	4	4	0
Total hips		**40**	**32**	**8**
Hips (sex)	m	22	17	5
	f	18	15	3
Number hips of 1 patient	1	32	24	8
	2	8	8	0
Repetitive measurement				
Cup inclination 1 week	< 55°	34	28	6
	≥ 55°	3	2	1
	Total	37	30	7
Cup inclination 3 months	< 55°	35	29	6
	≥ 55°	4	2	2
	Total	39	31	8
Cup inclination 1 year	< 55°	31	24	7
	≥ 55°	4	3	1
	Total	35	27	8
Arc of cover 1 week	<10 mm	5	4	1
	≥10 mm	32	26	6
	Total	37	30	7
Arc of cover 3 months	<10 mm	6	4	2
	≥10 mm	33	27	6
	Total	39	31	8
Arc of cover 1 year	<10 mm	6	4	2
	≥10 mm	29	23	6
	Total	35	27	8

3.1.1 Component adjustment

One week post-operatively

Cup inclination:

The group of steep implanted components contained three hips one week post-operatively (two ASR XL Head Systems and one ASR Resurfacing System) and the group of non-steep components contained 34 one week post-operatively (28 ASR XL Head Systems and six ASR Resurfacing Systems). At the two missing hips, cup inclination could not be determined because of missing radiographs (one ASR XL Head System and one ASR Resurfacing System). There were a total number of 37 radiographs.

Arc of cover:

There were five hips with an arc of cover of < 10 mm (four ASR XL Head Systems and one ASR Resurfacing System) and 32 hips with an arc of cover of ≥ 10mm (26 ASR XL Head Systems and six ASR Resurfacing Systems). There were also two radiographs missing.

Three months post-operatively

Cup inclination:

The group of steep implanted components contained four hips three months post-operatively (two ASR XL Head Systems and two ASR Resurfacing Systems) and the group of non-steep components contained 35 (29 ASR XL Head Systems and six ASR Resurfacing Systems). At the one missing hip, cup inclination could not be determined because of a missing radiograph (ASR XL Head System). There were a total number of 39 radiographs.

Arc of cover:

Six hips were in the group with an arc of cover of < 10 mm (four ASR XL Head Systems and two ASR Resurfacing Systems) and 33 hips were in the group of ≥ 10 mm (27 ASR XL Head Systems and eight ASR Resurfacing Systems). There is also one radiograph missing.

<u>One year post-operatively</u>

Cup inclination:

The group of steep implanted components contained four hips one year post-operatively (three ASR XL Head Systems and one ASR Resurfacing System) and the group of non-steep components contained 31 (24 ASR XL Head Systems and seven ASR Resurfacing Systems).

At the four missing hips, cup inclination could not be determined because of missing radiographs (four ASR XL Head Systems). There were a total number of 35 radiographs.

Arc of cover:

Six hips were in the group with an arc of cover of < 10 mm (four ASR XL Head Systems and two ASR Resurfacing Systems) and 29 hips were in the group of ≥ 10 mm (23 ASR XL Head Systems and six ASR Resurfacing Systems). There were also four radiographs missing.

3.1.2 Differences in metal ion levels respective component adjustment

We found no significant difference in metal ion levels between the steeply-inclined group and the group of non-steep components at all points of time (Mann-Whitney U test, $p > 0.05$ for Co and Cr at all times, see table 4).

There was also no significant difference in concentrations of Co and Cr between the group with an arc of cover of ≥10 mm and the group with an arc of cover of < 10 mm at all points of time (Mann-Whitney U test, $p > 0.05$ for Co and Cr at all times, see table 4).

Values of Co and Cr were significantly different pre-operatively, and three months and one year post-operatively (see table 5 and 6). We were able to find a steady increase of both cobalt and chromium levels up to one year.

Table 4: Summary of the test statistics of categorical hip arthroplasty characteristics and metal ions. This table contrasts the steeply-inclined group with the non-steeply-inclined group respective differences in metal ion levels (both cobalt and chromium) at different points of time as well as it contrasts the group with an Aoc < 10 mm with the group with an Aoc ≥ 10 mm. A p value of ≤ 0.05 was considered significant.

Mann-Whitney Test				Exact Sig. (2-tailed)
Co (µg/dl)	pre-operative	Cup inclination <55 and ≥55	1 week	.415
	3 months		3 months	.347
	1 year		1 year	.047
	pre-operative	Arc of cover <10 and ≥ 10 mm	1 week	.196
	3 months		3 months	.747
	1 year		1 year	.148
Cr (µg/dl)	pre-operative	Cup inclination <55 and ≥55	1 week	.927
	3 months		3 months	.882
	1 year		1 year	.389
	pre-operative	Arc of cover <10 and ≥10 mm	1 week	.340
	3 months		3 months	.451
	1 year		1 year	.462

Table 5: Test for difference of Co ion levels in serum at different follow-up points of time (*correction for multiple comparisons: Bonferroni)

Data	Statistics	Co (µg/dl) preOP	Co (µg/dl) 3 mo	Co (µg/dl) 1 year
all available	N	34	39	39
	Mean	.0274	.1321	.5077
	Std. Deviation	.09288	.14283	1.05460
	Median	.0000	.0900	.2600
	Minimum	.00	.00	.00
	Maximum	.54	.66	5.85
minimum available	N	32	32	32
	Mean	.0288	.1472	.5922
	Std. Deviation	.09564	.15234	1.14903
	Median	.0000	.0950	.2850
	Minimum	.00	.00	.00
	Maximum	.54	.66	5.85
Tests for Difference (exact Tests)		corrected p*		
Globaltest:	Friedman Test	<.001		
post-hoc Tests (Wilcoxon Signed Ranks Test):	preOP - 3 mo	<.001		
	3 mo - 1 year	<.001		
	preOP - 1 year	<.001		

Table 6: Test for difference of Cr ion levels in serum at different follow-up points of time (*correction for multiple comparisons: Bonferroni)

Data	Statistics	Cr (µg/dl) preOP	Cr (µg/dl) 3 mo	Cr (µg/dl) 1 year
all available	N	34	39	39
	Mean	.06126	.22595	.52536
	Std. Deviation	.131697	.151776	.568217
	Median	.02450	.16000	.31700
	Minimum	.007	.059	.081
	Maximum	.753	.724	2.656
minimum available	N	32	32	32
	Mean	.06416	.23481	.59225
	Std. Deviation	.135332	.157546	.607030
	Median	.02650	.18300	.35100
	Minimum	.007	.059	.081
	Maximum	.753	.724	2.656
Tests for Difference (exact Tests)		corrected p*		
Globaltest:	Friedman Test	<.001		
post-hoc Tests (Wilcoxon Signed Ranks Test):	preOP - 3 mo	<.001		
	3 mo - 1 year	<.001		
	preOP - 1 year	<.001		

3.1.3 Subgroup analysis of ASR XL Head System and ASR Resurfacing System

Further we noticed a slight but not significant difference between the ASR XL Head System and the ASR Resurfacing System group. Cobalt and chromium levels had a tendency to be higher in the ASR XL Head Systems than in the ASR Resurfacing Systems.

The mean values of cobalt were pre-operatively 0.03 µg/dl (0.00 up to 0.54; SD 0.09), after three months 0.13 µg/dl (0.00 up to 0.66; SD 0.14), and one year post-operatively 0.51 µg/dl (0.00 up to 5.85; SD 1.05). Split into subgroups of ASR XL Head System and ASR Resurfacing System, mean values were pre-operatively 0.03 µg/dl (0.00 up to 0.54; SD 0.10), three months post-operatively 0.14 µg/dl (0.00 up to 0.66; SD 0.15), and one year post-operatively 0.60 µg/dl (0.00 up to 5.85; SD 1.17) in the ASR XL Head System group and pre-operatively 0.01 µg/dl (0.00 up to 0.03; SD 0.01), three months post-operatively 0.09 µg/dl (0.00 up to 0.33; SD 0.11), and one year post-operatively 0.16 µg/dl (0.00 up to 0.39; SD 0.15) in the ASR Resurfacing System group. The complete values including six weeks and six months post-operative measurements are listed in table 7.

The mean values of chromium were pre-operatively 0.61 µg/dl (0.01 up to 0.75; SD 0.13), three months post-operatively 0.23 µg/dl (0.06 up to 0.72; SD 0.15), and one year post-operatively 0.53 µg/dl (0.08 up to 2.66; SD 0.57). Also split into the subgroups of ASR XL Head System and ASR Resurfacing System, mean values were pre-operatively 0.07 µg/dl (0.01 up to 0.75; SD 0.14), three months post-operatively 0.23 µg/dl (0.06 up to 0.72; SD 0.16), and one year post-operatively 0.59 µg/dl (0.11 up to 2.66; SD 0.61) in the ASR XL Head group and pre-operatively 0.02 µg/dl (0.01 up to 0.03; SD 0.01), three month post-operatively 0.19 µg/dl (0.10 up to 0.40; SD 0.11), and one year post-operatively 0.29 µg/dl (0.08 up to 0.97; SD 0.28) in the ASR Resurfacing System group. The complete values including six weeks and six months post-operative measurements are listed in table 8.

Table 7: Results of cobalt ion measurements in serum

Total /Subpopulation	Statistics	Co (µg/dl)					
		preOP	1 week	6 week	3 mo	6 mo	1 year
Total	N	34		30	39	36	39
	Mean	.0274		.0900	.1321	.2694	.5077
	SD	.09288		.08797	.14283	.48156	1.05460
	Median	.0000		.0700	.0900	.1300	.2600
	Minimum	.00		.00	.00	.00	.00
	Maximum	.54		.30	.66	2.81	5.85
ASR	N	29		25	31	29	31
XL Head System	Mean	.0297		.0932	.1442	.3059	.5981
	SD	.10052		.09218	.14999	.52757	1.16732
	Median	.0000		.0700	.1000	.1400	.2700
	Minimum	.00		.00	.00	.00	.00
	Maximum	.54		.30	.66	2.81	5.85
ASR	N	5		5	8	7	8
Resurfacing System	Mean	.0140		.0740	.0850	.1186	.1575
	SD	.01342		.06877	.10556	.14462	.14626
	Median	.0200		.0600	.0400	.0700	.1400
	Minimum	.00		.01	.00	.01	.00
	Maximum	.03		.19	.33	.38	.39

Table 8: Results of chromium ion measurements in serum

Total / Subpopulation	Statistics	Cr (µg/dl)					
		preOP	1 week	6 week	3 mo	6 mo	1 year
Total	N	34		30	39	36	39
	Mean	.06126		.13440	.22595	.36144	.52536
	SD	.131697		.101907	.151776	.321537	.568217
	Median	.02450		.10050	.16000	.22500	.31700
	Minimum	.007		.050	.059	.064	.081
	Maximum	.753		.443	.724	1.240	2.656
ASR	N	29		25	31	29	31
XL Head System	Mean	.06838		.14128	.23552	.39776	.58616
	SD	.141670		.110050	.160500	.342983	.609506
	Median	.02600		.10100	.17600	.23000	.32400
	Minimum	.007		.050	.059	.064	.111
	Maximum	.753		.443	.724	1.240	2.656
ASR	N	5		5	8	7	8
Resurfacing System	Mean	.02000		.10000	.18888	.21100	.28975
	SD	.010000		.029155	.112581	.146058	.284220
	Median	.02000		.10000	.13650	.17000	.20700
	Minimum	.010		.060	.097	.070	.081
	Maximum	.030		.140	.398	.475	.968

3.1.4 Correlations between metal ion levels and component adjustment

Cobalt

No correlation was found between cobalt and the cup inclination ($r = -0.027$ ($p = 0.874$) 3 months post-operatively and $r = 0.144$ ($p = 0.402$) 1 year post-operatively) or the arc of cover ($r = 0.080$ ($p = 0.642$) 3 months post-operatively and $r = -0.202$ ($p = 0.238$) 1 year post-operatively) 3 months post-operatively and 1 year post-operatively (see figures 8 and 9).

The only correlation found was between the pre-operative values of cobalt at 3 months post-operatively and 1 year post-operatively ($r = 0.62$ ($p < 0.001$) for 3 months and $r = 0.64$ ($p=0.007$) for 1 year). Also the 3 months post-operative values correlated with the 1 year post-operative values ($r = 0.36$ ($p = 0.026$)) (see figure 12).

Chromium

We found no correlation between chromium and the cup inclination ($r = 0.096$ ($p = 0.577$) 3 months post-operatively and $r = 0.046$ ($p = 0.788$) 1 year post-operatively) or the arc of cover ($r = -0.080$ ($p = 0.643$) 3 months post-operatively and $r = -0.092$ ($p = 0.595$) 1 year post-operatively) 3 months and 1 year post-operatively (see figures 10 and 11).

The only correlation found was between the pre-operative values of chromium and the values 3 months post-operatively and 1 year post-operatively ($r = 0.56$ ($p = 0.001$) for 3 months post-operatively and $r = 0.60$ ($p < 0.001$) for 1 year post-operatively). Also the 3 months post-operative value correlated with the 1 year post-operative values ($r=0.61$ ($p < 0.001$)) (see figure 13).

Both pre-operative cobalt and chromium were randomly distributed and did not correlate with the cup inclination or the arc of cover ($p > 0.050$).

After a further subgroup analysis between the ASR XL Head System and the ASR Resurfacing System, it turned out that this correlation between metal ion levels at different points of time only exists in the ASR XL Head System group for cobalt, as well as for chromium.

Renal function parameters and CRP were both within normal range (see table 9-12)

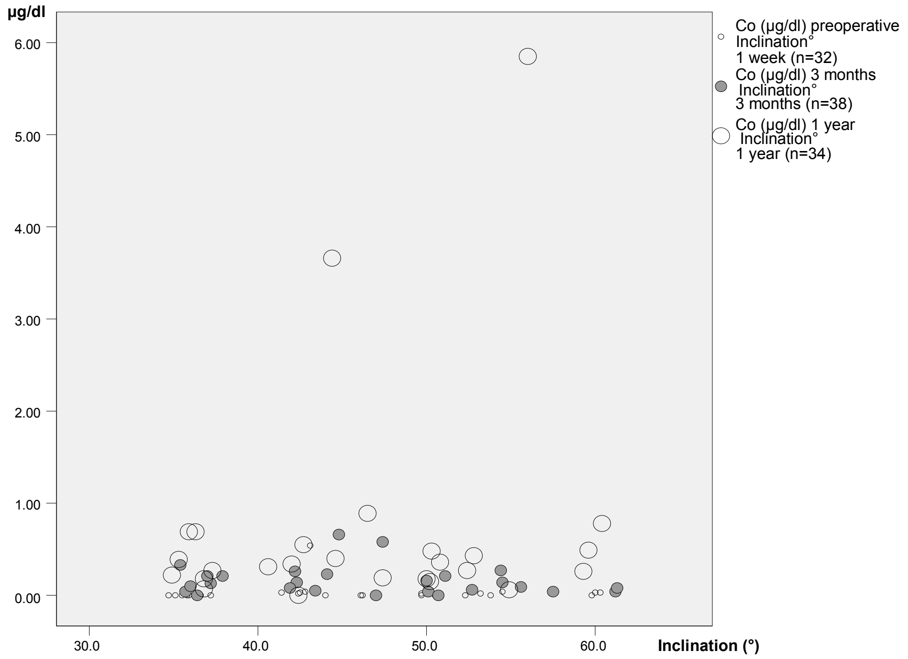

Figure 8: Graphic showing the relationship between cobalt ion levels and cup inclination one week, three months, and one year post-operatively. No correlation can be found between cobalt ion levels and cup inclination at any time.

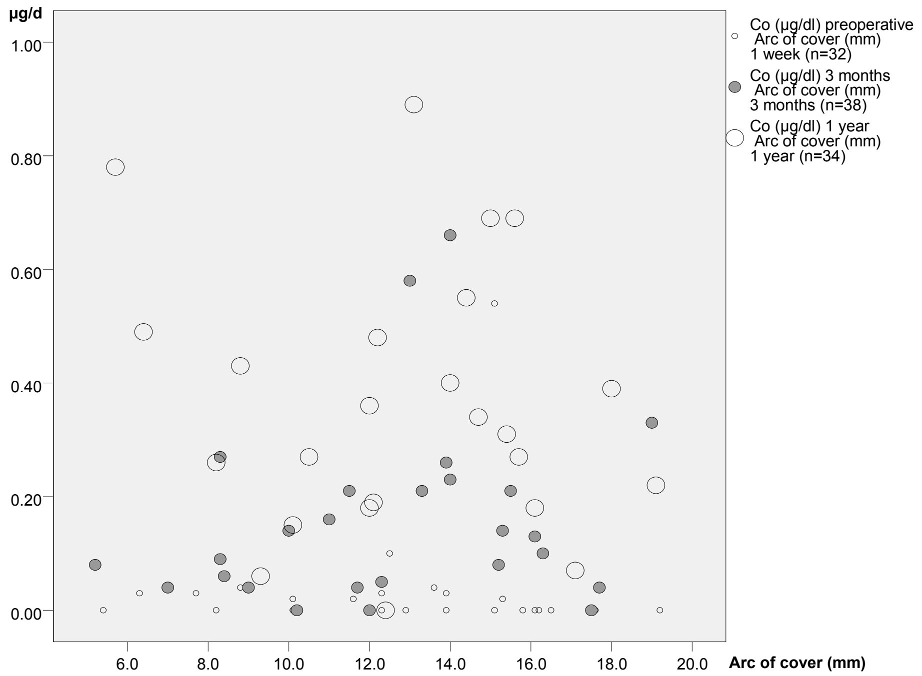

Figure 9: Graphic showing the relationship between cobalt ion levels and the arc of cover one week, three months, and one year post-operatively. No correlation can be found between cobalt ion levels and arc of cover at any time.

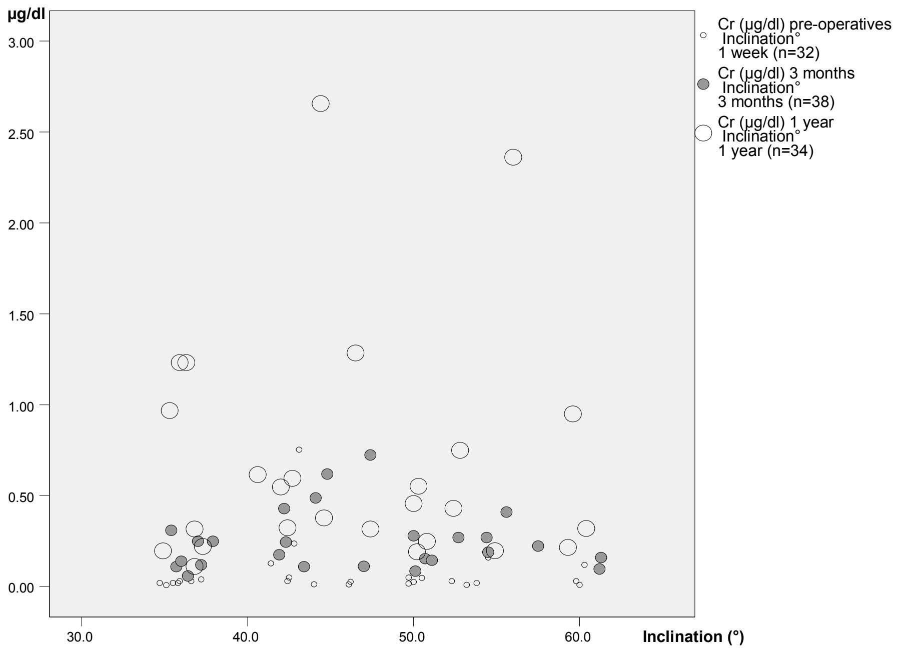

Figure 10: Graphic showing the relationship between chromium ion levels and the cup inclination one week, three months, and one year post-operatively. No correlation can be found between chromium ion levels and cup inclination at any time.

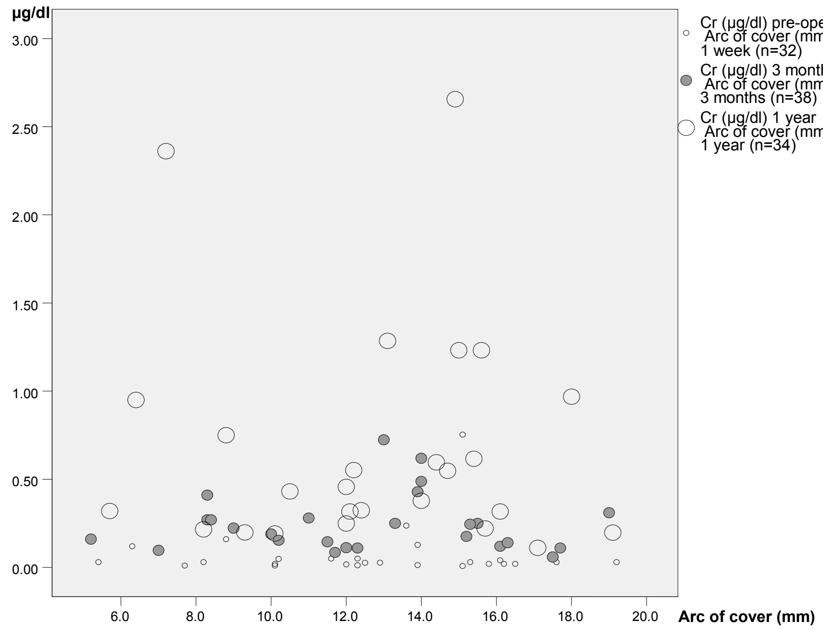

Figure 11: Graphic showing the relationship between chromium levels and the arc of cover one week, three months, and one year post-operatively. No correlation can be found between chromium ion levels and arc of cover at any time.

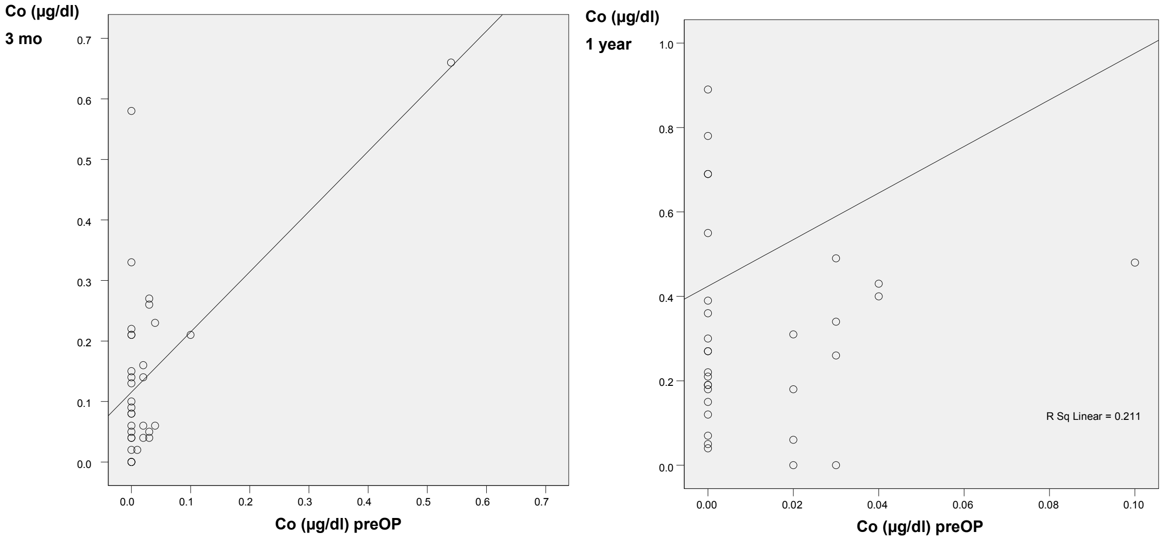

Figure 12: Correlations between pre-operative cobalt ion levels and three months post-operative (left graph) and one year post-operative (right graph) cobalt ion levels (n=33)

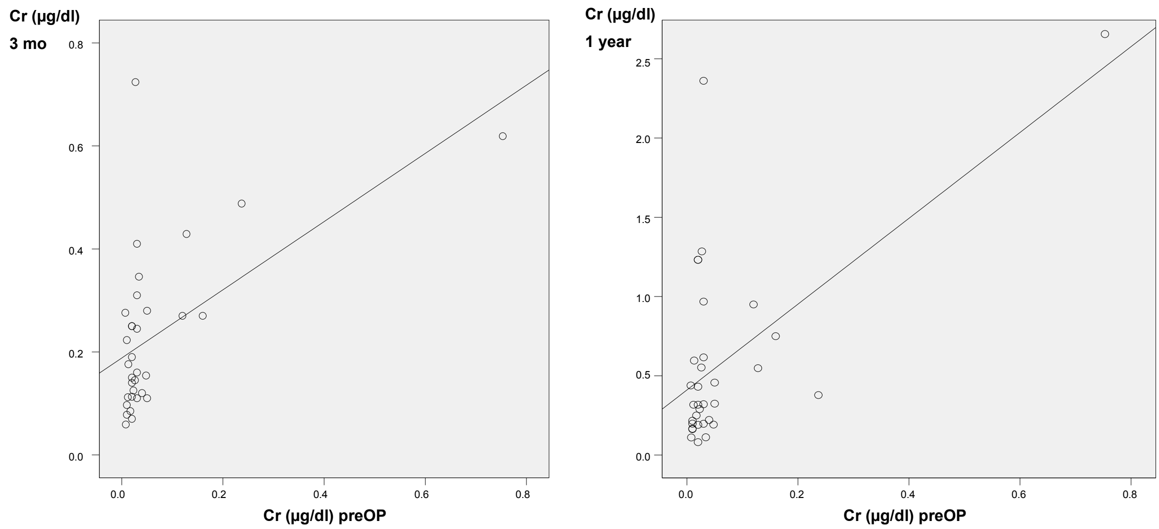

Figure 13: Correlations between pre-operative chromium ion levels and three months post-operative (left graph) and one year post-operative (right graph) chromium ion levels (n=33)

Table 9: Results of creatinine measurements

Total / Subpopulation	Statistics	Creatinine (mg/dl)					
		preOP	1 week	6 weeks	3 mo	6 mo	1 year
Total	N	40	40	14	19	16	31
	Mean	.8475	.7810	.8729	.8568	.8713	.8652
	SD	.15482	.15646	.16754	.12189	.15457	.13160
	Median	.8550	.7850	.8850	.8400	.8600	.8700
	Minimum	.46	.55	.54	.58	.57	.53
	Maximum	1.23	1.11	1.22	1.11	1.16	1.05

Table 10: Results of urea measurements

Total / Subpopulation	Statistics	Urea (mg/dl)					
		preOP	1 week	6 weeks	3 mo	6 mo	1 year
Total	N	40	40	14	19	16	32
	Mean	32.18	24.25	33.07	29.37	31.44	32.34
	SD	9.268	7.742	6.306	6.551	7.703	9.386
	Median	32.00	23.00	30.50	27.00	29.00	30.50
	Minimum	15	13	26	20	21	19
	Maximum	55	41	45	43	49	67

Table 11: Results of uric acid measurements

Total / Subpopulation	Statistics	Uric acid (mg/dl)					
		preOP	1 week	6 weeks	3 mo	6 mo	1 year
Total	N	39	30	14	19	16	32
	Mean	8.328	4.313	5.979	6.116	6.038	5.616
	SD	16.4392	1.2156	1.1570	1.3837	1.2816	1.3142
	Median	5.700	4.300	6.500	6.200	6.300	5.450
	Minimum	3.0	2.2	3.6	3.3	3.6	3.4
	Maximum	108.0	6.9	7.7	8.2	8.1	9.2

Table 12: Results of CRP measurements

Total / Subpopulation	Statistics	CRP					
		preOP	1 week	6 weeks	3 mo	6 mo	1 year
Total	N	40	40	31	38	37	34
	Mean	4.233	68.138	6.032	5.666	4.884	4.729
	SD	7.5763	47.0326	6.4218	7.6562	6.6095	4.8277
	Median	1.950	52.950	4.100	2.700	2.800	4.150
	Minimum	.0	8.6	.0	.0	.0	.0
	Maximum	45.7	222.4	28.9	32.5	32.5	19.6

3.2 Adverse events

Three patients reported a temporary clicking of the hip prosthesis one year after surgery, one out of these reported additional temporary squeaking in his hip. Apart from that there had happen one intraoperative calcar crack and we registered a loosening of the femoral component in one hip. This one had to be revised due to associated pain.

Within all but one patient reporting of adverse events we found no elevated metal ion levels. This patient reported clicking of the hip prosthesis six months post-operatively and additional squeaking one year post-operatively. He will be described further as an outlier patient in chapter 3.3 of this study.

3.3 Outliers

Because there is no general limit yet that defines whether a metal ion concentration is considered to be increased above normal levels in metal-on-metal THA, we set this limit to 1.00 µg/dl in our study. We set this limit after an appraisal of metal ion levels in our figures. Within our study group we detected at least four patients with outliers at one year follow-up. We intended to have a closer look on these patients with outliers to see if we could detect any causes for their especially high metal ion levels.

Patient 1 (hip 105)

This patient is a 60.8 year old female patient with a BMI of 37.6 at the time of surgery. She had an ASR XL Head System implanted with a 46 mm cup diameter and a 41 mm femoral head diameter combined with a Corail® stem.

Six months after surgery, there was only one value with elevated levels for cobalt with 2.81 µg/dl and chromium with 1.24 µg/dl. Afterwards cobalt and chromium levels decreased again one year post-operatively to 0.78 µg/dl (cobalt) and 0.32 µg/dl (chromium). But these levels were still above the ones measured three months post-operatively (Co 0.08 µg/dl and Cr 0.16 µg/dl).

Noticeable was the amount of drugs the patient had to take because of a resection of the colon six months before hip surgery and an essential hypertension. Most of them have to be eliminated through renal clearance.

Medication she took is listed:

- Enoxaparin sodium
- Diclofenac
- Pantoprazole
- Amlodipin
- A calcium and Vit D3 supplementation
- Bisoprolol
- Raloxifen
- A magnesium supplementation
- Tetrazepam
- A Vit. B1, B6 and B12 supplementation

Figure 14: Post-operative radiograph of the pelvis of patient 1

She also has still a metal plate after a fracture of her left ankle in place and had a conventional THA on the left side with a wire cerclage after an intra-operative calcar crack before implanting the ASR XL Head System. Six months after surgery she also reported clicking in her arthroplasty and the cup inclination of her arthroplasty was greater than 55° and the arc of cover was less than 10 mm. Later in this study, she has undergone a revision of her ASR XL Head System due to chronic instability after luxation.

Patient 2 (hip 117)

This patient is a 59 year old, female patient with a BMI of 24.7 at the time of surgery. She had an ASR XL Head System implanted with a 46 mm cup diameter and a 41 mm femoral head diameter combined with a Future® stem.

There was only one, but a massive outlier of cobalt one year post-operatively (Co 5.85 µg/dl) but two outliers of chromium six months and one year post-operatively (Cr 1.06 µg/dl and Cr 2.36 µg/dl).

Analysis of radiographs revealed an arc of cover less than 10 mm and a cup inclination greater than 55°.

Medication she took is listed:

- Naftidrofurylhydrogenoxalate
- Pantoprazole
- Levothyroxine sodium
- Latanoprost

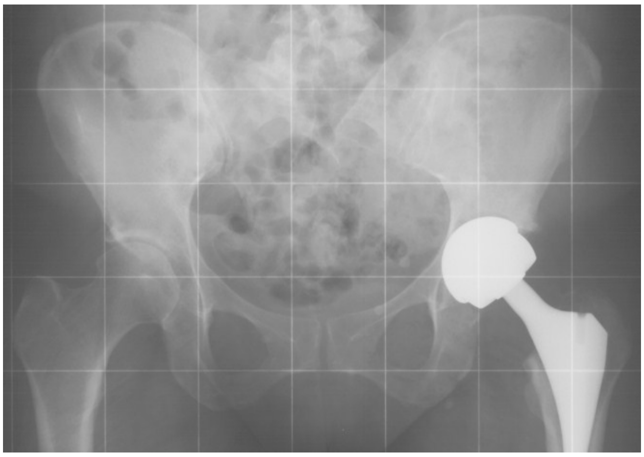

Figure 15: Post-operative radiograph of the pelvis of patient 2

In her medical history she had hypothyroidism after resection of her thyroid gland and a resection of both of her breasts because of bilateral mamma CA in 1994/95. She also had an acute hearing loss in December 2006. The hip surgery was performed at the end of April, 2007.

However, despite these very high metal ion levels in serum comparing to the rest there has been no revision of her prosthesis because there were no clinical complaints, yet and MRI-scan and radiographs showed no signs of prosthesis loosening or pseudotumours.

Patient 3 (hip 133)

This patient is a 56.3 year old, male patient with a BMI of 24.5 at the time of surgery. He had an ASR XL Head System implanted with a 54 mm cup diameter and a 47 mm femoral head diameter combined with a Corail® stem.

In his case the behaviour of cobalt and chromium were different. While cobalt only showed a peak six months after surgery (Co 0.94 µg/dl), chromium had continuously high levels three months, six months and one year after surgery (Cr 0.72 µg/dl, 1.17 µg/dl and 1.29 µg/dl).

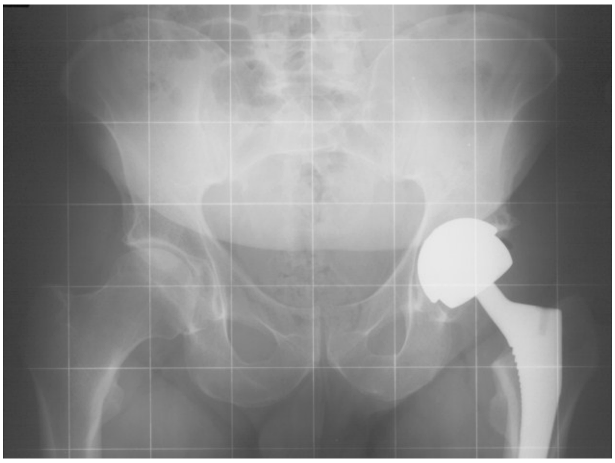

Figure 16: Post-operative radiograph of the pelvis of patient 3

The only medication he took was nitrazepam up to three months after surgery. Further the study nitrazepam has been disposed.
In contrast to patients 1 and 2 evaluation of radiographs showed an arc of cover greater than 10 mm and a cup inclination less than 55°.
Before surgery he had a two times relapsing meningitis. Seven months after implantation of the ASR XL Head System, general joint pain occurred (but not in the operated hip joint). Therefore a systemic rheumatic disease was suspected and further evaluation by an internist was performed. The patient also reported of occasional squeaking of the prosthesis after a long walk.
However, despite these high metal ion levels in serum comparing to the rest there has been no revision of her prosthesis because there were no clinical complaints, yet and MRI-scan and radiographs showed no signs of prosthesis loosening or pseudotumours.

Patient 4 (hip 137)

This patient is a 52.2 year old, male patient with a BMI of 26.7 at the time of surgery. He had an ASR XL Head System implanted with a 54 mm cup diameter and a 47 mm femoral head diameter combined with a Corail® stem. This has been his second metal-on-metal total hip arthroplasty surgery on the left side in a two-step bilateral procedure. The first contralateral ASR XL Head System consists of the same devices with the same diameters on the right side. It has been implanted one year before the implantation of the second one on the left and is also included in this study (hip 109).

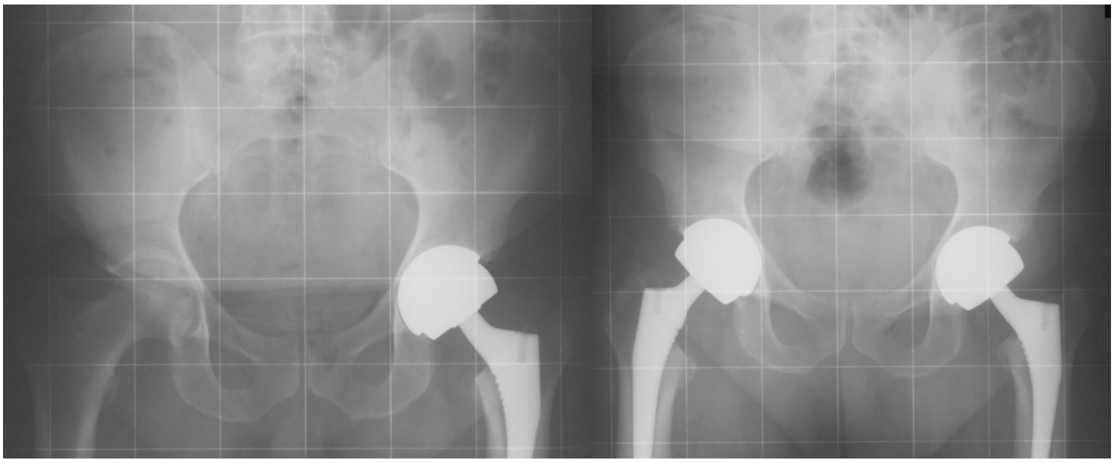

Figure 17: Post-operative radiograph of the pelvis of patient 4. Left: After first step THA. Right: After second step THA

Both values of cobalt and chromium were affected: While cobalt and chromium serum levels had stayed continuously below 1.00 µg/dl up to the implantation of the second ASR XL Head System, metal ion levels rose up to 3.66 µg/dl for cobalt and 2.66 µg/dl for chromium one year afterwards (two years after first-step surgery). The only medication he took was trazodone.

Both implanted ASR XL Head Systems showed an inclination less than 55° and an Arc of cover greater than 10 mm although the first arthroplasty was a little steeper than the second one and had a smaller Arc of cover (First ASR XL Head System: Inclination 49.7°, Arc of cover 11.6 mm; Second ASR XL Head System: Inclination 43.1°, Arc of cover 15.1 mm).

In his medical history he developed an ulnar nerve syndrome (eight months after his first ASR XL Head System implantation and four months before his second one) and he suffered from a mitral regurgitation grade II-III and an arterial hypertension (detected at the second implantation).

However, despite these high metal ion levels in serum comparing to the rest there has been no revision of her prosthesis because there were no clinical complaints, yet and MRI-scan and radiographs showed no signs of prosthesis loosening or pseudotumours.

Table 13: Characteristics of the outlier patients

Patient	1	2	3	4
Device	ASR XL Head System	ASR XL Head System	ASR XL Head System	ASR XL Head System
Sex	Female	Female	Male	Male
Age	60.8	59	56.3	52.2
BMI	37.6	24.7	24.5	26.7
Head size (mm)	41	41	47	47
Cup diameter (mm)	46	46	54	54
Shaft	Corail®	Future®	Corail®	Corail®
Arc of cover	<10	<10	>10	>10
Cup inclination	>55°	>55°	<55°	<55°
Indication	Coxarthrosis	Coxarthrosis	Secondary coxarthrosis	Coxarthrosis
Number of drugs	10	4	1	1
Additional metal implant	Metal plate, conventional THA, wire cerclage	-	-	Second metal-on-metal THA
Adverse events	Clicking, intraoperative calcar crack (Conventional THA)	-	Occasional squeaking, systemic rheumatic disease	-
Medical history	Colon resection, essential hypertension	Thyroid gland resection, bilateral Mamma-CA	Two times relapsing meningitis	Ulnar nerve syndrome, MR grade II-III, arterial hypertension

4 Discussion

From our findings, it was not possible to draw conclusions if the cup inclination or the arc of cover influence the serum metal ion levels of cobalt and chromium in patients treated with the DePuy ASR Resurfacing System or ASR XL Head System. The number of acetabular cups with an inclination greater than 55° and an arc of cover less than 10 mm was too small to make a serious statement about the correlation between the cup inclination or the arc of cover and metal ion levels in the serum at all points of measurement. One week post-operatively, there were only 8.1% (three out of 37) acetabular cups with an inclination greater than 55° and only 13.5% (five out of 37) with an arc of cover less than 10 mm. Three months post-operatively, there were only 10.3% (four out of 39) acetabular cups with an inclination greater than 55° and only 15.4% (six out of 39) with an arc of cover less than 10 mm. And one year post-operatively, there were only 11.4% (four out of 35) acetabular cups with an inclination greater than 55° and only 17.1% (six out of 35) with an arc of cover less than 10 mm. Therefore we could neither approve nor disapprove the findings of other studies in this regard.

Irrespective of the low number of hips in the steeply-inclined group and the group of hips with an arc of cover less than 10 mm, neither the cup inclination nor the arc of cover have shown a significant influence on cobalt and chromium concentrations in our study. This has been shown both in the running-in phase and the steady-state phase, considering that the steady-state phase begins no later than after one year of surgery as most of other studies state (30,31,44). But whether the steady-state phase is already reached after one year or not in the arthroplasties of our study has not yet been shown, because cobalt and chromium concentrations have risen continuously up to one year after surgery. And to make a statement about the correlation between the cup inclination or rather the arc of cover and serum metal ion levels in the steady-state phase, we had to be sure if the steady-state phase was already reached. Since the first results of our two-year-measurements revealed a further increase of metal ions in the serum, we have to wait for further results at two year follow-up and in addition to it.

4.1 The results in context to recent literature

4.1.1 Is there a general correlation between component adjustment and metal ion levels?

Summarizing the results, only two hips out of four with steeply inclined acetabular cups and only two hips out of six with an arc of cover < 10 mm had increased metal ion concentrations in the serum. But in contrast to expectation, also two hips out of 35 with non-steeply inclined acetabular cups and two hips out of 32 with an arc of cover ≥10 mm had increased metal ion levels. Similar findings within our outlier patients, only two out of the four had a greater cup inclination than 55° and an arc of cover < 10 mm. So for a short breakdown we could conclude that in both groups outliers are presented.

In comparison to the study results by De Haan *et al.* (42), we found the same issue. But because De Haan *et al.* (42) gave no information about the single values of his measurements in his study, our findings are based on an analysis of his figures and given information. Setting the limit for outliers at 1.00 µg/dl as we did in our study, there were nine outliers of chromium in the steep group but nearly equal count of ten outliers of chromium in the non-steep group in his study. For cobalt the number of outliers was nine in the steep group and three in the non-steep group. On the other hand, 65 of 74 patients (87.8%) did not have outliers of chromium and cobalt although the inclination of their acetabular cup was listed as steep. The only difference between the steep and the non-steep group was the range of outlier values. While the range of outlier values of cobalt and chromium in the non-steeply group was only 1.0 to 3.2 µg/dl, in the steep group it was 1.0 µg/dl up to 11.2 µg/dl. We had similar findings with the arc of cover, although the total number for the arc of cover groups was not given (see table 14): There were outliers in both the group with an arc of cover < 10 mm and the group with an arc of cover ≥ 10 mm but the range of outliers in the group with an arc of cover < 10 mm was wider and most patients had no metal ion outliers regardless the arc of cover of their acetabular cups.

In summary this means that most of the values remain below 1.00 µg/dl, although the acetabular cup is steeply implanted or shows an arc of cover < 10 mm (Inclination Co and Cr: 65 out of 74, Arc of cover: not exactly available).

In contrast to that fact there are also outliers of cobalt and chromium if the acetabular cup is not steeply implanted or shows an arc of cover ≥ 10 mm. Therefore we think that the significant difference in metal ion levels for steep or not steep implanted cups, published by previous studies, cannot explained only by the arc of cover or the cup inclination. This does not mean the cup inclination and the arc of cover do not have any effect on metal ion concentrations, but we think there have to be other factors that aggravate these elevations of cobalt and chromium in combination with the adjustment of prosthesis.
Further hypotheses and facts that could be responsible for these differences are discussed below in chapter 4.1.5.

Table 14: Results of De Haan *et al*. (46) respective outliers and arthroplasty adjustment

	Cup inclination				Arc of cover			
	Co		Cr		Co		Cr	
	steep	non steep	steep	non steep	<10mm	>10mm	<10mm	>10mm
Total number	74	140	74	140	n/a	n/a	n/a	n/a
Number of outliers	9	3	9	10	6	3	8	10
Range of outliers (µg/dl)	1.0-11.1	1.0-3.2	1.0-9.5	1.0-3.2	1.0-11.1	1.0-3.2	1.0-9.5	1.0-3.2
% of outliers	12.2	2.1	12.2	7.1	n/a	n/a	n/a	n/a

It is commonly accepted that the adjustment of prosthesis alignment is a basic requirement for good function and a reduction of debris. Nevertheless, our results and those of De Haan *et al*. (42) that show elevated metal ion levels in patients with correctly implanted devices and many metal ion levels within the normal range in patients with steeply implanted devices, raise the issue that reasons other than device configuration and adjustment influence metal ion levels. Considering that cup inclination and arc of cover measurements are only snapshots in time on a two plane radiograph, we should have a closer look on gait at three dimensional rotation of the hip.

4.1.2 Correlation between pre-operative metal ion levels and further measurements

We found a significant correlation between pre-operative and post-operative metal ion levels. Therefore patients with a higher pre-operative metal ion level also had higher levels at three months and one year post-operatively. To learn more about the reasons for elevated metal ion levels in serum, it is important for future studies on metal ion levels to have a look on pre-operative metal concentrations and detect the elevated ones. Furthermore, patients where pre-operatively elevated metal ion levels are detected should be investigated more intensely.

4.1.3 Differences in the duration of the running-in phase in literature

As already mentioned in the introduction, there are different time periods of running-in phase and different time points of reaching steady-state published through the literature dealing with metal ion levels after metal-on-metal THA. In the study of Heisel *et al.* (44), metal ion levels of cobalt and chromium rose up to six months post-operatively and showed an insignificant decrease thereafter. Daniel *et al.* (30) reported that there was a difference in their findings between cobalt and chromium ions. Cobalt levels rose up to six months after surgery and chromium levels up to one year. In the study of Back *et al.* (46), cobalt levels also rose up to six months, but chromium levels only up to nine months. Contrary to this the study by Iminashi *et al* (31) found no difference between the three months and the one year results. While steady state phase is already reached after one year in the previously mentioned studies, in the most recent study by deSouza *et al*. (47) cobalt and chromium ion levels increase up to 18 months after surgery. Until this study, no reported running-in phase had exceeded the one-year-limit yet.

Regarding the first results of the two-year-post-operative measurements of our study, it is conceivable that there is also a further elevation of metal ion levels after the measurements one year post-operatively. This would mean that the duration of the running-in phase in our study will probably also exceed the one-year-limit. Comparing the five studies from Heisel *et al.* (44), Daniel *et al.* (30), Back *et al.* (46), Iminashi *et al.* (31), and deSouza *et al*. (47), it can be seen that all their findings are based on different conditions (See table 16).

Table 15: Differences in the running-in phases of cobalt and chromium in literature

	Duration running-in phase cobalt	Duration running-in phase chromium
Heisel *et al.*: "Characterization of the running-in period in total hip resurfacing arthroplasty: an in vivo and in vitro metal ion analysis."	6 months	6 months
Daniel *et al.*: "Six-year results of a prospective study of metal ion levels in young patients with metal-on-metal hip resurfacings."	6 months	1 year
Back *et al.:* "How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing?"	6 months	9 months
Iminashi *et al.:* "Serum metal ion levels after second-generation metal-on-metal total hip arthroplasty."	3 months	3 months
deSouza *et al*.: "Metal ion levels following resurfacing arthroplasty of the hip. Serial results over a ten-year period"	18 months	18 months

As tables 15 and 16 show, the conditions the different authors describe differ from each other like the results that they get. All of the studies listed in table 16 have renal impairment and unilateral metal-on-metal total hip arthroplasty in common. While Daniel *et al.*, Iminashi *et al.* and Back *et al.* excluded patients with additional metal implants from their studies, deSourza *et al.* and Heisel *et al.* did not.

Additionally, Daniel *et al*. excluded all patients with other diagnoses than osteoarthritis; Iminashi *et al*. excluded patients with metal allergy and pregnant patients and Back *et al*. excluded patients whose metal ion levels could be affected by additional factors as described in table 16. Other differences exist between the femoral head size of the arthroplasties in use and the inclusion of patients who had bilateral surgery like in the study of deSourza *et al*.. These inconsistences in patients selection, exclusion criteria, different head diameters, probably cause the differences between the findings. At least for the influence of different head diameters Leslie *et al.* (34) state that an increasing head diameter would shorten the running-in phase as mentioned in the introduction.

Table 16: Different conditions in studies about the running-in phases

	Conditions				
	Number patients	Head size (mm)	Unilateral / bilateral	Renal function	Exclusion criteria
Heisel *et al.*	15	mean 48	unilateral	normal	no further
Daniel *et al.*	24	50 and 54	unilateral	normal	additional metallic implant, indication other than osteoarthritis
Back *et al.*	20	38-58	unilateral	normal	additional metallic implant, occupational exposure to Co or Cr, taking proprietary multivitamins and minerals
Iminashi *et al.*	33	36	unilateral	normal	additional metallic implant, metal allergy, pregnancy
deSouza *et al.*	52	n/a	bilateral	normal	Occurring of sudden rise in metal ion levels (exclusion from statistical analysis)

4.1.4 Insignificant higher levels in ASR XL Head System compared to ASR Resurfacing System

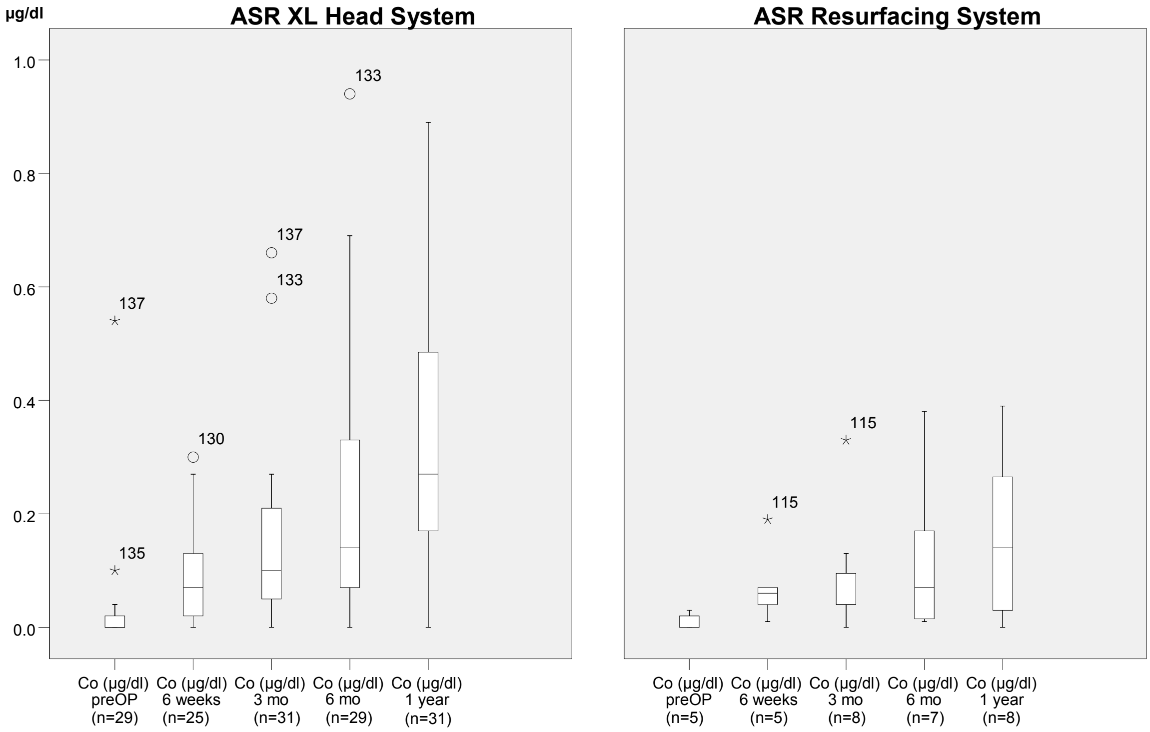

Figure 18: Co ions in the two subgroups ASR XL Head System and ASR Resurfacing System. This figure shows slightly increased Co levels in the ASR XL Head System group compared to the ASR Resurfacing System group (not significant) with outliers in the ASR XL Head System group appearing after six months and after one year. (Out of range: 105 = 2.81 at 6 mo; 137 = 3.66 at 1 year; 117 = 5.85 at 1 year; all in the left figure)

The tendency of higher levels in the ASR XL Head System compared to ASR Resurfacing System revealed in our study (see figure 14 and 15) has also been detected by other authors. Garbuz *et al.* (36) actually reported significantly elevated serum levels of cobalt and chromium in large-head metal-on-metal THAs compared to resurfacing. They explained that the additional modular junction between the femoral head and stem may be responsible for this elevation. Already Jacobs *et al.* (17) suspected the modular junction to be another source of metal ion release due to fretting and corrosion. Against this background, it is interesting that all the patients with outliers of our study have implanted the ASR XL Head System.

Although the difference between the ASR XL Head System and the ASR Resurfacing System in our study is not significant, this is a finding we will have to take into account in further evaluations of this study population.

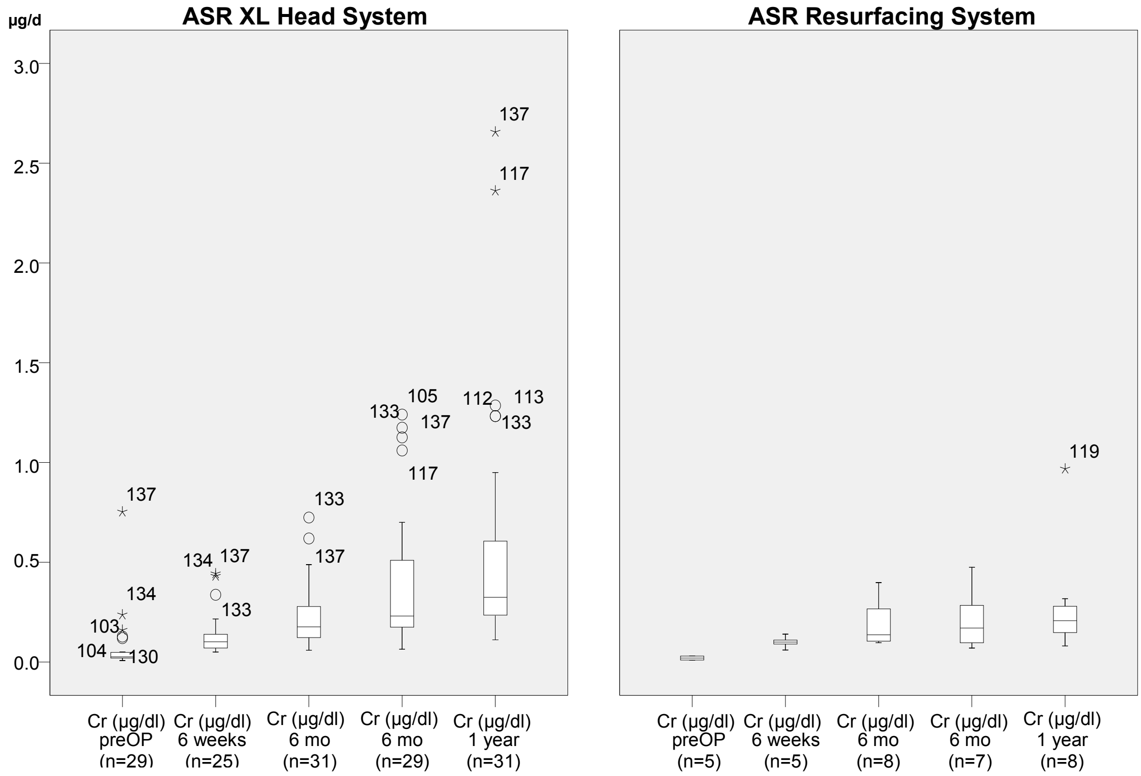

Figure 19: Cr ions in the two subgroups ASR XL Head System and ASR Resurfacing System. This figure also shows slightly increased Cr levels in the ASR XL Head System group compared to the ASR Resurfacing System group (not significant) with outliers in the ASR XL Head System group appearing after six months and after one year.

4.1.5 Hypotheses and facts for additional influences on metal ion level

Additionally to influencing factors on metal ion level which derive from the implant or its implantation adjustment, we found several facts in literature and considered several hypotheses that could influence metal ion levels as well.

Meltzer *et al.* (48) found an association between low ferritin levels and elevated cobalt levels in blood in 448 healthy, menstruating, non-smoking women. She also underlines the fact of “complexities in the body's handling” with the investigated metal ions including cobalt.

Patlar *et al.* (49) supplemented Taekwondo athletes with Vitamin E and revealed significantly increased metal ion levels for chromium and cobalt under this additional nutrition in their study group.

Davis-Whitenack *et al.* (50) investigated the influence of IL-1α on chromium levels in rats. They observed a significant decrease of chromium levels in the rats treated with IL-1α and interpreted this as a consequence of the interleukin-induced increase of prostaglandins and the resulting deprivation of gastric acid. This is an example of how the immune system can influence metal ion levels as IL-1α is produced mainly in monocytes and macrophages.
Another potential influence that has been reported is diabetes mellitus. Zhao *et al.* (51) have seen significantly lower chromium levels in patients with diabetes.
We also should focus on the anteversion of the acetabular component. Langton *et al.* (52) found a significant increase of cobalt and chromium levels in the serum of patients with an anteversion of more than 20°.

Table 17: Factors influencing metal ion levels and way of influence

Factors influencing metal ion level	Way of influence
↓ ferritin levels	↑ cobalt levels
Vitamin E supplementation	↑ cobalt and chromium levels
IL-1α treatment (in rats)	↓ chromium levels
Diabetes mellitus	↓ chromium levels
Anteversion of the acetabular component >20°	↑ cobalt and chromium levels

A not proven hypothesis questions whether drugs the patients have to take may compete with cobalt or chromium levels for albumin binding. Both cobalt and chromium interfere with albumin. How these possible changes in binding relation to albumin could affect the clearance of metal ions or their detectability in serum should be investigated, although we are aware about the complexity of this research question.
Another hypothesis would be that in some people the affinity or phagotization rate of macrophages for metal ions is higher than in other people. Such an increased phagotization rate would withdraw more metal ions and make them less detectable in serum metal ion measurement and therefore lower the metal ion serum levels.
The results of Heisel *et al* (44) lead to further hypotheses. He revealed that there is a delayed running-in period in simulator measurements compared to in-vivo measurements.

He explained this would probably be due to differences in distribution, accumulation, and excretion in patients. And because all of these factors can also be different among patients, they all can have influence on metal ion levels in-vivo. Therefore, renal function could be an additional factor influencing metal ion levels in the serum. There is the possibility that in some patients the excretion capability for metal ions could be lower than in other patients. In patients with a lower excretion capability, metal ions would stay in the blood circulation longer and accumulate and would therefore be measurable at a higher concentration than in patients with a higher excretion capability for metal ions.

But if excretion could possibly have an effect on metal ion levels, intake could also have an effect. This additional intake could be co-medications, nutrition, or drinking water rich in cobalt or chromium.

These are only examples of possible additional influences on metal ion levels in the serum. It could not be a complete listing of factors but shows that metal ion levels not only depend on metal devices and their adjustment.

Table 18: Hypotheses for additional factors influencing metal ion level

Hypotheses for additional factors influencing metal ion level
Drug interaction with metal ions (competition for albumin binding)
Affinity/phagotization rate for metal ions
Renal excretion capability for metal ions
Additional intake (co-medication, nutrition, drinking water)

4.2 Outliers

We found several possible reasons in our outlier patients for their elevated metal ion levels. They all had in common that they have ASR XL Head Systems implanted.

Patient 1 (hip 105)

We came up with four possible general reasons for elevated metal ion levels in general in patient 1. The first is that she had to take a lot of drugs because of the resection of her colon and we considered three of them to possibly have an effect on cobalt or chromium levels. The ones we referred to are the magnesium supplementation (Magnosolv®), the calcium and Vitamin D3 supplementation (Cal-D-Vita®) and the Vitamin B1, B6 and B12 supplementation (Neuromultivit®).

The magnesium supplementation and the supplementation of calcium and Vitamin D3 could have an influence because of possible interactions on albumin binding level. Vitamin B1, B6 and B12 supplementation even contains cobalt in form of Vitamin B12, cobalamin. Maybe a temporary overdose of these drugs could have led to the punctual raise in metal ion levels after six months post-operatively, although there is no evidence that magnesium supplementation, calcium and Vitamin D3 supplementation or Vitamin B1, B6 and B12 supplementation could raise metal ion level in the serum to that extent (2.81 µg/dl cobalt and 1.24 µg/dl chromium; 0.08 µg/dl cobalt and 0.16 µg/dl chromium one week post-operatively; 0.78 µg/dl cobalt and 0.32 µg/dl chromium one year post-operatively). Additionally, we detected temporary clicking at the follow-up six months post-operatively which also could have an effect on raising metal ion levels at this time. The fact that the inclination of the implanted cup was greater than 55° and the arc of cover was less than 10 mm could be a reason for elevated metal ion levels in general but that it is a reason for this punctual raise is unlikely.

Patient 2 (hip 117)

At this patient we only noticed a cup inclination steeper than 55° and an arc of cover less than 10 mm that could have influenced serum levels of cobalt and chromium.

Patient 3 (hip 133)

This patient had a cup inclination less than 55° and an arc of cover more than 10 mm in contrast to patients 1 and 2. This is another indication that not only the adjustment and the head size for their selves were responsible for elevated metal ion levels. Maybe the suspected rheumatic disease which occurred seven months after surgery has an effect in an immunological way, for example by increasing the permeability of the blood-tissue-barrier and therefore promoting metal ion transfer from the joint to the blood circulation. It is not clear whether the occasional squeaking the patient reported after long walks is affecting his high metal ion levels. We could not find any study that investigated the correlation between squeaking and metal ion levels in the serum.

Patient 4 (hip 137)

Patient 4 has undergone bilateral metal-on-metal hip resurfacing implanting the ASR Resurfacing System. It seems logical that this would have to be a reason for his outliers in cobalt and chromium measurement, because metal ion levels have already been elevated from the first metal-on-metal hip resurfacing. But we have additional three patients in our study who also had bilateral ASR XL Head Systems and all of them had metal ion levels in the same range like patients with only one device. This indicates that bilateral implanted large head metal-on-metal hip arthroplasties it is not assured to cause high metal ion levels.

The cup inclination of his first implanted ASR Resurfacing System (49.7° measured one week post-operatively) was even steeper than the second one (43.1° measured one week post-operatively). But after the first surgery he had no outlier metal ion levels. Both acetabular cups were implanted with an inclination less than 55° and an arc of cover greater than 10 mm.

5 Conclusion

Regarding the results of our study we could not affirm a statistical significant correlation between increased metal ion levels for cobalt or chromium after implantation of metal on metal ASR Resurfacing System or metal-on-metal large-head ASR XL Head System at one year follow-up. To do so, our groups of steeply-inclined acetabular cups and acetabular cups with an arc of cover < 10 mm were too small. Therefore we could neither affirm nor refute previous studies which found a correlation between the cup inclination or the arc of cover and serum metal ion levels of cobalt and chromium.

But nevertheless, a carefully reviewing our own study and the recent literature lead us to following suggestions to improve further investigations on metal ion release from metal-on-metal hip arthroplasties.

5.1 Suggestions for further investigations

Regarding our results and results in the literature, further studies should be more aware of additional factors that have influence on metal ion levels. In most studies – our study included – the focus is only on the implanted devices with their adjustment, tribological characteristics or the type of device used. They disregard the effect on the arthroplasty from the body’s side. This could be done by taking additional possibilities of influence into consideration while elaborating the inclusion and exclusion criteria. Some of them we have already mentioned above. According to the fact that certainly not all effects on metal ion levels are known yet, further research should have a closer look on patients with outliers in order to detect irregularities in these. Maybe a review of a large number of such patients with outliers should be investigated. Especially these extraordinary high levels of cobalt and chromium are clinically relevant and associated with negative effects like pseudotumours.

Additional to the patients with outliers, the awareness of a significant correlation between pre-operative cobalt and chromium levels with the levels after three months and one year should lead to a further investigation of patients with pre-operatively elevated metal ion levels in future studies. This could also help to improve the understanding of influencing factors on metal ion levels in serum others than from the component’s point of view.

These investigations should also look at effects on molecular, immunological and genetic level. According to our review of recent literature it seems likely that some patients are due to current unknown reasons more sensitive to adjustment of the metal devices and their tribological characteristics, and metal ion release.
The discrepancy between a few outliers in the steeply-inclined group and the majority of the patients in the steeply-inclined group within “normal” metal ion ranges reported in the study of De Haan *et al.* (42) serves as an example.
Another suggestion from our side would be to give attention to drugs the patients are taking during the study. Sridevi *et al.* (53) reported a rapid in vitro screening of drug-metal interactions. They investigated this screening test amongst several essential metal ions. Maybe this test could be used for patients who are taking medication or supplementary nutrition planned to be included into a metal ion related study. Drugs that show an interaction with chromium and possibly cobalt could be tested for their clinical relevance. If a clinical relevance is verified, patients that take these drugs would have to be excluded or continuously monitored.

Although the difference we found between metal ion levels in ASR XL Head Systems and ASR Resurfacing Systems is not significant, we recommend a separated look on these two devices. We recommend this according to findings by Garbuz *et al*. (36).

At last we recommend appointing the time of the steady-state phase later than after one year as a precaution in studies that only work with steady-state values. Regarding the different results in literature and the preliminary data in our study with continuing increase of metal ion levels after one year it seems not to be sure yet if the running-in phase is over after one year. The most recent study by deSourza *et al.* (47) corroborates this assumption.

5.2 General clinical consequences

In the context of the international recall of the ASR Resurfacing System and the ASR XL Head System by DePuy, the Department of Orthopaedics and Orthopaedic Surgery of the Medical University of Graz has started to identify and invite patients with an implanted ASR system for a control examination. We have taken current radiographs, blood samples for cobalt and chromium determination and performed clinical examination inclusive scores. Accordingly to the sequence of operation diagram by DePuy, we are filtering patients with elevated metal ion levels or symptomatic hips for further investigation via MRI scan. The analysis of these data is still in progress.

Despite this recall, reviewing the literature we could not find any proven reason that would justify the abandoning of the metal-on-metal bearing in total hip arthroplasty in general. In a study including 4226 hips by Langton *et al.* (54) the ASR Resurfacing System showed the highest failure rates in comparison to the Conserve Plus system (CP) and the Birmingham Hip Resurfacing System (BHR) (ASR: 9.8% at five years, CP: < 1% at five years, BHR: 1.5% at ten years). That shows that parallel to this big recall by DePuy there are still resurfacing system with good outcome. The reasons for the poor outcome of the ASR Resurfacing System and the ASR XL Head System are still unknown and under investigation. Also the incidence of local tissue reactions in general seems to be low. Engh *et al.* (55) reported only three local tissue reactions out of 828 patients (945 hips).

Because of the lack of long-term results, we recommend to use large-head THAs with metal-on-metal bearing and metal-on-metal resurfacing systems only in constant touch with continuous measurements of metal ion levels in the serum and continuously clinical and radiographic follow-up for patients. If metal ion levels outside the normal range are detected, a revision should be considered because of the danger of occurring side effects. Part of this consideration should also be clinical appearance, MRI (pseudotumours) and x-ray findings going along with these elevated metal ion levels. Also helpful for such a consideration would be the detection of a threshold level for metal ions when a revision is advised because of the high risk of occurring side effects although there are no clinical findings, yet.

Based on our results, we assume that there is no single correlation between cup inclination, arc of cover and increased metal ion levels. Nevertheless, the surgeon has to pay attention to the adjustment, because it can affect the metal ion level at least in some patients.

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Appendix - CRF

Case Report Form

Prospektive Studie zur Metallionenspiegelmessung im Serum bei Patienten vor und nach Implantation einer Hüfttotalendoprothese mit Metall Metall (MoM) Gleitpaarung

Vorname:

Nachname: Patientenetikette

Geb.datum:

Geschlecht: □ weiblich □ männlich

Initialen: ___________ (Vorname Nachname)

Patientenfortlaufnummer: ___________

Hüftseite: □ links □ rechts

Datum Studieneinschluss: _____ / _____ / ___________ TT MM JJJJ

Körpergröße (m): ___________

Körpergewicht (kg): ___________

Art der HTEP: □ DePuy-ASR-Hüftoberflächenersatz □ DePuy-ASR-Großkopfsystem

Anzahl HTEP (davon in der Studie): _____(___)

Größe/Durchmesser Femurimplantat: ___ /____mm

Größe/Durchmesser Pfannenimplantat: ___ /____mm

OP-Termin: ____/_____/___________ TT MM JJ

Einschlusskriterien

- Alter 18-65 ☐ ja ☐ nein
- Primäre Osteoarthritis ☐ ja ☐ nein

nur DePuy-ASR-Großkopfsystem:

- Knochen-Morphologie und –Qualität, die eine Standard-Me/Me-Oberflächenversorgung nicht zulässt ☐ ja ☐ nein
- Für eine zementfreie Pfanne und ein großes Me/Me-Gleitlager geeignet ☐ ja ☐ nein

Auschlusskriterien

- Nierenfunktion beeinträchtigt ☐ ja ☐ nein
- Metallsensibilität ☐ ja ☐ nein
- Infektiöse, hochansteckende Krankheiten ☐ ja ☐ nein
- Schwangerschaft o. geplanter Schwangerschaft binnen 2 Jahren nach OP ☐ ja ☐ nein
- Drogen-/Alkoholabhängigkeit ☐ ja ☐ nein
- Psychische Erkrankungen ☐ ja ☐ nein
- Teilnahme an einer klinischen Studie innerhalb der letzten 6 bzw. 12 Monate ☐ ja ☐ nein
- Corticosteroide Behandlung ☐ ja ☐ nein
- Aktive oder kürzliche Gelenkssepsis ☐ ja ☐ nein
- Signifikante Osteoporose und schlechte Knochenqualität ☐ ja ☐ nein
- Merkliche Atrophie und Deformitäten am oberen Femur, unausgereiftes Skelett, Verlust an Muskel oder neuromuskoläre Krankheiten ☐ ja ☐ nein
- Anatomischer CCD-Winkel unter 120° ☐ ja ☐ nein
- Bestrahlungen der betroffenen Hüfte ☐ ja ☐ nein

Messergebnisse Metallionen

	Datum	**Cobalt (µg/dl)**	**Chrom (µg/dl)**
PräOP			
6 Wochen			
3 Monate			
6 Monate			
1 Jahr			
2 Jahre			

Messergebnisse Nierenparameter

	Datum	**Kreatinin (mg/dl)**	**Harnstoff (mg/dl)**	**Harnsäure (mg/dl)**
PräOP				
1 Woche				
6 Wochen				
3 Monate				
6 Monate				
1 Jahr				
2 Jahre				

Messergebnisse CRP und RSH

	Datum	**CRP**	**RSH**
PräOP			
1 Woche			
6 Wochen			
3 Monate			
6 Monate			
1 Jahr			
2 Jahre			

Radiologische Auswertung

- Beinlängenausgleich ☐ ja ☐ nein
- Wenn ja, wie viel: _________cm ☐ li ☐ re

- Zusätzliche Metallimplantate im Körper ☐ ja ☐ nein
- Wenn ja, welche:

____

	Datum	**Inklination**	**Reelle Inklination**	**Stem-shaft-angle**	**Stem-neck-alignment**	**Arc of cover (mm)**
PräOP						
1 Woche						
6 Wochen						
3 Monate						
6 Monate						
1 Jahr						
2 Jahre						

Sonstige Ereignisse während der Studie (OP, Revision, Implantat, u.a.):

____

____

____

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Appendix - Results of measurement

Pat.#	Sex	Nr. of hips	ASR XL Head system	ASR Resurfacing System	Age	Weight (kg)	Height (m)	BMI	Head size (mm)	Cup size (mm)
101	f	1	0	1	52,5	72	1,78	22,72	46,0	52
102	f	1	1	0	49,1	78	1,70	26,99	43,0	48
103	f	1	1	0	53,6	70	1,67	25,10	43,0	48
104	f	1	1	0	42,9	87	1,69	30,46	41,0	46
105	f	1	1	0	60,8	100	1,63	37,64	41,0	46
106	f	1	1	0	56,8	67	1,69	23,46	45,0	50
107	m	1	0	1	45,2	76	1,76	24,54	49,0	56
108	m	1	1	0	50,9	106	1,74	35,01	49,0	56
109	m	2	1	0	51,1	82	1,73	27,40	47,0	54
110	f	2	1	0	53,8	86	1,68	30,47	47,0	54
111	f	1	1	0	54,9	82	1,63	30,86	45,0	50
112	f	2	1	0	50,1	72	1,57	29,21	43,0	48
113	f	2	1	0	50,1	72	1,57	29,21	43,0	48
114	m	1	1	0	60,4	81	1,68	28,70	46,0	52
115	m	1	0	1	47,0	75	1,77	23,94	51,0	58
116	m	2	1	0	49,6	95	1,80	29,32	49,0	56
117	f	1	1	0	59,0	60	1,56	24,65	41,0	46
118	f	1	1	0	59,2	78	1,63	29,36	46,0	52
119	m	1	0	1	49,3	80	1,75	26,12	49,0	56
120	f	1	1	0	44,8	54	1,58	21,63	41,0	46
121	m	1	0	1	33,0	77	1,84	22,74	51,0	58
122	m	1	1	0	60,3	69	1,72	23,32	47,0	54
123	f	2	1	0	54,4	84	1,68	29,76	47,0	54
124	m	1	0	1	56,9	84	1,74	27,74	51,0	58
125	f	1	0	1	36,4	58	1,65	21,30	45,0	50
126	f	1	0	1	53,1	78	1,70	26,99	46,0	52
127	m	1	1	0	53,1	81	1,79	25,28	49,0	56
128	m	1	1	0	58,8	73	1,80	22,53	51,0	58
129	f	1	1	0	44,0	63	1,68	22,32	45,0	50
130	m	1	1	0	39,2	78	1,78	24,62	45,0	52
131	f	1	1	0	47,0	74	1,56	30,41	43,0	48
132	m	1	1	0	60,0	100	1,92	27,13	47,0	54
133	m	1	1	0	56,3	76	1,76	24,54	47,0	54
134	m	2	1	0	50,5	93	1,80	28,70	46,0	52
135	m	1	1	0	46,1	75	1,62	28,58	51,0	58
136	m	1	1	0	48,0	98	1,76	31,64	47,0	54
137	m	2	1	0	52,2	80	1,73	26,73	47,0	54
138	m	1	1	0	48,6	80	1,75	26,12	49,0	56
139	m	1	1	0	42,5	86	1,79	26,84	49,0	56
141	m	1	1	0	58,3	105	1,82	31,70	47,0	54

m = male
f = female
0 = no
1 = yes

Pat.#	Co (µg/dl) preOP	Co 6 weeks	Co 3 mo	Co 6 mo	Co 1 year	Cr (µg/dl) preOP	Cr 6 weeks	Cr 3 mo	Cr 6 mo	Cr 1 year	Creatinine (mg/dl) preOP	Creatinine 1 week	Creatinine 6 weeks	Creatinine 3 mo	Creatinine 6 mo	Creatinine 1 year	Urea (mg/dl) preOP	Urea 1 week	Urea 6 weeks	Urea 3 mo	Urea 6 mo	Urea 1 year
101	-	-	0,04	0,26	0,27	-	-	0,160	0,290	0,317	0,89	0,59	-	-	-	0,89	32	16	-	-	-	29
102	-	-	0,10	0,28	0,22	-	-	0,320	0,310	0,310	0,82	0,59	-	-	-	-	16	14	-	-	-	-
103	0,03	0,12	0,27	0,28	0,49	0,120	0,130	0,270	0,480	0,950	0,90	0,67	-	-	-	0,86	30	19	-	-	-	37
104	0,04	-	0,06	0,08	0,43	0,160	-	0,270	0,450	0,750	0,68	0,59	-	-	-	-	28	16	-	-	-	-
105	0,00	0,05	0,08	2,81	0,78	0,030	0,070	0,160	1,240	0,320	0,77	0,59	-	-	-	-	42	20	-	-	-	-
106	-	-	0,11	0,12	0,16	-	-	0,130	0,190	0,280	0,88	0,69	-	-	-	0,86	29	33	-	-	-	34
107	-	0,01	0,00	0,01	0,00	-	0,060	0,100	0,070	0,099	0,94	0,85	-	-	-	0,98	36	24	-	-	-	32
108	0,00	0,00	0,05	0,03	0,04	0,020	0,080	0,150	0,160	0,190	0,78	0,62	-	-	-	-	39	28	-	-	-	31
109	0,02	-	0,16	0,06	0,18	0,050	-	0,280	0,230	0,457	0,75	0,68	-	-	-	0,73	30	14	-	-	-	24
110	0,01	0,07	0,02	-	-	0,020	0,070	0,070	-	-	0,77	0,91	-	-	-	0,75	32	40	-	-	-	30
111	0,00	0,09	0,13	0,13	0,27	0,040	0,120	0,120	0,140	0,221	0,70	0,72	-	-	-	0,80	31	21	-	-	-	26
112	0,00	0,02	0,21	0,37	0,69	0,020	0,080	0,250	0,510	1,232	0,61	0,57	-	-	-	0,64	39	23	-	-	-	30
113	0,00	0,02	0,21	0,37	0,69	0,020	0,080	0,250	0,510	1,232	0,61	0,57	-	-	-	0,64	39	23	-	-	-	30
114	0,00	-	0,10	0,10	0,18	0,020	-	0,140	0,220	0,317	0,93	0,94	-	-	-	1,02	29	21	-	-	-	37
115	0,00	0,19	0,33	-	0,22	0,030	0,110	0,310	-	0,197	0,86	0,86	-	-	-	1,04	34	20	-	-	-	28
116	0,00	0,13	0,14	0,17	0,27	0,020	0,190	0,190	0,210	0,431	1,23	0,95	-	-	-	0,88	46	39	-	-	-	33
117	0,00	0,00	0,09	0,55	5,85	0,030	0,060	0,410	1,060	2,361	0,46	0,56	-	-	-	0,53	19	25	-	-	-	19
118	-	-	0,04	0,06	0,02	-	-	0,120	0,180	0,126	0,65	0,67	-	-	-	0,86	16	24	-	-	-	32
119	0,00	0,06	0,04	0,08	0,39	0,030	0,090	0,110	0,170	0,968	0,97	0,92	-	-	-	1,02	48	34	-	-	-	36
120	0,03	0,13	0,05	0,09	0,00	0,050	0,120	0,110	0,300	0,324	0,66	0,55	-	-	-	0,68	24	13	-	-	-	29
121	0,02	-	0,06	0,01	0,00	0,020	-	0,113	0,100	0,081	0,99	0,99	-	1,11	1,14	0,97	15	21	-	20	28	24
122	0,00	0,03	0,06	0,00	0,21	0,010	0,050	0,078	0,064	0,166	0,87	0,86	-	0,92	0,91	1,01	17	32	-	24	26	24
123	0,02	0,08	0,14	0,16	0,31	0,030	0,120	0,245	0,275	0,616	0,89	0,80	-	0,78	0,75	0,79	39	37	-	31	30	42
124	0,03	0,07	0,04	0,02	0,26	0,010	0,100	0,097	0,094	0,216	1,03	0,92	-	0,77	0,77	0,87	29	24	-	24	24	27
125	0,02	0,04	0,04	0,07	0,06	0,010	0,140	0,223	0,278	0,198	0,76	0,83	0,77	0,78	0,79	0,87	27	17	31	35	21	22
126	-	-	0,13	0,38	0,06	-	-	0,398	0,475	0,242	0,85	0,93	-	0,87	0,94	0,98	37	36	-	43	38	43
127	0,00	0,00	-	0,04	0,12	0,010	0,088	-	0,179	0,163	1,03	1,11	1,05	-	1,16	1,05	44	30	45	-	49	33
128	0,00	0,11	0,04	0,15	0,36	0,017	0,060	0,085	0,169	0,249	0,94	0,98	0,93	0,96	0,97	1,05	36	24	27	25	29	31
129	0,00	0,07	0,00	0,00	0,19	0,012	0,050	0,112	0,175	0,317	0,79	0,69	0,72	0,73	0,70	0,84	33	15	43	26	25	28
130	0,03	0,30	0,26	0,33	0,34	0,128	0,216	0,429	0,700	0,548	0,84	0,74	0,77	0,84	0,82	0,95	27	21	28	29	38	35
131	0,00	0,03	0,00	0,14	0,15	0,048	0,139	0,154	0,151	0,192	0,60	0,56	0,54	0,58	0,57	0,83	33	29	30	42	43	67
132	0,00	0,20	0,22	-	0,05	0,034	0,203	0,346	-	0,112	1,11	0,73	0,90	0,93	-	0,85	55	15	33	31	-	31
133	0,00	0,26	0,58	0,94	0,89	0,027	0,337	0,724	1,174	1,285	0,82	0,92	0,79	0,82	0,82	0,77	24	41	28	26	26	29
134	0,04	0,27	0,23	-	0,40	0,237	0,431	0,488	-	0,378	1,00	1,05	0,88	0,94	-	-	33	23	33	27	-	-
135	0,10	0,08	0,21	0,39	0,48	0,026	0,100	0,145	0,558	0,552	0,80	0,73	0,89	0,78	0,91	0,87	47	21	41	39	39	56
136	0,00	0,00	0,00	0,07	0,07	0,008	0,101	0,059	0.077	0,111	0,95	0,90	1,07	0,95	1,01	-	27	28	39	31	30	-
137	0,54	0,23	0,66	0,69	3,66	0,753	0,443	0,619	1,126	2,656	0,81	0,77	0,79	0,76	0,78	-	38	17	30	25	28	-
138	0,00	0,00	0,15	0,26	0,30	0,007	0,060	0,276	0,321	0,439	0,98	0,87	0,90	0,88	0,90	-	29	26	29	32	29	-
139	0,00	-	0,02	0,13	0,19	0,023	-	0,125	0,216	0,290	0,95	0,85	-	0,83	-	0,94	37	30	-	21	-	26
141	0,00	0,04	0,08	0,07	0,55	0,013	0,134	0,176	0,160	0,596	1,03	0,92	1,22	1,05	-	-	21	16	26	27	-	-

Pat.#	Uric acid (mg/dl) preOP	1 week	6 weeks	3 mo	6 mo	1 year	CRP preOP	1 weeks	6 weeks	3 mo	6 mo	1 year	Inclination (°) 1 week	3 mo	1 year	Arc of cover (mm) 1 week	3 mo	1 year
101	4,9	2,9	-	-	-	4,6	2,6	70,4	4,1	2,0	5,4	1,6	35,1	36,9	39,2	16,9	16,1	15,8
102	3,7	4,3	-	-	-	-	2,9	18,8	-	2,6	2,1	2,1	-	-	-	-	-	-
103	5,0	-	-	-	-	4,7	0,0	8,6	0,0	0,0	0,0	0,0	60,3	54,4	59,6	6,3	8,3	6,4
104	5,7	-	-	-	-	-	5,7	50,5	-	4,4	5,0	5,4	54,5	52,7	52,8	8,8	8,4	8,8
105	6,0	4,3	-	-	-	-	0,0	21,4	0,0	0,0	0,0	19,6	59,8	61,3	60,4	5,4	5,2	5,7
106	3,9	2,6	-	-	-	4,4	2,7	18,7	-	1,6	0,0	1,0	43,2	43,5	45,8	13,2	13,9	13,0
107	5,1	-	-	-	-	5,3	1,4	25,2	3,1	1,0	0,0	0,0	44,9	43,4	45,3	14,3	14,9	14,1
108	7,3	-	-	-	-	6,7	2,8	44,9	4,3	2,5	3,1	4,7	45,2	44,7	-	14,3	14,6	-
109	7,0	3,7	-	-	-	6,1	7,3	161,7	-	17,1	16,1	13,6	49,7	50,0	50,0	11,6	11,0	12,0
110	5,4	5,6	-	-	-	6,4	5,6	39,1	10,4	5,3	4,8	6,0	34,0	33,7	34,4	18,0	18,1	17,9
111	4,1	2,2	-	-	-	4,4	2,3	67,4	3,3	5,5	6,8	5,8	37,2	37,2	37,3	16,1	16,1	15,7
112	4,9	3,1	-	-	-	4,3	6,4	40,8	5,9	3,7	4,8	6,1	34,7	37,0	36,3	16,2	13,3	15,0
113	4,9	3,1	-	-	-	4,3	6,4	40,8	5,9	3,7	4,8	6,1	35,8	37,9	35,9	15,8	15,5	15,6
114	6,1		-	-	-	5,2	8,5	25,0	-	12,6	6,1	9,7	35,5	36,0	36,8	16,5	16,3	16,1
115	7,7	5,5	-	-	-	8,4	1,3	21,7	2,5	-	0,0	4,0	35,9	35,4	34,9	19,2	19,0	19,1
116	7,1	6,0	-	-	-	6,7	1,5	78,1	2,0	1,3	0,0	10,2	53,8	54,5	52,4	10,1	10,0	10,5
117	10,4	5,6	-	-	-	9,2	2,2	33,3	5,5	8,6	8,7	4,3	52,3	55,6	56,0	8,2	8,3	7,2
118	4,1		-	-	-	4,8	2,2	95,6	-	1,7	1,6	2,8	49,8	53,4	51,5	11,1	10,3	11,1
119	5,7	4,5	-	-	-	4,8	1,2	40,5	0,0	0,0	0,0	1,8	36,6	35,7	35,3	17,6	17,7	18,0
120	4,9		-	-	-	4,5	6,0	38,3	16,9	3,3	9,4	2,3	42,5	43,4	42,4	12,3	12,3	12,4
121	3,7	4,8	-	7,4	6,6	6,5	45,7	111,7	-	20,3	32,5	17,5	-	38,4	37,5	-	17,2	16,7
122	5,1	5,2	-	7,2	6,7	6,3	1,5	142,0	2,6	0,0	1,0	0,0	30,4	30,7	-	19,9	19,9	-
123	-	-	-	5,1	6,4	6,3	4,3	88,1	7,4	4,2	6,0	5,0	42,4	42,3	40,6	15,3	15,3	15,4
124	6,0	5,3	-	6,2	6,2	6,1	1,1	72,3	3,1	1,5	1,5	1,2	60,0	61,2	59,3	7,7	7,0	8,2
125	4,3	2,7	4,3	3,7	4,2	4,2	1,1	55,4	1,9	0,0	1,3	1,2	53,2	57,5	54,9	10,1	9,0	9,3
126	6,6	5,2	-	6,6	6,3	6,2	1,1	29,9	-	1,2	1,2	0,0	43,8	44,1	42,6	14,6	14,3	14,6
127	7,4	4,9	7,7	-	7,6	7,8	1,0	95,1	10,2	-	1,5	2,6	37,1	18,3	17,3	17,1	18,3	17,3
128	5,6	4,3	6,2	6,2	6,3	6,6	0,0	94,2	1,3	0,0	1,0	0,0	49,7	50,1	50,,8	12,0	11,7	12,0
129	3,0	2,7	3,6	3,3	3,8	3,4	3,7	64,8	13,8	13,8	4,7	4,7	46,1	47,0	47,4	12,3	12,0	12,1
130	108,0	-	6,1	5,2	5,0	4,7	1,0	47,9	2,6	3,0	1,9	4,6	41,4	42,2	42,0	13,9	13,9	14,7
131	4,6	2,9	4,8	3,9	3,6	4,4	2,0	96,8	2,3	2,1	3,2	1,8	50,5	50,7	50,2	10,2	10,2	10,1
132	6,2	4,1	6,6	6,7	-	5,8	1,9	120,7	4,9	8,7	-	5,7	46,9	51,3	-	12,5	11,1	-
133	5,1	4,2	6,5	5,8	5,8	4,7	1,2	28,7	1,8	2,8	2,8	0,0	46,2	47,4	46,5	12,9	13,0	13,1
134	7,5	6,9	6,7	7,7	-	-	1,5	31,6	10,2	1,4	-	-	42,8	44,1	44,6	13,6	14,0	14,0
135	5,6	3,1	4,7	5,8	6,3	5,6	1,7	144,1	4,3	26,5	6,1	9,4	50,0	51,1	50,3	12,5	11,5	12,2
136	6,7	5,0	6,5	7,7	8,1	-	1,3	57,0	1,4	0,0	1,2	-	35,1	36,4	36,8	15,1	17,5	17,1
137	5,8	3,7	6,7	8,2	7,0	-	18,3	222,4	28,9	32,5	15,2	-	43,1	44,8	44,4	15,1	14,0	14,9
138	6,5	5,1	6,7	6,0	6,7	-	10,7	121,1	19,8	4,6	19,8	-	-	44,0	43,5	-	13,9	14,7
139	7,4	5,9	-	7,0	-	6,3	1,2	123,1	-	1,0	1,1	-	43,0	43,7	-	15,6	14,6	-
141	5,8	-	6,6	6,5	-	-	0,0	37,8	6,6	14,8	-	-	44,0	41,9	42,7	13,9	15,2	14,4

Appendix - Curriculum vitae

Personal data

Surname:	Trennheuser
First name:	Matthias
Address:	Brockmanngasse 57
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Phone:	+43-699-81129247
Email:	trenn_m@web.de
Date of birth:	08.04.1986
Birthplace:	D-66740 Saarlouis

Education

Sept. 1992 – Jun. 1996:	Grundschule im Vogelsang, Saarlouis (Elementary)
Sept. 1996 – May 2005:	Gymnasium am Stadtgarten, Saarlouis (High school) graduated with "Abitur" in April 2005
Aug. 2005 – Sept. 2005:	Two-month care internship at the surgery ward of the DRK-Krankenhaus Saarlouis
Since Oct. 2005:	Human medicine studies at the Medical University of Graz
Jul.-Aug. 2007:	4-week clinical elective in general, abdominal and vascular surgery at the Krankenhaus der Barmherzigen Brüder in Treves
Feb. 2008:	2-week clinical elective at the orthopaedic surgery practice Dr. med. Martin Trennheuser in Wadgassen
Aug.-Sept. 2008:	4-week clinical elective in cardiology of the Herz Zentrum Saar
Jul.-Aug. 2009:	3-week clinical elective at the Department of Orthopaedic Surgery, Medical University of Graz
Feb. 2010:	4-week clinical elective at the Department of Orthopaedic Surgery at the Marienhaus Klinikum St. Elisabeth Klinik

Jul. 2010: 4-week clinical elective at the Department of Infectious Disease at the UMKC School of Medicine in Kansas City, Missouri (USA)

Oct.-Dec. 2010: 2nd subject group of the "Praktisches Jahr": Neurology at the Department of Neurology, Medical University of Graz

Dec. 2010-April 2011: 1st subject group of the "Praktisches Jahr": Trauma Surgery at the Department of Trauma Surgery, Medical University of Graz

May-Jun. 2011: Clinical elective in General Medicine at Dr. Heinz Klinger's in Graz

Jul. 2011: 3rd subject group of the "Praktisches Jahr": Dermatology at the Department of Dermatology, Venereology and Allergology, Univeritätsklinikum des Saarlandes in Homburg, Saar

Additional qualifications

Spoken languages
English (fluent)
French (basic)
Spanish (basic)