Diplomarbeit

Serum metal ion levels 5 years after total hip replacement with ceramic-on-metal bearing

eingereicht von

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Unter der Anleitung von

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und

Ass. Dr. Jörg Friesenbichler

Graz, der 15.11.2016

Affidavit

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

Graz, der 15.11.2016 Diana Pranckh-Matzke eh.

Acknowledgment

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In particular, my two supervisors, OA Dr. Werner Maurer-Ertl and Ass.Dr. Jörg Friesenbichler, for the suggestion of the theme and the support through all phases of the development.

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Last but not least, I would like to thank my family and friends, who supported me during the whole time of studies.

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Abbreviations

ASR	Metal-on-metal bearing, DePuy, Johnson &Johnson Company, New Brunswick, USA
ALVAL	Aseptic lymphocyte-dominated vasculitis-associated lesion
ARMD	Adverse reactions to metal debris
BMI	Body mass index
Co	Cobalt
CoM	Ceramic-on-metal bearing
Cr	Chrome
CRP	C-reactive protein
CT	Computed tomography
ET ASS	Electrothermal atomic absorption method
HHS	Harris Hip Score
MARS-MRI	Metal artefact reduction sequence MRI
Mo	Molybdenum
MoM	Metal-on-Metal bearing
NSAID	Non-steroidal anti-inflammatory drugs
SD	Standard deviation
THA	Total hip arthroplasty
WOMAC	Western Ontario and McMaster Universities Arthritis Index

Abstract

English

Background: Increased metal ion levels following total hip replacement with metal-on-metal bearings are currently a highly debated topic. Known effects of increased metal debris are local soft tissue reactions (Adverse Reactions to Metal Debris, ARMD) with chronic pain. Further systemic side effects such as central and peripheral neuropathy, allergic skin lesions or chromosomal aberrations are described. The aim of the current study was to determine the serum metal ion concentrations of cobalt (Co) and chrome (Cr) after total hip replacement with a ceramic-on-metal bearing, and their correlation with the implant position.

Patients and Methods: Between 2008 and 2010, 20 patients were treated with total hip replacements for osteoarthritis using a ceramic-on-metal bearing at our department. The mean age at time of surgery was 61 years (range, 41 to 85 years). The postoperative follow-up was on average 60 months and ranged from 49 to 70 months. Out of these 20 patients, 16 patients took part in the current series. One of the study participants receives a bilateral implantation of ceramic-on-metal bearing. That implies a total number of 17 hips with ceramic-on-metal bearing. In addition, x-rays were performed in two planes. To determine the inclination and anteversion of the cup the mediCAD program was used. Furthermore, the arc of cover was calculated.

Results: The average metal ion concentration of Co was 5.0 µg/L (range, 0.3 to 39.0 µg/L) and 3.3 µg/L (range, 0.09 to 22.6 µg/L) for Cr. After exclusion of patients (n = 3) with a metal-on-metal large-head device implanted at the contralateral side, the remaining patients (n=13) showed an average concentration of 3,2 µg/L (range, 0.3 to 15.2 µg/L) for Co and 1.6 µg/L (range, 0.09 to 5.5 µg/L) for Cr.

The statistical analysis showed a strong correlation between the anteversion and the measured Co and Co concentrations (Co: Pearson 0.684, p =0.007; Cr: Pearson 0,678, p=0,008) after exclusion of 3 patients with contralateral ASR (MoM) hips.

Conclusion: The current series showed increments for Co and Cr following metal-on-ceramic hip arthroplasty. Nevertheless, compared with patients with metal-on-metal large-head prostheses or metal-on-metal hip resurfacing, these patients showed significantly lower serum concentrations of Co and Cr. We detected two patients with Co and Cr values over the international accepted reference value of 7 µg/L. The get a term for a control of the metal ion levels a few months after the first measurement. However, routine follow-up is recommended with investigation of serum metal ion concentrations at least once.

Zusammenfassung

Problemstellung: Erhöhte Metallionenspiegel nach Hüfttotalendoprothesen mit Metall-Metall-Gleitpaarungen sind derzeit ein stark diskutiertes Thema. Bekannte Effekte durch erhöhten Metallabrieb sind lokale Weichteilreaktionen (Adverse Reactions to Metal Debris, ARMDs) mit chronischen Schmerzen. Aber auch systemische Folgen wie zentrale und periphere Neuropathien, allergische Hautveränderungen oder chromosomale Aberrationen werden beschrieben. Ziel der aktuellen Studie war die Messung der Serum-Metallionenkonzentrationen für Co und Cr nach Implantation einer Metall-Keramik-Gleitpaarung, sowie deren Korrelation mit der Implantatposition.

Patienten und Methoden: Zwischen 2008 und 2010 wurden an unserer Klinik 20 Patienten mit einer Metall-Keramik-Gleitpaarung versorgt. Das durchschnittliche Alter zum Zeitpunkt der Operation betrug 61 Jahre (41 bis 85). Das postoperative Follow-up lag zwischen 49 und 70 Monaten. Von diesen insgesamt 20 Patienten nahmen 16 an der laufenden Studie teil, wovon 1 Patient eine bilaterale Implantation einer Metall-Keramik-Gleitpaarung erhalten hat. Es ergibt sich somit eine Gesamtzahl von 17 Hüften mit einer Metall-Keramik-Gleitpaarung. Zusätzlich wurden aktuelle Röntgenaufnahmen in zwei Ebenen durchgeführt. Am Beckenübersichtsröntgen wurden die Inklination und die Anteversion mittels mediCAD vermessen und der Arc of Cover errechnet. Schließlich wurden diese Messwerte mit den Serumkonzentrationen für Co und Cr in Korrelation gesetzt.

Ergebnisse: Die durchschnittliche Metallionenkonzentration für Co lag bei 5,0 µg/L (0,3 bis 39,0µg/L) und bei 3,3 µg/L (0,09 bis 22,6 µg/L) für Cr. Nach Ausschluß der Patienten (n=3) die auf der Gegenseite mit einer Metall-Metall Großkopfprothese versorgt wurden, zeigten sich durchschnittliche Konzentrationen von 3,2 µg/L (0,3 bis 15,2 µg/L) für Co und 1,6 µg/L (0,09 bis 5,5 µg/L) für Cr. Die statistische Auswertung zeigte eine starke Korrelation zwischen der Anteversion und den gemessenen Cobalt- und Chromkonzentrationen (Co: Pearson 0.684, p=0.007; Cr: Pearson 0,678, p=0,008) nach Ausschluss der 3 Patienten mit kontralateralen ASR (MoM) Hüften.

Fazit: Die durchgeführte Studie zeigt erhöhte Kobalt- und Chromwerte nach der Implantation der Keramik-Metall-Gleitpaarung. Dennoch zeigten sich deutlich niedrigere Kobalt- und Chromwerte im Vergleich zu Patienten mit Metall-Metall Großkopfprothesen oder Metall-Metall Oberflächenersatz. Zwei der Studienteilnehmer zeigten Kobalt- und Chromwerte über dem internationalen Referenzwert von 7 µg/L. Diese werden für eine Verlaufskontrolle nach einigen Monaten wieder einbestellt. Es wird für alle Teilnehmer eine weitere Verlaufskontrolle der Serum-Metallionenkonzentrationen empfohlen.

1. General Part

1.1. History of hip replacement

The history of hip arthroplasty began in the 1880ies by Professor Themistocles Gluck. He was the first, who implanted artificial hip joints, made of ivory to replace femoral heads of patients with tuberculosis joints (1, 2). His replacements were very successful in the short term, but over longer time they failed because of chronic infection. Gluck realised that prior joint infection was a contraindication for hip replacement. A joint implantation during active tuberculosis led to a recurred infection. Thereafter he passed into oblivion.

In the late 19th and early 20th century, orthopaedic surgeons tried to use various tissues like fascia lata, skin or even submucosa of pig´s bladder for joint replacement and they put it between the articulating surfaces of the hip joint (3).

In 1923 Smith-Petersen introduced the mould arthroplasty. He implanted a glass cup at the femoral head to make the surface of the hip joint smooth and to stimulate the regeneration of the cartilage. The problem of this technique was the breakage of the devices because of the great forces during walking. The next generation of joint replacement was developed between 1937 and 1939 by Smith-Peterson and Nathaniel Allison, whereby the femoral head was coated with an unfixed Vitallium cup (1936 Venable & Stuck, a cobalt chromium alloy) (4).

The next better performing design was introduced in the 1950s by Sir John Charnley. It was the first complete surface replacement made of two Teflon cups. On the other hand, there were high rates of aseptic loosening, because of necrosis of the femoral head and enormous wear rates (4-6).

Metal-on-Polyethylene

At the same time, Sir John Charnley developed the hard-on-soft bearing, a combination of metal and polyethylene. This kind of bearing has been in practice

for more than 40 years. The first generation showed very good survival rates. Nevertheless, in this kind of bearing the wear rates were also high and polyethylene wear particles lead to inflammatory reaction next to the implant causing massive bone loss and periprosthetic loosening.

Immunohistochemistry showed macrophages with wear particles at the inflammatory reaction. Initially in 1987, these particles were thought to be bone cement leading to the impulse to work without bone cement. New methods for fixation have been sought and implants with a rough surface or porous coatings were introduced for press-fit fixation (5, 6).

Metal-on-Metal

The first metal-on-metal bearings were implanted in 1938 by Wiles (7).

In 1967, McKee and Watson-Farrar tested a cemented metal-on-metal bearing in a group of 18 persons whereby 50% of these implants had to be revised for different indications. These early and high failures led to an abandonment of metal-on-metal bearings in the 1980s (8).

In the 1970s, the Wagner cup was developed. This was the first system with the possibility to choose between a ceramic component and a Co/Cr-alloy in combination with a 4 mm thick polyethylene acetabular component. The preparation technique was imprecise and implant loosening was observed (5, 6, 9).

The advantage by using metal femoral heads were the high fracture strength, the possibility to use femoral heads with a larger diameter and an increased joint stability (2).

In 1988, Weber developed the “Metasul” alloy, a cobalt-chrome-alloy with reduced wear. This was used for a new design with a titanium alloy as a socket and the metasul inlay (9). This second-generation metal-on-metal bearing showed good medium-term results and minimal rate of osteolysis due to wear debris (8).

Ceramic-on-ceramic

The first implantation of a ceramic-on-ceramic bearing was performed by Boutin in 1970 (10). The problems with this first generation of ceramic bearings were the inadequate fixation and the high fracture rates. In the 1980ies, the Mittelmeier Autophor ceramic prosthesis was widely introduced (11). An advantage of this

system was the reduced fracture rate, but the problems with high rates of aseptic loosening remained. Since the early 1990ies, many designs with a rough surface or porous shells with a ceramic liner are used for total hip arthroplasty(12). At the beginning of the 21th century, the fourth generation of alumina ceramic was evolved with improved material characteristics, which has been shown to be the gold standard in hip arthroplasty until now (5).

The benefits of ceramic were the high level of hardness, the resistance, against scratches, an improved lubrication and great wear resistance (2). One of the most common complications observed in ceramic-on-ceramic bearing is the breakage of the bearing surfaces.

The problems of the metal-on-metal bearings were the production of wear particles on the one hand, and the release of metal ions, which have a local and/or systemical toxicity, on the other hand. To improve this frailty, a ceramic-on-metal bearing was tested. It should reduce ion release of the metal component and also the breakage of ceramics (13).

The aim of the hard-on-hard bearings was a decrease of the wear rates and an improvement of the longevity of the total hip replacement. These facts are becoming more importance because patients, who are getting a total hip replacement, are getting younger and physically more active (3).The most common and practiced combinations of bearing surfaces within the last years were metal-on-metal, metal-on-polyethylene and ceramic-on-ceramic bearings (5).

2. Special Part

2.1. Introduction

The topic of metal-on-metal bearings was discussed intensively within the last years because of the voluntary recall of the ASR™ XL Head System and ASR™ Hip Resurfacing System by DePuy (Johnson & Johnson Company, New Brunswick, USA), which started in August 2010 (14). This matter was caused due to higher than anticipated revision rates of these devices. The national joint registry of England and Wales found elevated revision rates 5 years after implantation of the ASR™ XL Head System and the ASR™ Hip Resurfacing System (14). Since the voluntary recall of the implants, shorter follow-up intervals and determination of serum metal ion levels of Co and Cr are recommended.

Further, the discussion concerning metal ion concentrations led to the question, if there are also elevated serum metal ion levels in patients with a ceramic-on-metal bearing.

In the last years, some studies concerning that topic have been published (15-18). Another issue was, if serum metal ion concentrations showed a correlation to the alignment of the prosthesis´ components or the BMI.

Nonetheless, it is not entirely clear what the effects of elevated metal ion levels on the whole body are. A proven fact is that metal ions may lead to adverse reactions to metal debris (ARMDs) (19, 20). This term includes inflammatory pseudotumours, aseptic lymphocytic vasculitis associated lesion (ALVAL) and metallosis. The spectrum reaches from asymptomatic small cystic lesions to large pseudotumours (21). Pandit et al. (22) published a study with 17 patients who developed pseudotumours after hip resurfacing with a metal-on-metal bearing. This group estimated that 1% of all persons receiving a metal-on-metal resurfacing device will develop a pseudotumour within 5 years following index surgery (22).

Another possible negative side effect may be an intoxication of Co and/or Cr due to massive elevated metal ion concentrations. Therapy of choice in case of intoxication is the chelation therapy as well as revision of the tribological bearing. In the context of metal ion intoxication a few case reports are published (23-28).

2.2. Reason and effects of elevated serum metal ion levels

Many studies concerning metal ion levels in blood, serum or organs after use of metal-on-metal or ceramic-on-metal bearings have been published (15-18, 29, 30). The main question is, which the effects of these elevated metal ion levels are. It is a proven fact that metal-on-metal bearings may lead to elevated metal ion levels due to high wear rates and surface corrosion. There are also some studies concerning the wear behaviour of ceramic-on-metal bearings over a short time (15-18, 29, 30).

High metal ion levels may lead to an accumulation of Co and Cr in the regional lymph nodes, the liver, the spleen and the bone marrow (31). Especially, the kidney can get impaired severely, by the Cr ions. Co ions are quickly eliminated and it would require higher doses to impair the renal function (32, 33).

Metal ions can modulate the immunocompetent cells by different mechanisms and lead to a reduction of the circulating lymphocytes (33). Lymphocytes showed a reduced variability and increased apoptosis (34). Further studies showed that metal ions, especially Co, may lead to a T-cell lymphopenia in the peripheral blood (35, 36).

In addition, it is reported that elevated metal ion concentrations following implantation of a metal-on-metal bearing may lead to allergic skin disease and hypersensitivity reactions (37-39). It has been shown that these symptoms disappear after removing the prosthesis (40). A hypothesis is that this hypersensitivity reaction is caused by a lymphocyte-dominated immunological response in the tissue next to the hip joint.

Other reported important systemic effects might be the neuro-ocular toxicity, thyroid toxicity, cardiotoxicity and polycythemia, which get symptomatic several months or even years after implantation and remain even after removal of the prosthesis (24-27, 41, 42).

Clinical symptoms are for example blindness caused by destruction of the optic nerve, abnormal function of the retina or other alterations of the eye (43). These alterations might be reversible or irreversible. Other symptoms are deafness based on the loss of sensory cochlear hair cells and peripheral neuropathy (44).

Some of these adverse effects after using metal-on-metal bearings got discussed in the literature review by Friesenbichler et al.(45).

Studies have also shown that metal wear from knee or hip prostheses may lead to chromosomal aberration or to a disruption of the DNA repair mechanisms (46), whereas, this reaction was only observed in Co-Cr alloys and not in stainless steel implants (47). The amount of damage depends on the grade of wear, respectively the metal ion concentrations (48). Aneuploidy and translocations have also been described in other studies (49-51).

Another issue has been for several years the topic of carcinogenicity of orthopaedic devices. Therefore some studies have been performed. On that account it was evaluated if patients with metal-on-metal bearings would have a higher risk for cancer compared to general population or other bearing types, whereas, this assumption could not be shown in these studies (52-54).

In the reported cases of Co or Cr intoxication, the most common treatment was removal of the prosthesis, leading to the decrease of the blood concentration of Co and an improvement of the symptoms (41). Apart from that, Co can also stimulate the erythropoietin production, which leads to increased number of red blood cells and elevated haemoglobin or haematocrit levels. The study of Tvermoes et al. (55) showed that there were none of these effects at a whole blood concentration lower than 117 µg/l of Co.

Paustenbach et al. (42) described, that the systemic effects of Co poisoning will not appear if a blood Co concentration is lower than 300 µg/l, except patients with special risk factors. Also sustained blood concentrations of about 10-70 µg/l up to 90 days, seem to have no relevant clinical effects.

2.2.1. Physiological functions and effects of Co and Cr in the human body

However, metal ions don´t have just negative effects, they also have some physiological functions. Co is an important trace element. It gets into the body as a part of vitamin B12 and is part of meat, egg and milk products. It is very important for the production of red blood cells, the function of nerve cells and the metabolism of nucleic acids. The daily required dose of Co is 0,1 µg.

Cr is a naturally occurring heavy metal, which gets ingested through vegetables and meat. The daily requirement is less than 1 mg per day.
It is a very important nutrient for the activity and function of insulin and so for the metabolism of sugar, fat and proteins. Cr increases the insulin binding to cells, the sensitivity and the number of insulin receptors (56). Cr also has effects on the immune system. High Cr levels may result in a immunostimulation or immunosuppression, so there is an influence on different components of the immune system (57).

2.3. Indications for total hip replacement

There are a lot of different indications for total hip replacement (THR).
Main indication is primary osteoarthritis of the hip. It is a degenerative disease caused by attrition of the femoral and/or the acetabular cartilages. This is characterised by pain and loss of function.

Furthermore, secondary osteoarthritis, caused by different factors, is another indication for a total hip replacement:

- rheumatoid arthritis
- avascular necrosis of the femoral head
- collagen disease
- comminuted fracture of the femoral head or the acetabulum,
- congenital dysplasia of the hip with secondary arthritis
- epiphysiolysis capitis femoris
- perthes syndrome

Contraindications against THR

- local or systemic infections
- comorbidity which makes an operation impossible

2.4. Aim of the study

In the last century, different types of endoprostheses were used. All of them showed different benefits but also some disadvantages (2, 5, 13). As known from other studies, the main problem of metal-on-metal bearings were the high levels of Co and Cr measured in the blood in consequence of wear (15, 31, 58, 59). This topic was highly controversial discussed during the recall of the ASR devices, caused by higher than anticipated revision rates.

Based on our previous data of ceramic-on-metal bearings the current study was started. The aim of the study was to investigate if the serum metal ion levels would also be elevated in ceramic-on-metal bearings.

Further, several parameters were correlated with the results of serum metal ion determination such as inclination, anteversion, arc of cover and BMI, which might influence the results.
High serum metal ion levels in combination with other factors might be also an indication for a revision surgery.

2.5. Materials and Methods

2.5.1. Design

This study was a monocentric, non-randomized study, which included 20 patients, which were operated at the Department of Orthopaedics and Orthopaedic Surgery at the Medical University of Graz, between 2008 and 2010.
At the Department of Orthopaedics and Orthopaedic Surgery in Graz, 1961 patients underwent THA for several indications between 2005 and 2012. The identification of the patients was done due to a database, which was compiled for quality management. 1789 of them got a total hip replacement with different bearing types. Out of this patient group, 991 patients received a THA using the Pinnacle-Corail System of DePuy (Johnson & Johnson Company, New Brunswick, USA). Of these 991 patients 20 patients received the ceramic-on-metal bearing. All patients with a ceramic-on-metal bearing were contacted by a letter and 16 of them took part in our study. One of the participants had a bilateral implantation of the ceramic-on-metal bearing at our department.
All patients gave their informed consent to participate at the study. All data and results were anonymised.

2.5.2. Ethics

The study was approved by the local ethics committee in August 2014.
EK-Number: 26-536 ex 13/14

2.5.3. Inclusion and exclusion criteria

These 16 persons took part by choice and were informed about the procedure. They all signed a consent form by their own will.

Inclusion

- Men and women between the age of 18 and 99 years at the time of operation
- First implantation of a total hip replacement

- Implantation between 2008 and 2010
- Primary or secondary arthritis of the hip

Exclusion

- Patient did not want to participate in the study
- Revision of the implant prior to the study

2.5.4. Used prosthesis components

The used stems for THA were parts of the Corail system manufactured by DePuy or the Allo Pro AG system vended by Zimmer Inc. (Zimmer, Warsaw, USA). All prosthesis´ components were fixed cementless. Two different types of the Corail stems were implanted. In 12 cases the Corail standard stem was used and in four cases the Corail high offset stem, for more lateralisation. In one further case, the Allo Pro stem was implanted.

The Corail stem consists of a titanium alloy with a full hydroxyapatite coating for a better and faster osteointegration.

The used cup types were “Pinnacle 100” in 12 cases and the “Pinnacle sector” in five cases, whereby this type of cup allows a further fixation with screws.

All patients got a “Biolox® Delta” femoral ceramic head, a zirconia-toughened alumina ceramic of the fourth generation. The used metal inlay was Ultamet®, also produced by DePuy. It consists of a Co-Cr-Mo alloy and had a diameter of 36 mm in all cases.

2.5.5. Procedure

Blood samples were taken one time after an average of 5 years (49 to 70 months) following index surgery. The parameters of the kidneys and CRP were compared with the normal values of our department. The metal ion levels were compared with serum metal ion levels from a control group who had no implants.

As a normal range we assumed the following:

- Cr 0–1,9 µg/l
- Co 0–0,6 µg/l

The international reference value is 7µg/l

- Creatinine - 1,0 mg/dl
- Urea 10–45 mg/dl
- Uric acid 2,4–5,7 mg/dl

- CRP <5 mg/l

To evaluate the renal function, the measurement of the kidney parameters was important. On the one hand, the function can be reduced when metal ions get eliminated by renal clearance. On the other hand, the urine is the major route for excretion of the metal ions. If the renal function is limited significantly, the metal ions will not be eliminated and therefor, they will accumulate in the body (60, 61).

The CRP is a precise parameter for an active inflammation, but unspecific for the location meaning and the CRP can be elevated because of another kind of infection not related to the endoprosthesis.

At the metal ion measurement we included the ion values of cobalt, chromium and molybdenum because they constitute the main part of the prosthesis. Later on we focused on cobalt and chromium, because none of our study participants showed elevated molybdenum levels.

At the follow-up outpatient care x-rays in anterior-posterior view of the pelvis and the hip were taken, which were used for the measurements with the “Danube mediCAD” system (Hectec GmbH, Altdorf, Germany).

Further, some questionnaires were requested from the patients including the Harris Hip score and the WOMAC score. In addition size and the weight of the patients were asked to calculate the body mass index (BMI).
Over the course of the Harris hip score we made a clinical examination about the range of motion of the hip.

2.5.6. Instruments for blood taking

To take blood the Vacuette® (Greiner Bio-One, Kremsmünster, Austria) multi extraction cannula model 21 G x 1½´´; 0.8 mm x 38 mm (LOT: 06G29B) was used. For the different analyses several tubes were used but all were from the same batch. For the renal function and CRP we took Vacuette® 4 ml LH lithium heparin tubes (LOT: A010901). For the metal ions we used Vacuette® 6 ml Z No additive tubes (LOT: L090609).

The lithium heparin tube was directly analysed in the on-site laboratory. Two hours after taking the blood the No additive tubes were centrifuged for 10 minutes at 4300 rpm. Then the supernant liquor was filled in 5ml cryo-tubes, which were stored at 4° Celsius, until the analysis at the Medical and Chemical Laboratory Diagnostic Lorenz & Petek GmbH. One tube remained at -20° Celsius at the department for further questions or a repetition of the metal ion analysis.

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
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

2.5.7. Metal ion measurement

For serum metal ion measurement blood was taken from all study participants at one time on equal setting conditions. A vacuum assisted system was used and all samples were centrifuged stored at 4° Celsius until the analysis.

For serum metal ion determination, electrothermal graphite furnace atomic absorption spectrometry (ET ASS) was used. The analysis was performed by an external laboratory (Medical and Chemical Laboratory Diagnostic Lorenz & Petek GmbH). This analytic method was selected because of high sensitivity and reduced matrix effects (Zeeman Effect).

A second tube was stored at -20° Celsius at the department for further questions or a repetition of the analysis.

Three-hundred microliters of each serum sample were diluted with 50µl modifier and 550 µl Aqua dest. The samples of the patients and a control group were diluted equally.

The samples were evaporated in an atomisation device and transferred into atomic condition. The samples were inserted in the graphite tube with a micro pipette. By heating the samples got ridded of solvents and other concomitant agents. The analysis produced a signal with an area, which is proportional to the searched element and the concentration can be calculated by using the dose volume of the sample.

Every ET ASS was performed twice for each sample and the levels were expressed as µg/dl.

2.5.8. Functional Scoring System

2.5.8.1. Harris Hip Score

The first version was published in 1969 by William H. Harris and was designed for the evaluation of the results of hip surgery (62). The Harris hip score allows an evaluation of pain and function in relation with activities, deformity and range of motion. It is composed of questions and a physical examination, which has to be carried out by the doctor. The score has a maximum of 100 points and the test can be executed in about 10 minutes.
In seven of our cases, a comparison of preoperative and 5-years postoperative values of the Harris Hip Score was possible.

2.5.8.2. WOMAC score

The WOMAC score is used for evaluation of knee and hip diagnostics. It consists of 24 questions which get rated with points on a scale from 0 to 10. The main points are pain, stiffness and physical ability, including questions about daily routine and movement, like using stairs, putting on socks or standing up from chair or bed. This questionnaire can be filled out within 10 minutes from the patients alone.

2.5.9. Radiological analysis

The radiological analysis was one of the most important parts of the study for further evaluation. The results were set in correlation with the measured metal ion levels. The whole radiological analysis was executed with Danube mediCAD Classic version 2.55 from Hectec Gmbh. For the measurements standing x-rays were taken of the pelvis and the relevant hip in an anterior-posterior view.

2.5.9.1. Inclination

The inclination of the cup was measured first time immediately following surgery and second time at 5-years of follow up. The inclination is determined as the angle between a line through the teardrop sign on both sides of the pelvis and the opening area of the implanted cup. The ideal range for the inclination is an angle between 35 and 55 degrees. If the measured angle departed from the normal value, we expected elevated metal ion levels.

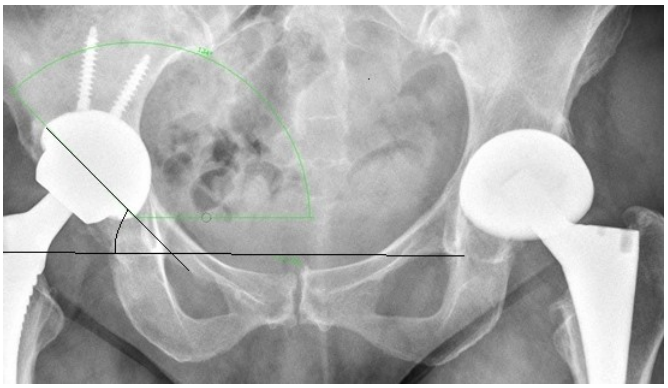

Figure 2: Cup inclination

2.5.9.2. Anteversion

The anteversion of the cup was measured one time 5-years postoperatively.
The anteversion gets determined by the angle between sagittal plane and the orientation of the implanted cup. With the mediCAD system we had just to position an ellipse after determine the inclination through two points on the opposite edges of the inlay.
A normal anteversion has an angle between 10 and 20 degrees. Is the angle lower or higher, higher metal ion levels should be expected than in hips with a normal orientation.

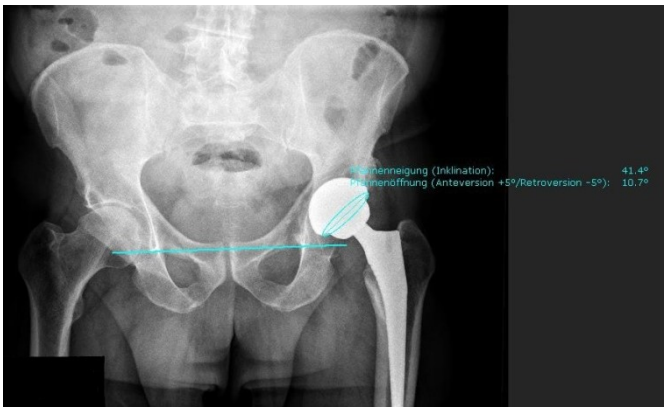

Figure 3: Anteversion

2.5.9.3. Arc of cover

The arc of cover is the product of the radius of the femoral head (r) and the angle (in radian) between a vertical line through the centre of the head and the lateral edge of the acetabular component (γ).
The arc of cover gets calculated with the following formula (53):

$$a=r*\alpha$$

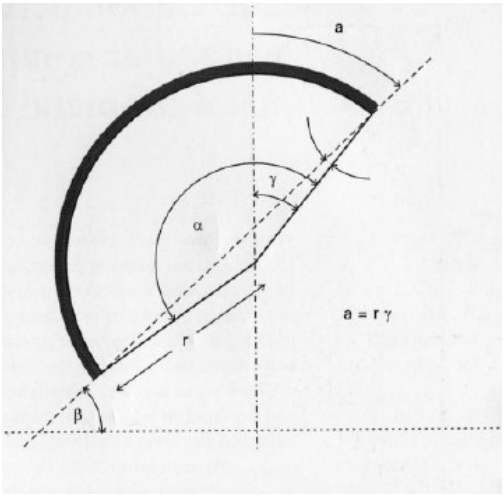

Figure 4: The figure shows the calculation of the arc of cover (63).

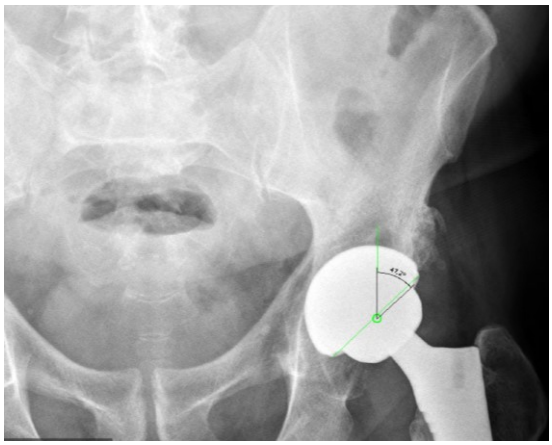

Figure 5: This figure sows the measuring of the arc of cover.

The arc of cover is the part of the acetabular component which covers the femoral head and influences the edge–loading. The more millimetres the arc of cover has, the less stressed gets the rim.
As a normal range for the arc of cover we expected it to be more than 10 mm. At a value less than 10 mm elevated metal ion levels are expected.

2.5.10. Statistical Analysis

For the statistical analysis we used Microsoft Excel for Windows, Version 14.0.7173.5000 and IBM SPSS Statistics, Version 23.
Results with a p-value of 0,05 or below were accepted as significant.
The explorative analysis was used to determine the mean, median, standard deviation (SD), minimum and maximum of the variables (e.g. creatinine, Co, Cr). Correlation analysis was used to evaluate correlations between the metal ions and the component adjustment, the renal parameters or the BMI.

3. Results

3.1. General results

Between 2008 and 2010 20 patients received a total hip replacement with a ceramic-on-metal bearing at the Department of Orthopaedic and Orthopaedic Surgery at the Medical University of Graz.
The mean postoperative follow up was 60 months (range, 49-70). Sixteen of these patients took part in the current study. One patient received the ceramic-on-metal bearing on both sides. Overall, there was a total number of 17 hips with ceramic-on-metal bearing in the current study. Four patients did not take part of the study. Two of them did not want to participant and two died. The first died by a pneumonia with high fever, the second person died on cardiac decompensation. Three of the patients had an ASR^{TM} (metal-on-metal bearing) hip on the contralateral side. One patient had a ceramic-on-ceramic bearing and one further patient a ceramic-on-metal bearing on the contralateral hip, which was not part of our study. Two other patients of the current series had a polyethylene-on-ceramic bearing on the contralateral side.

Ten of the patients who took part in the study were female and six were male. The participants had a mean age of 61 years (range, 41-85) at the time of operation. The average BMI was 27,8 (range, 23,0-38,3) and the preoperative Harris hip score was 50 points (range, 39-61).

N=16 patients	mean	minimum	maximum
Age at operation (years)	61	41	85
Ratio (m:f)	6:10		
BMI	27,8	23,0	38,3
Harris Hip score (points)	50	39	61

Table 1: Table one shows the preoperative data of the study-participants.

The indication for hip replacement was osteoarthritis of the hip in 15 cases and hip dysplasia with secondary arthritis of the hip in 2 cases.

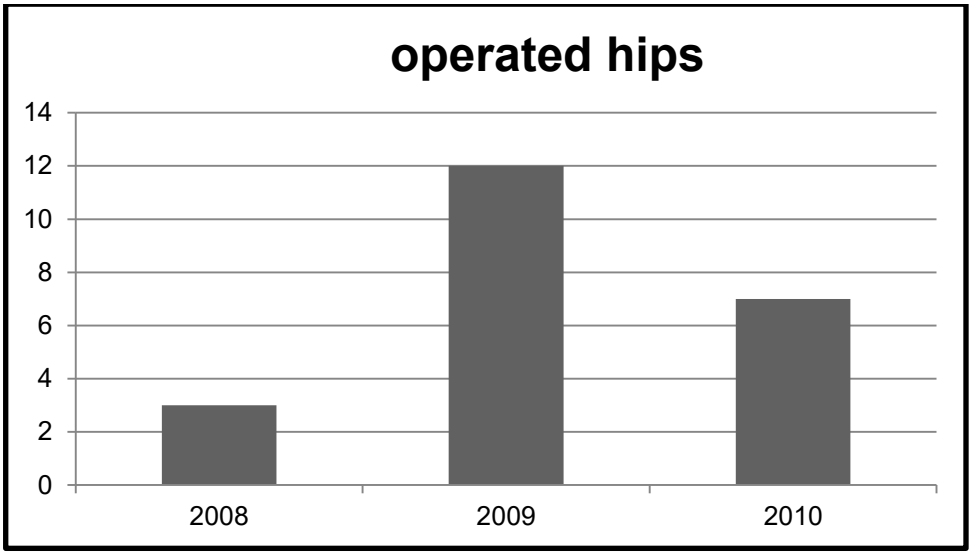

Figure 6: Figure five shows the number of operated hips at the department in each year.

3.2. X-ray measurements

Inclination:

The mean inclination angle measured was 43 degrees (range, 32-62 degrees) on the postoperative x-rays and at 5-years follow-up, the mean inclination angle was 43 degrees (range, 35-61). Therefore, it can be stated that the mean value was within the normal range between 35 and 45 degrees. Six of the study participants had values out of this range.

Arc of cover:

The calculation of the arc of cover, based on the x-rays, resulted in a mean value of 14,51 mm (range, 9,30-17,66). Only one patient of the current series had a lower arc of cover than the limit of 10 mm.

Anteversion:

We got a mean value of 12,2 degrees (range, 5,6-17,7) at the measurement of anteversion. This was within the normal range of 10 to 20 degrees. Three of the study participants were out of this ideal range.

3.3. Metal ion levels

	min.	max.	Ø
Cr (µg/l)	**0,09**	**5,49**	**1,59**
Co (µg/l)	**0,3**	**15,2**	**3,2**
inclination (°)	**34,8**	**60,9**	**43,2**
anteversion (°)	**5,6**	**17,7**	**12,2**
arc of cover (mm)	**9,3**	**17,7**	**14,5**

Table 2: Results of the measurement of the serum metal ion levels and the measurement of the X-rays.

On the current study mean serum Cr levels detected were 3,26 µg/l (range,0,09 to 22,55, SD 5,35) including the ASR hips and our two outliers. After excluding the three ASR hips, the mean Cr levels decreased to 1,59 µg/l (range, 0,09-5,49). The mean value without ASR hips and outliers account on average 0,93 µg/l (range, 0,09-2,56). Nevertheless, the mean measured results were within the limits of the department.

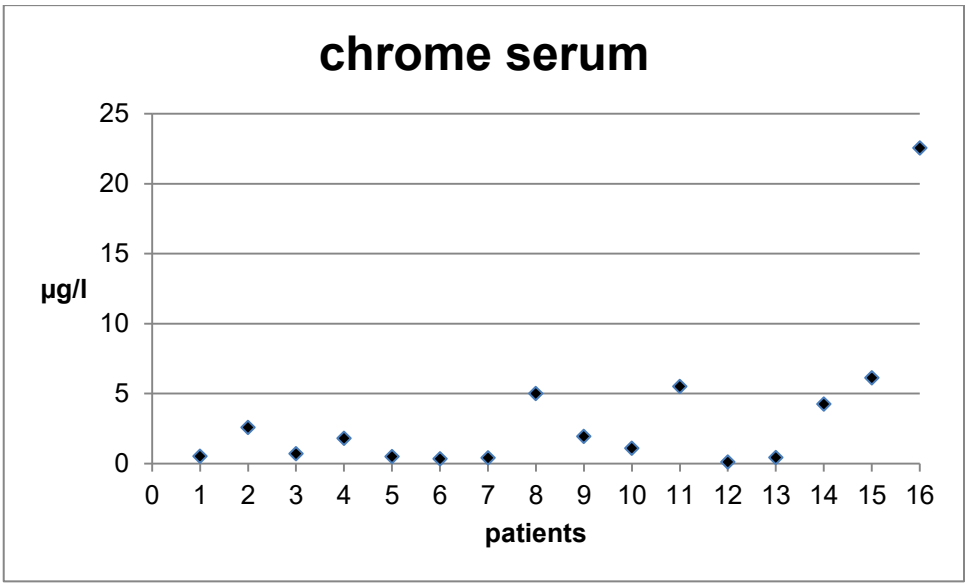

Figure 7: This figure offers the measured chromium levels including outliers (8 and 11) and ASR hips (14 to 16).

The measured Co levels were on an average of 5,02 µg/l (range, 0,3 to 39,0, SD 9,86) also including the ASR hips and the outliers. The mean value without the ASR hips was 3,15 µg/l (range, 0,3-15,2). After excluding the ASR hips and the outliers the mean Co level was 1,22 µg/l (range, 0,03-2,9). These values were increased compared to the upper limit which was set on 0,6 µg/l.

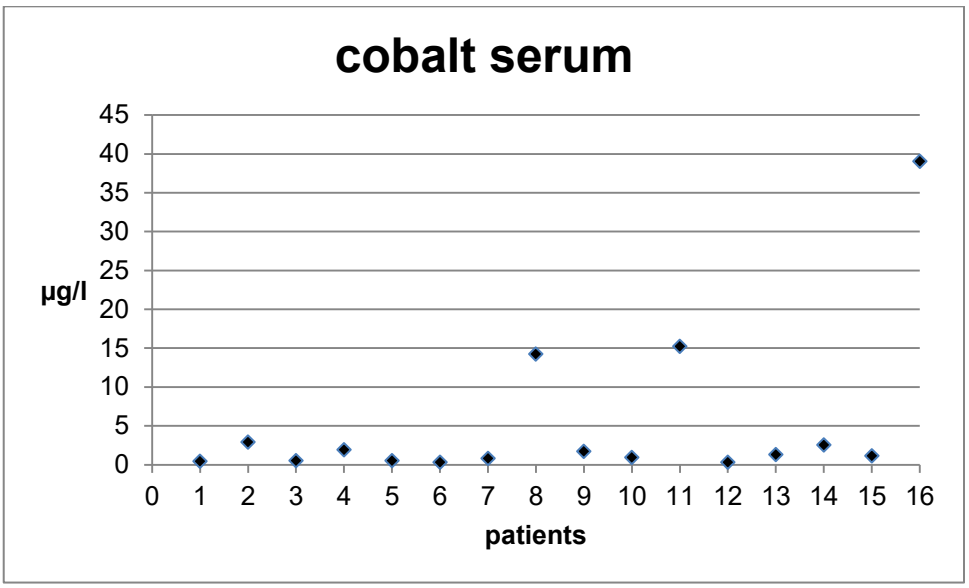

Figure 8: This illustration shows the measured cobalt levels including outliers and ASR.

We observed a large variation of the measured Co and Cr levels at our patients caused by two outliers and the ASR devices.
There was one patient in the current study that had a bilateral implantation of the ceramic-on-metal bearing within the relevant period at our department. Whereby, it was shown, that the levels of Co and Cr were not higher in this person compared, to the values of the patients with unilateral hip replacement. This patient showed values of Cr of 1,79 µg/l and Co of 1,9 µg/l.

3.4. Analysis of the renal parameters and the CRP

All renal parameters shown, are from the analysis 5-years postoperatively.

The measurement of all renal parameters showed mean values of creatinine, urea and uric acid which were within the normal range. One of the patients had elevated renal parameters, whereby, this was one of our outliers (Pat. No. 8).
The mean CRP was also lower than the limit of 5 mg/dl.

Creatinine (µg/dl)

n	16
mean	0,888
median	0,780
SD	0,308
minimum	0,52
maximum	1,67

Table 3: This table takes point on the results of the creatinine levels at the analysis of the kidney parameters.

CRP (mg/dl)

n	16
mean	4,300
median	2,900
std. deviation	4,765
minimum	0,70
maximum	19,50

Table 4: This table shows the results of the CRP measurement, as an indicator for an active inflammation.

3.5. Functional scoring system

The mean Harris hip score of all patients was 80 points (range, 37 to 99) 5 years following the operation.
The reason for the deducted HHS was one patient with a total score of 37 points due to severe pain and reduced function. Nevertheless, this patient had serum metal ion concentrations which were within the limits of the department.

The Harris hip score of seven patients showed a significant improvement from the status pre- to the status 5-year postoperatively (mean improvement: 37 points).

All patients together showed a mean WOMAC score of 40 points (range, 0 to 136) at the 5-year follow up. The patient with the WOMAC score of 136 points was the same patient with the Harris hip score of 37 points.

3.6. Correlation between component adjustment and metal ion levels

The different characteristics of the prosthesis components were set into relation with the measured Co and Cr levels. Only for the inclination we compared the results measured direct postoperatively and from 5-years follow up.

3.6.1. Chromium:

In the current study we found no correlation between the measured Cr levels and the inclination (r= -0,307, p=0,231). Furthermore, there was no correlation between the Cr levels and the anteversion(r=0,437, p= 0,079). There was also no correlation between the measured Cr levels and the arc of cover (r=0,435, p= 0,081).

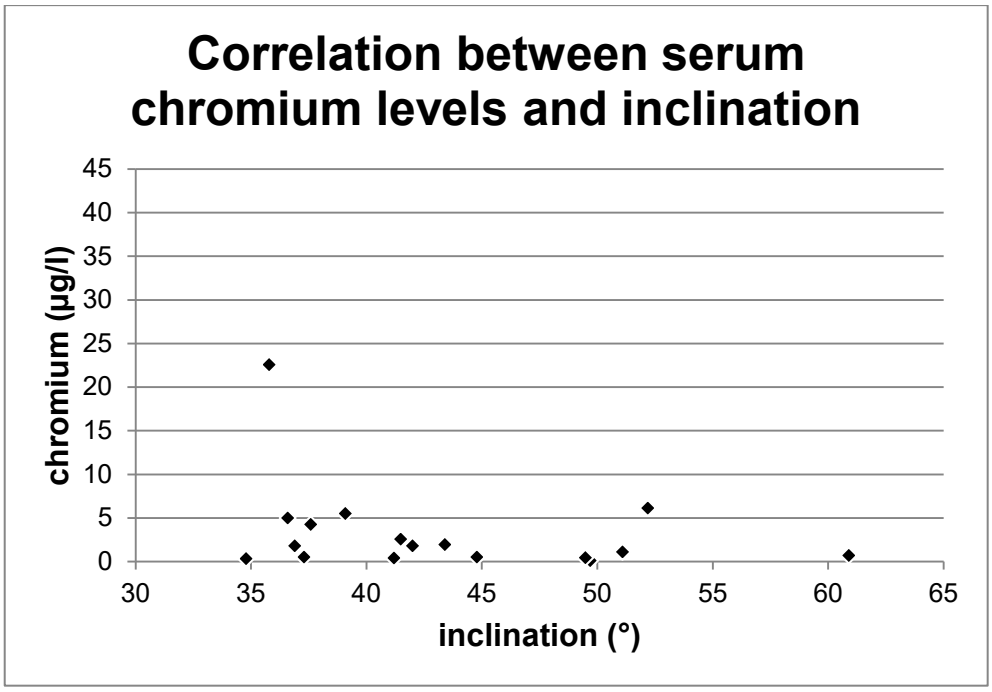

Figure 9: This figure offers the correlation between inclination angle and the measured chromium levels.

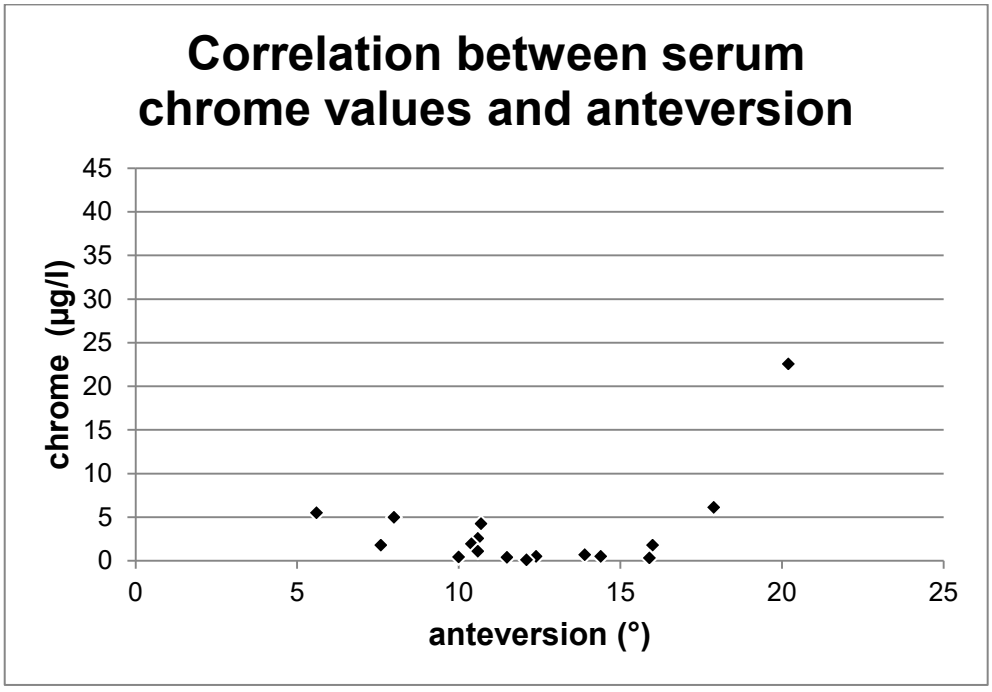

Figure 10: This chart shows the correlation between the anteversion and the serum chromium levels.

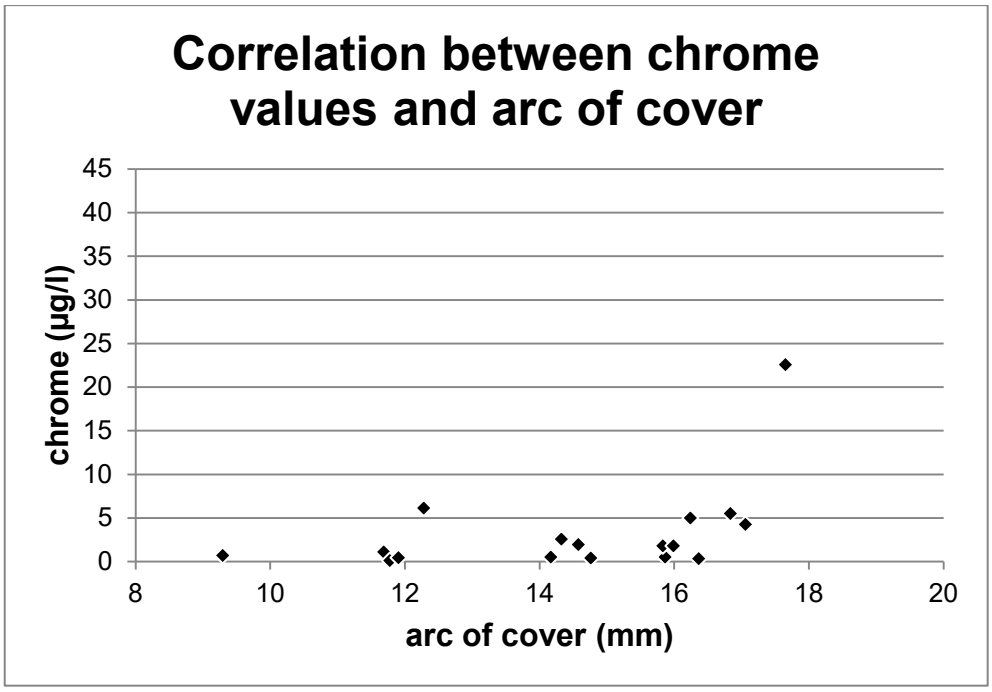

Figure 11: In this figure the correlation between the arc of cover and the serum chrome levels is shown.

After exclusion of the ASR devices, there was also no correlation between the inclination and the Cr levels (r= -0,382, p=0,178). Further, there was no correlation between the arc of cover and the measured Cr levels (r=0,497, p=0,070). On the other hand, there was a strong correlation between the serum Cr levels and the anteversion following exclusion of the ASR hips (r= -0,684, p=0,007).

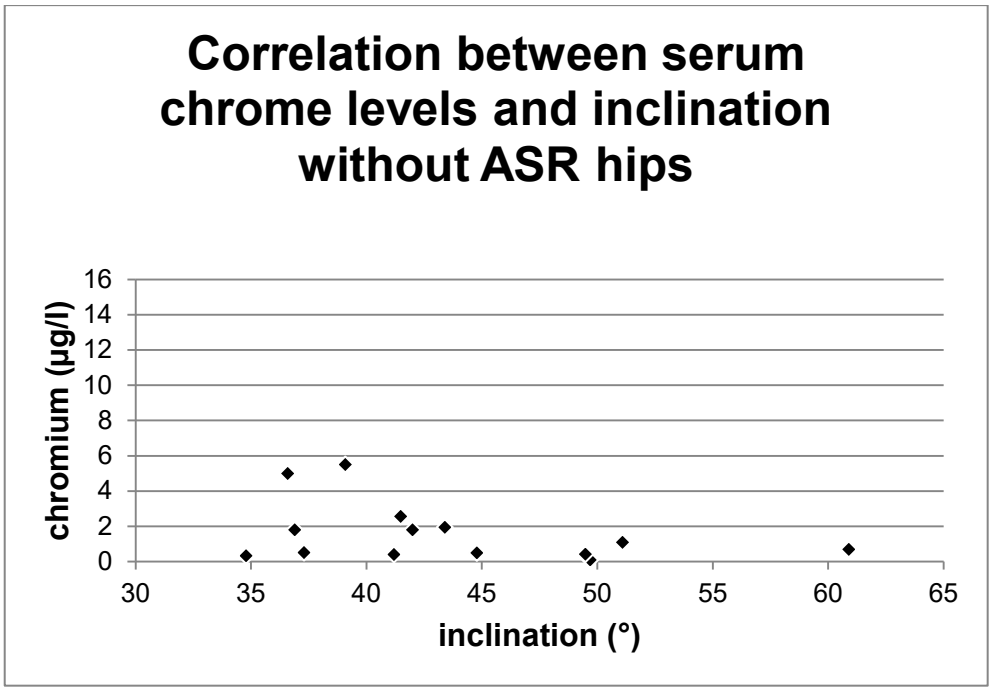

Figure 12: This figure shows the correlation between serum chrome levels and the inclination after excluding the ASR hips.

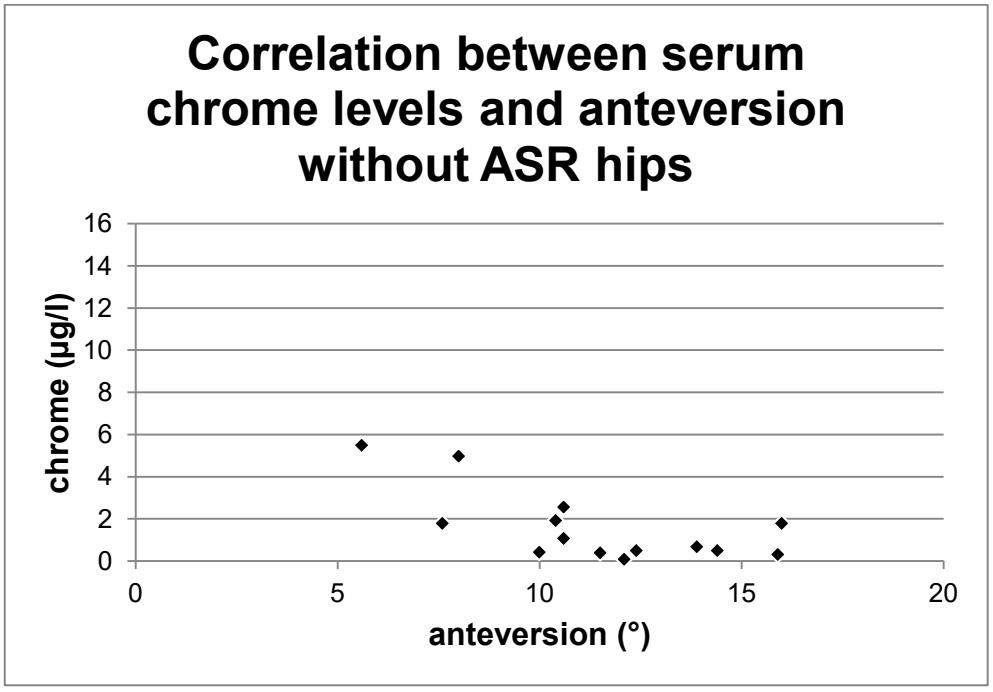

Figure 13: The diagram shows the correlation between serum chrome levels and anteversion after excluding the ASR hips.

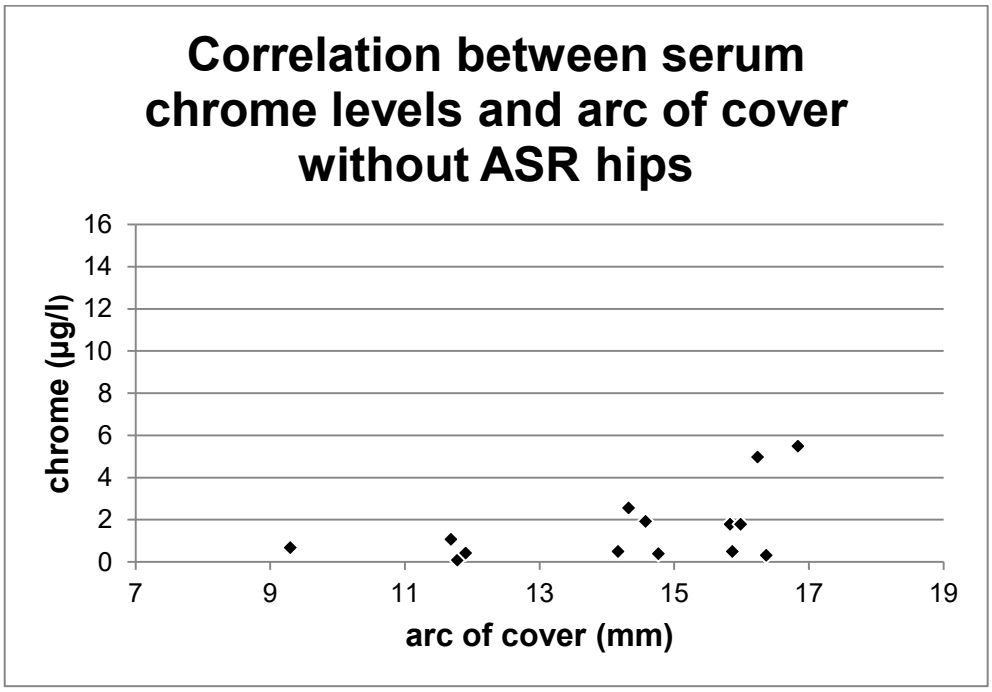

Figure 14: In this figure the correlation between serum chrome levels and the arc of cover after excluding the ASR hips is posed.

3.6.2. Cobalt:

Concerning the Co levels we found no correlation between the serum concentrations and the inclination angle (r= -0,391, p=0,121). There was also no correlation between the measured Co levels and the anteversion (r=0,236, p=0,361). There was a weak correlation between the Co levels and the arc of cover (r=0,494, p= 0,044).

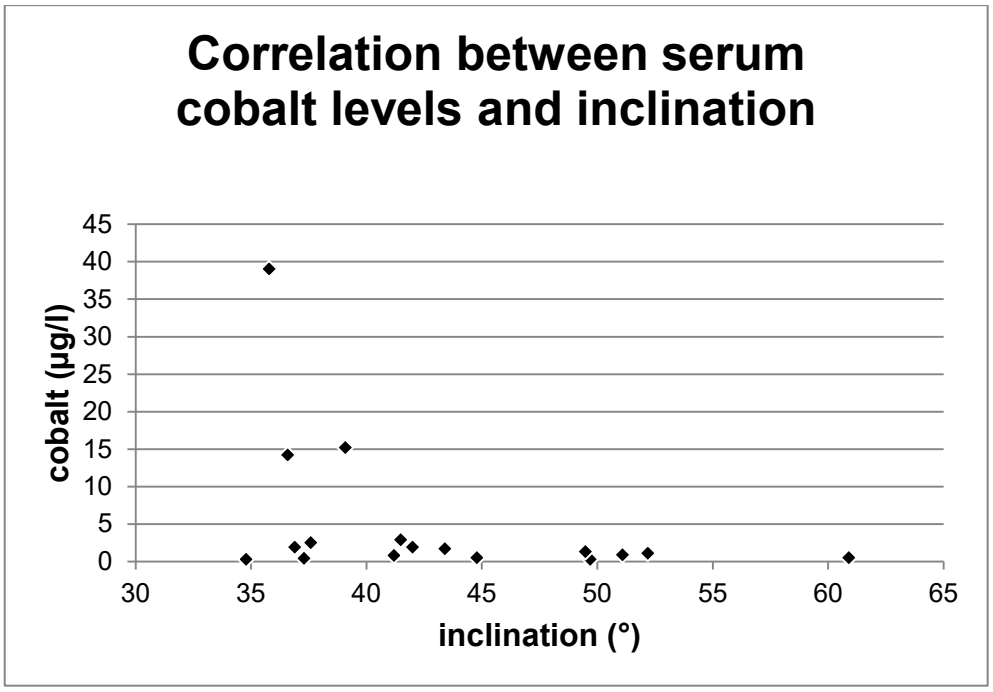

Figure 15: This figure shows the correlation between the inclination angle and the measured cobalt levels.

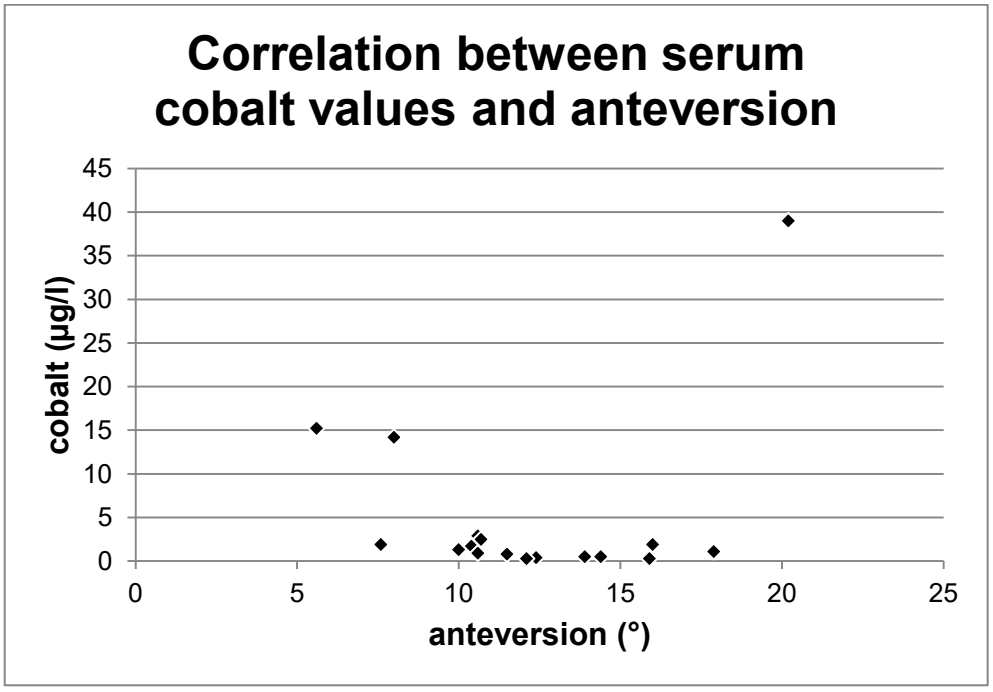

Figure 16: This diagram shows the correlation between serum cobalt levels and the anteversion.

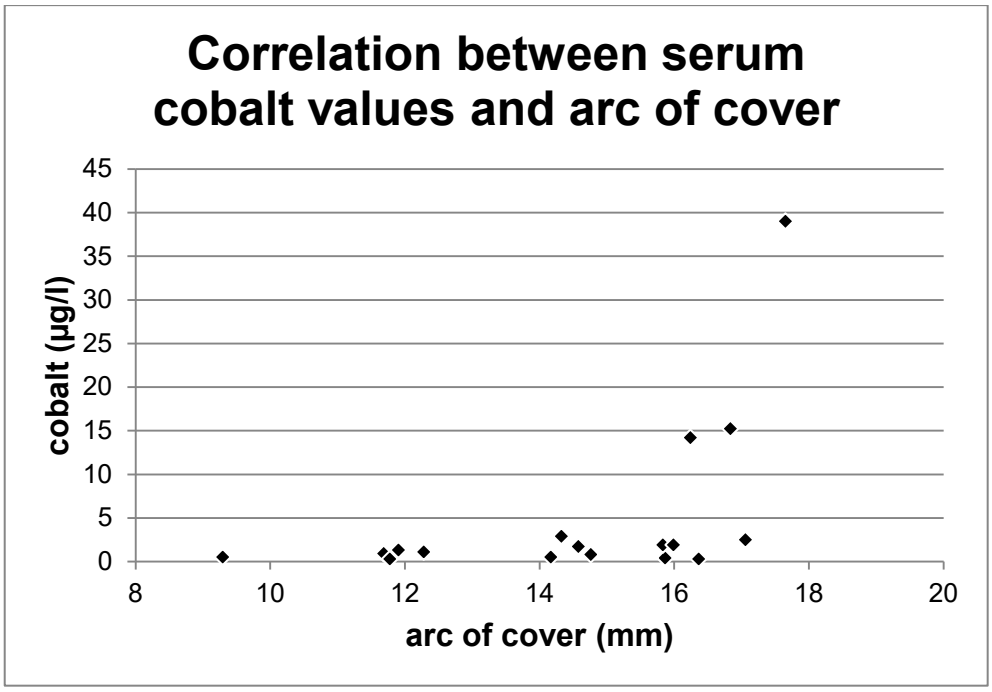

Figure 17: In this figure the correlation between serum cobalt levels and the arc of cover is posed.

After exclusion of the ASR devices, there was found no correlation between the inclination and the measured Co levels (r= -0,357, p=0,210). There was also no correlation between the arc of cover and the Co values (r=0,459, p=0,099). On the other hand, a strong correlation between the measured serum Co levels and the anteversion could be detected (r= -0,678, p=0,008).

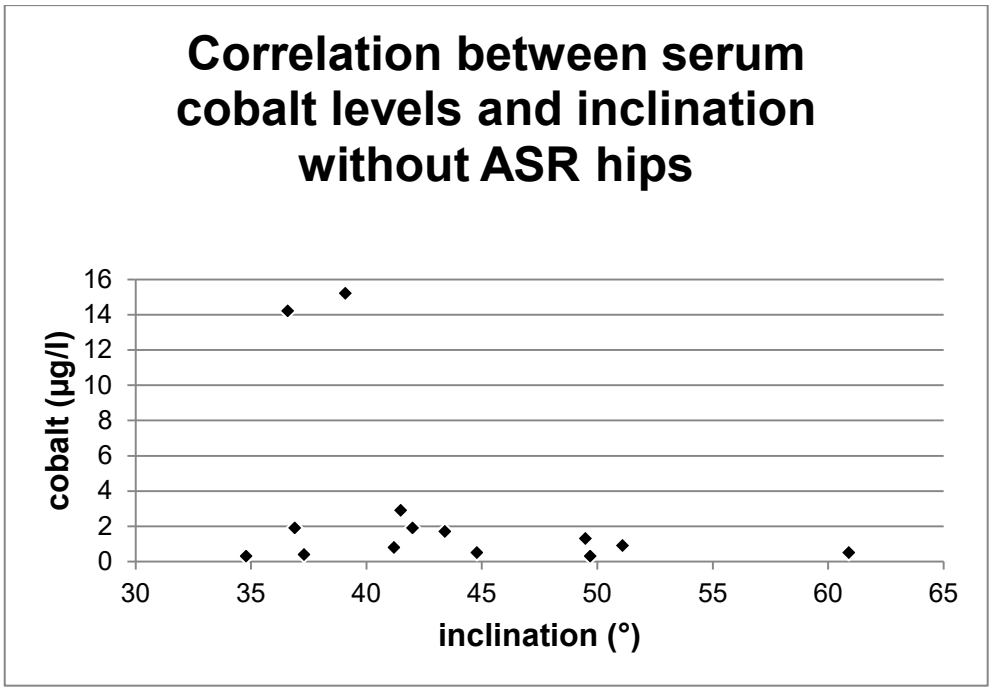

Figure 18: This figure shows the correlation between serum cobalt levels and the inclination after exclusion of the ASR hips.

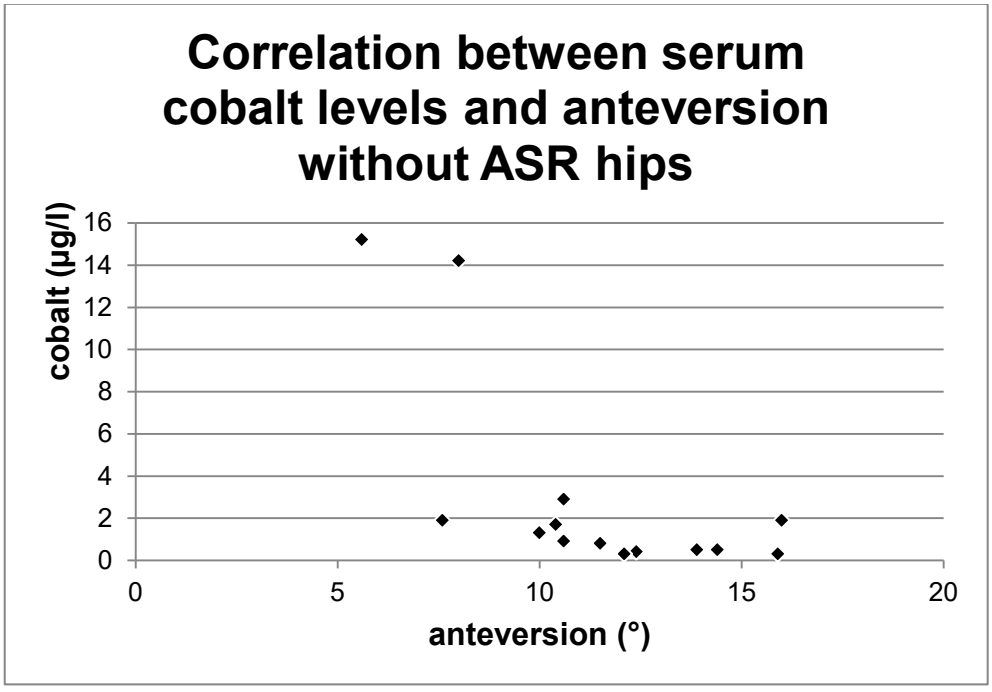

Figure 19: The diagram exhibits the correlation between serum cobalt levels and the anteversion after excluding the ASR hips.

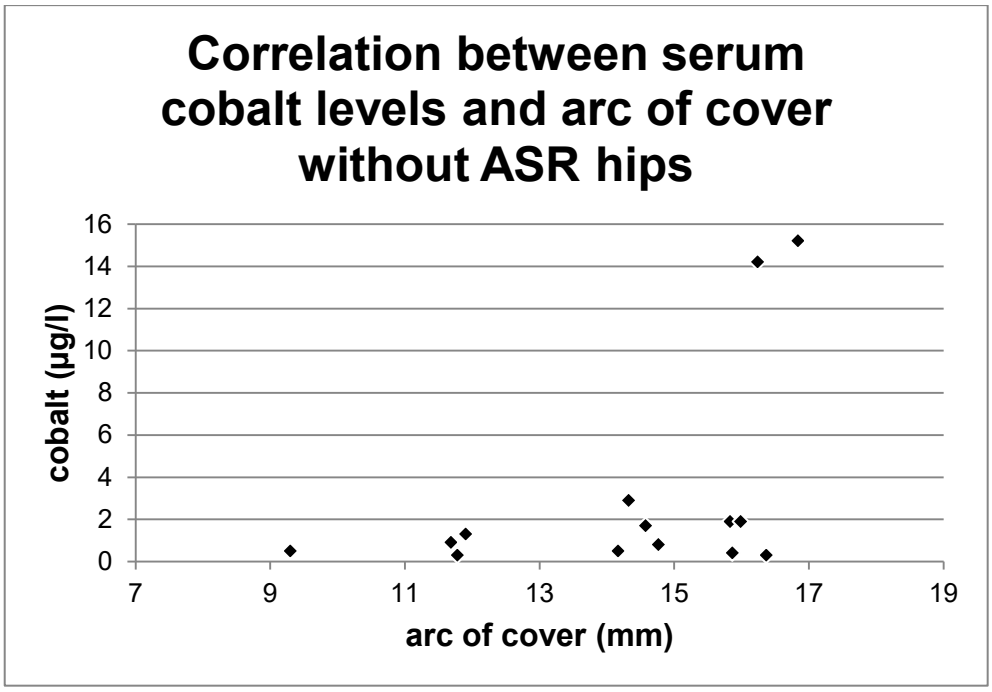

Figure 20: In this diagram the correlation between serum cobalt levels and the arc of cover after exclusion of the ASR hips is shown.

A further analysis showed that there was no correlation between the BMI and the levels of Co or Cr (see Table 5 and 6).

		Cobalt	BMI
Cobalt	Pearson-Korrelation	1	-,077
	Sig. (2-seitig)		,778
	N	16	16
BMI	Pearson-Korrelation	-,077	1
	Sig. (2-seitig)	,778	
	N	16	16

Table 5: This table shows an extract of the correlation analysis of the cobalt values and the BMI.

		Chromium	BMI
Chromium	Pearson-Korrelation	1	-,049
	Sig. (2-seitig)		,857
	N	16	16
BMI	Pearson-Korrelation	-,049	1
	Sig. (2-seitig)	,857	
	N	16	16

Table 6: The table illustrates the correlation analysis of chromium levels and the BMI.

3.7. Outliers

During the analysis we detected two patients with Co and Cr levels which were comparable high, as measured in patients with ASR devices. These two patients will be discussed separately, to identify possible reason for the elevated serum metal ion levels.

3.7.1. Patient 1

The first patient was a 89 year-old male patient with a BMI of 23,4 at time of operation. The patient received a total hip replacement on the right side in consequence of an osteoarthritis of the joint.
The preoperative Harris hip score was 36 points, which improved to 97 points 5 years postoperatively. The actual WOMAC score was 4 points at time of follow-up.

The measured Cr value was 4,98 µg/l, which was obviously over the limit of 1,9 µg/l. The Co value was with 14,2 µg/l, also higher than the reference value of 0,6 µg/l.

The renal parameters were:

- 1,67 mg/dl for creatinine
- 79,00 mg/dl for urea
- 7,3 mg/dl for uric acid.

All renal parameters were higher than the upper limits from the laboratory. The CRP value was within the normal range.

The measured inclination angle was 36,6 degrees and the arc of cover was 16,2 mm. The anteversion was 8,00 degrees and therefore lower than the normal range of 10 to 20 degrees.
The reason for the elevate serum metal ion levels in this patient might be his low degree of anteversion or the elevated renal parameters.

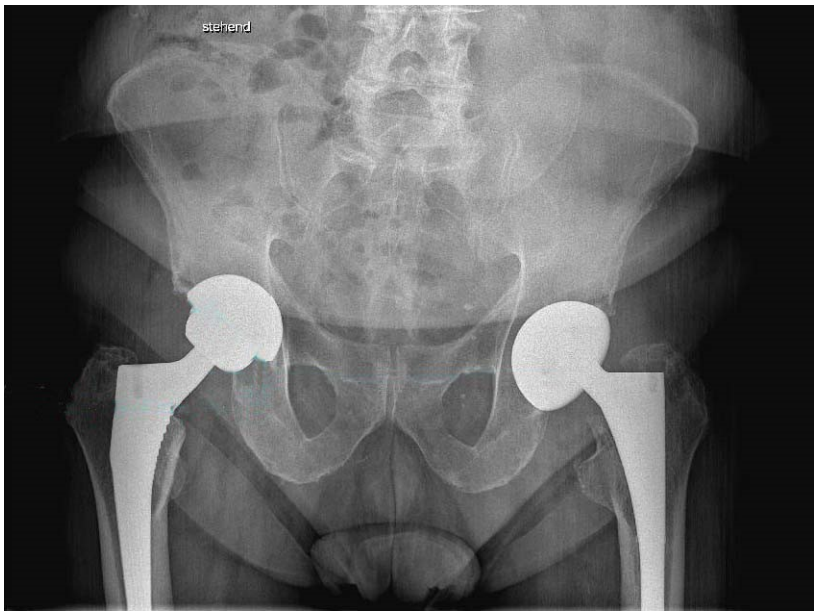

Figure 21: The figure shows the X-ray of patient one in anterior-posterior view

3.7.2. Patient 2

The second patient was a 91 year-old man with a BMI of 28,7. He also received the hip replacement on the right side in consequence of osteoarthritis. The preoperative Harris hip score was 41 points and enhanced to 76 points at 5-years of follow-up. The WOMAC score was 14 points.
The measured Cr level was 5,49 µg/l at a limit of 1,9 µg/l. The Co level was 15,2µg/l at a limit of 0,6µg/l. This was also higher than the normal range.
The analysis of the renal parameters showed, that all were in the normal range. They were as following:

- 0,97 mg/dl for creatinine
- 22 mg/dl for urea
- 5,8 mg/dl for uric acid

The CRP was also lower than the limit of 5 mg/l.

The measurement showed an inclination angle of 39,1 degrees and an arc of cover of 16,84 mm, whereas the anteversion was 5,6 degrees. This was under the normal range of anteversion (10 to 20 degrees).

Also this patient might have elevated metal ion levels caused be his low degree of anteversion.

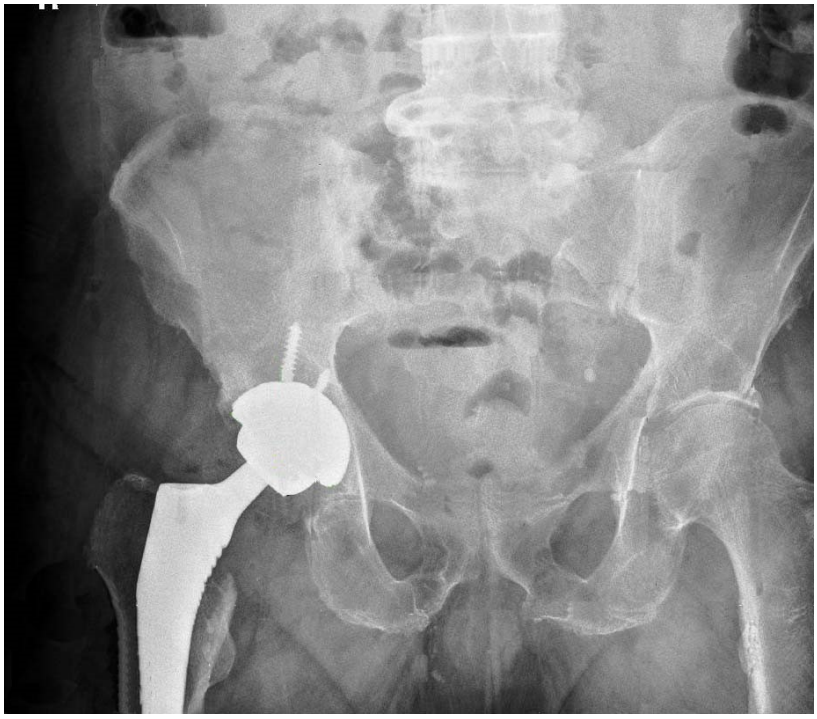

Figure 22: This figure shows the x-ray in anterior-posterior view of patient two

3.7.3. Patient with revision

One female patient was included in the study although there was a revision surgery in January 2014.

The patient received the ceramic-on-metal bearing in January 2010 but she had persistent pain in the right hip. In January 2014, a metal ion determination of serum and the puncture fluid was done. These measurements showed a Co value of 0,03 µg/l and a Cr level of 1,17 µg/l in the serum but the analysis of the punctate showed high elevated levels of Co and Cr. Therefore, the patient underwent revision surgery with exchange of the tribological bearing to a ceramic-on-ceramic bearing due to pain and metal wear.

The actual measurements of serum metal ion concentrations showed decreasing Cr values (from 1,17 to 0,09 µg/l from January to October 2014) and whereas the Co values remained unchanged at 0,3 µg/l.

The inclination, anteversion and the arc of cover were in a normal range and also the renal parameters were unremarkable.

4. Discussion

The aim of the study was to determine the serum Co and Cr levels of patients, who received a THA with a ceramic-on-metal bearing. Further, a correlation analysis of the metal ion levels with the alignment parameters of the implants was calculated. Except of patients with ASR devices on the contralateral side, two outliers were detected with elevated Co and Cr levels over the international reference level of 7µg/l. The statistical analysis showed a strong correlation between the anteversion of the cups and the measured Co and Cr levels. A correlation of the inclination and the arc of cover with the serum metal ion levels could not be detected.

In 2010, the UK medicines and Health Products Regulatory Agency (MHRA) related, that Co and Cr levels higher than 7 µg/l were associated with higher revision rates, soft tissue reactions and pain. In the current study the participants had serum metal ion levels lower than 7 µg/l, except of patients with ASR devices on the contralateral side as well as the two outliers.

A further result of the current series was elevated serum Co and Cr levels compared to control group. The normal Co levels in serum were between 0 and 0,6 µg/l. The mean value of the study participants excluding the ASR devices and the two outliers amounted 1,2 µg/l. The range of the Cr levels in serum were between 0 and 1,9 µg/l and the mean measured levels in our patients after exclusion of ASR devices and outliers was 0,93 µg/l. Similar results were published in the study of Zeng et al. (16) which were structured like the current series. Apart of the metal ion levels, which are higher than the levels measured in our patients, they also did not find a correlation between the Co and Cr levels and the cup abduction angle or bilateral arthroplasty. In contrast to the current study, Zeng et al. detected a correlation between the metal ion levels and the BMI. Similar results are reported in the MoM literature (18, 64). Like in the recent study, the levels of inflammatory factors and the mean renal parameters were within the normal range as reported by Zeng et al. (16).

Studies from Williams et al. (15), Isaac et al. (17) and Kazi et al. (18) concerning ceramic-on-metal bearings show significant lower metal ion levels compared to metal-on-metal bearings. In the study of Kazi et al. (18) no correlation between the metal ion levels and the BMI, the version of the cup or the inclination were

detected. But they observed significantly higher metal ion levels in these patients with bilateral THA. This could not be observed in patients with bilateral implantation in the current series.

In comparison to the study of Williams et al. (15) for CoM bearings, with an observation time of two years, the patients of the current series showed lower metal ion levels. Williams et al. (15) related 45 µg/l for Co and 13 µg/l for Cr as maximal values. In our study, we found the highest Co value in serum of 39 µg/l and the highest Cr value of 22,55 µg/l in a patient with an ASR device on the contralateral side. Excluding the patients with ASR devices, we found a maximum Co value of 15,2 µg/l and a maximal Cr value of 5,49 µg/l at one of our outliers. These values are clearly below the levels presented by Williams et al. (15).

One reason for the high levels in the study of Williams et al. (15) may be, that the metal ion levels are higher within the first years after implantation, which decreases towards the running in period. Further, the above-mentioned ceramic-on-metal studies are mostly over a shorter period of follow-up compared to the current study. Increased metal ion levels during the running in period, were first described for example for metal-on-metal bearings by Heisel et al. (65). One limitation of the actual study was, that the serum metal ion determination was done only once at a follow up of 5 years. Therefore, it is not possible to make any statement about the course of serum metal ion concentrations.

Another publication of Zeng et al. (30) investigated nearly the same parameters for ceramic-on-metal bearings compared to our study and included cases with a mean follow-up of 50 months. Another similarity of the two studies is the used prosthesis components. The CoM bearing contained the Biolox® delta ceramic head and the Ultamet® acetabular liner of a Co-Cr-Mo alloy. Another accordance of these two studies is the use of the Harris Hip score and the WOMAC score. Zeng et al. (30) showed a strong improvement of preoperative scores compared to the values at 50 months of follow-up. The same result could be observed in our study. The mean Co value in this published study amounts to 2.82 µg/l and the mean Cr level was 2,41 µg/l at the 50-months follow-up point. The mean serum metal ion levels found in our study were 1,59 µg/l for Cr and 3,1 µg/l for Co after exclusion of the ASR devices. Zeng et al. (30) found a correlation between the serum metal ion

levels (Co, Cr and Mo) and the BMI but there was no coherence among the ion levels and the position of the implant. In contrast to the current study, Zeng et al. (30) did not describe an analysis of the renal parameters. These values, especially the creatinine, have an important influence on the serum metal ion levels on the one hand and it is an indicator for a renal dysfunction on the other hand, which might result in enhanced ion levels in blood.

Another study concerning serum metal ion levels after THA was carried out at the Department of Orthopaedics and Orthopaedic Surgery at the Medical University of Graz. In 2011, Matthias Trennheuser published the first results in his diploma thesis “Metal ion levels in patients before and after total hip arthroplasty with metal-on-metal large-head bearing” (66). The first results were from one year post operation. The publication of Maurer-Ertl et al. presented the data of the same study two years postoperatively (59). This study was continued and we took the values of on an average of 5 years post operatively to compare them with the results of the ceramic-on-metal bearing also taken on an average of 5 years following operation.

The comparison of the mean values of Co and Cr in the serum resulted in significant lower values at the ceramic-on-metal than in the values of metal-on-metal bearings. The mean Co value in MoM bearings amounted 6,0 µg/l and the mean Cr level was 6,02 µg/l, whereas the mean Co levels of the CoM bearings after exclusion of the ASR devices was 3,15 µg/l and the mean Cr level was 1,59 µg/l.

Further studies compared the CoM and MoM bearings in laboratory (15, 29, 58, 67).

Concerning the alignment of the prosthesis components, the study of Hart et al. (68) showed that the metal ion levels are higher in patients with an inclination angle higher than 50 degrees. Three patients in the current study, having an inclination angle higher than 50 degrees, showed Co and Cr levels in a normal range. A comparison of these two studies was not possible because Hart et al. analysed MoM and MoP bearings in contrast to our CoM bearings. There are further results, which lead to the opinion, that the inclination has an impact on the metal ion levels, measured in patients and simulator studies (69, 70).

Different studies on CoM, as well as MoM bearings have shown that malposition of the prosthesis, especially the cup, leads to strong contact between head and rim of the cup. In a simulator study, this malposition and increased exposure led to elevated metal ion levels in the lubricant. This was observed for example in the study of Williams et al. (15).

The study´s hypothesis was that a deviation of the standard inclination, anteversion and the arc of cover results in higher metal ion levels, than in patients with a normal implant alignment. In three cases of our study, the inclination angle was out of the ideal range between 35 and 55 degrees. One patient showed normal Co and Cr levels, the second was one of the outliers and the third was a patient with an ASR device on the contralateral side. Concerning the anteversion, we detected four patients, who had devices out of the normal range. Two of them were the outliers, one had unobtrusive serum metal ion levels and the fourth was the patient with the ASR implant. We detected just one patient with an arc of cover less than 10mm and this patient showed normal Co and Cr concentrations.

In our study we could not find neither a correlation between the inclination angle of the cup, nor the arc of cover and the measured Cr or Co levels but we found a correlation between the anteversion in context to the Co and Cr values. The study of Hart et al. (71) showed that the inclination and anteversion angles had more effect on the Co levels than on the Cr levels. This observation could also be made in the current series

Outliers

Following exclusion of the outliers from the analysis the mean metal ion levels in patients with CoM bearings were lower. This resulted also in a higher difference compared to the values of MoM bearings measured at our department. These two outliers have extremely raised the mean levels of Co and Cr.

Outlier 1 had extremely high levels of Co and Cr. In this patient we found some characteristics which were described as risk factors for elevated metal ion levels.

The first one was an inclination angle barely in the normal range. This could lead to these elevated levels as well as his lower angle of anteversion.

Another explanation for his high Co and Cr values could be, that all of his renal parameters were elevated. As we described before, impaired renal function can lead to an accumulation of the metal ions in the body and further to higher levels in serum.

Outlier 2 showed also highly elevated metal ion levels compared to the other patients with CoM bearings. The patient had no other metal implants in the body and the measurement showed an inclination angle of 39,1 degrees, which was barely in the normal range. Also the arc of cover was in the normal range. The analysis of the renal parameters and the CRP were absolute unobtrusive.
According to our hypothesis, one reason for elevated metal ion concentrations in this could be a low anteversion angle (5,6 degrees).

The current series also included patients with malpositioned implants or patients who are barely in the normal range, but they do not exhibit abnormally high metal ion levels. Therefore, it can be stated that metal ion levels might be influenced by other factors than the component alignment, or differ from patient to patient.

During the literature research we found some articles concerning factors, which might influence the absorption, metabolism and excretion of different metal ions.

1. Vitamin E: Patlar et al. (72) showed that the supplementation of vitamin E leads to an increase of Co and Cr levels. Vitamin E has an influence on the metabolism of minerals as calcium, but also for Cr, iron and other elements.
2. Albumin: Co can be transported through the circulation of albumin. In combination with fatty liver disease this binding capacity can be reduced (73).
3. Diabetes: Studies have shown that diabetes can have an influence on the metabolism of Cr and other elements. Furthermore these elements can influence the sensitivity for insulin (74, 75).

4. Interleukin 1-α: This protein leads to decreased absorption, retention and urinary excretion of Cr (76).
5. Indomethacin (NSAID): The mechanism works by blocking prostaglandin synthesis, which leads to an enhanced chromium absorption (77).
6. A supplementation of Co or Cr, uptaken for example by nutrition, can lead to elevated levels.

It was not possible to check all the parameters in the current series. The medication at time of operation of our outliers did not point to one of the influencing factors, listed above.

Another important factor is the consequence of high metal ion levels. Therefore, a review of the literature was done and some cases were found concerning intoxication, caused by total hip replacement with ceramic-on-metal bearing or metal-on-metal bearing (24-28).

In the case published by Steens et al. (24) the patient showed the typical symptoms for an injury caused by extremely high Co and Cr levels: Loss of hearing, aggravation of the eyesight and a decreased sensibility at the feet. The results of the serum measurement revealed a Co concentration of 398 µg/l and a Cr concentration of 56 µg/l. After exchange arthroplasty of the prosthesis, total synovectomy and resection of the periarticular soft tissues as well as chelation therapy, the metal ion concentration decreased and the auditory ability as well as the sensibility of the feet showed an improvement.

Oldenburg et al. (25) presented a case of a man with a sever Co intoxication of a metal-on-polyethylene implant. The patient underwent revision-surgery of the implant due to breakage of the ceramic head. After this revision surgery, the patient developed symptoms of Co intoxication like neurological symptoms, hypothyroidism, cardiac symptoms and hearing loss. During the 2nd revision surgery, massive metallosis was found and blood concentrations of 625 µg/l for Co and 81 µg/l for Cr were detected. These values decreased following revision surgery.

Another case of Co intoxication was published by Pazzaglia et al. (78) following revision surgery of a broken ceramic-on-ceramic bearing to a metal-on-polyethylene bearing. The first symptoms appeared 5 months after the operation, and were denoted as reduction of sight and hearing. Beside the complete loss of eyesight and hearing, the patient developed paraesthesia and weakness of the upper and lower limbs. One year later, the metal ion levels in blood were measured. During revision surgery a part of the ceramic stayed embedded on the surface of the polyethylene socket, which was used in revision, and led to high wear of the Co-Cr-Mo alloy head due to third body wear (78).

Rizzetti et al. (28) presented a case of 58-year old woman with the typical symptoms of Co or Cr intoxication. She complained about a progressive loss of hearing and eyesight which resulted in completely blindness and severely deafness. The first step in therapy was a chelation therapy with edetic acid which led to decreased metal ion levels. The neurological symptoms improved only after the revision surgery (28).

All of these cases have one in common, that all patients had highly elevated Co and Cr levels in serum or plasma. The quoted values are manifold higher, than the measured levels at our patients, including the outliers and the ASR patients.
Therefore, the values of 0,09 to 22,55 µg/l for Cr and 0,3 to 39,0 µg/l for Co, measured in the current study, seem not alarming, but a regularly follow-up with metal ion determination is recommended.

Another important factor is the influence of metal ions on the renal function. On the one hand, we found studies, showing that the metal ions have influence on the function and the values of the kidney. On the other hand, there is also a study which disproves this predication (79). At our analysis, we could not find a correlation between the renal parameters and the levels of Co and Cr. One patient in the current series had an elevation of creatinine, urea and uric acid but this was one of our outliers and his high Co and Cr values could be also attributable to the implant alignment with low degrees of anteversion. Some further patients showed also an enhancement of single parameters of the kidney. However, this increase of the renal parameters was not clear relatable to the elevated metal ions.

The approach to the patients with elevated serum metal ion levels should be adapted to that of the metal-on-metal bearing. Therefore a consensus recommendation was published by the European Federation of National Associations of Orthopaedics and Traumatology (EFORT), the Arbeitsgemeinschaft Endoprothetik (AE) and the Deutsche Arthrosehilfe (DAH) in April 2012. All patients who received the bearing should be re-examined in regularly clearances. If abnormalities occur during these follow-up checks, further imaging like MARS-MRT should be considered and metal ion levels should be determined. If the metal ion levels would be higher than the international reference value of 7 µg/l, further diagnostics with MARS-MRT, ultrasound and/or CT should be performed to exclude ARMD. This should also be done if the patient was asymptomatic (80).

The current study had some limitations. We performed the measurement just one time, 5 years after the operation, but we have no preoperative metal ion levels or values measured during the first months after implantation. It would be very helpful to compare the particular preoperative and postoperative values of the persons, to see, if there is a change and also to trace the exact development of the values.
The second limitation of the study was that not all persons received the same prosthesis´ components. In one case, an Allo Pro stem was implanted instead of the Corail stem, which was used at the remaining implantations.
Another problem is the small group of study participants. Most of our patients have another hip implant system on the contralateral side. Patients with an ASR device on the contralateral side showed metal ion levels which were not representative for ceramic-on-metal bearing. On that account these patients were excluded from analysis.

5. Conclusion

Concerning our study we found a significant correlation between the anteversion and the measured metal ion levels in the serum whereas there was no correlation between the component alignment and the BMI.

Nevertheless, it can be stated that metal ion levels of patients with the ceramic-on-metal bearings are lower compared to Co and Cr concentrations of patients with metal-on-metal bearings. This assumption was confirmed by the result of the current series and on the other hand by the results of the recent literature.

In the current series the results were extremely influences by the two outliers. In context to that, it would require a more precise analysis of other factors, which can lead to higher Co and Cr levels.

Following exclusion of the two outliers and one ASR device, all patients had Co and Cr concentrations lower than the international reference value of 7 µg/l.

For the outliers we recommend regular follow-ups with further serum metal ion level determination. In case of still increasing serum metal ion concentration and/or appearance of an ARMD we would recommend revision surgery with exchange of the tribological bearing.

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7. Appendix

7.1. informed consent - Patienteninformation und Einwilligungserklärung zur Teilnahme an der klinischen Studie

Serum-Metallionenspiegel 5 Jahre nach einer totalen Hüftendoprothese mit Keramik-Metall-Gleitpaarung

Sehr geehrte Patientin, sehr geehrter Patient!

Wir laden sie sehr herzlich ein, an der oben genannten klinischen Studie teilzunehmen. Bitte lesen sie die folgenden Seiten aufmerksam durch. Wir stehen ihnen jederzeit gerne für Fragen zur Verfügung.

Ihre Teilnahme an dieser klinischen Prüfung erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Ihre medizinische Betreuung.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der klinischen Prüfung vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Prüfung im Klaren sind.

1. Was ist der Zweck dieser Studie

In den letzten Jahren wurde Ihnen an der Universitätsklinik für Orthopädie in Graz eine Hüfttotalendoprothese mit einer speziellen Metall-Keramik Gleitpaarung implantiert. Zweck der klinischen Studie ist es, nach erfolgter Blutabnahme die Konzentrationen von Kobalt und Chrom im Serum zu messen, welche international als Indikatoren für das Abriebverhalten der Gleitpaarung verwendet werden.

2. Wer organisiert diese Studie

Diese Studie wird von der Universitätsklinik für Orthopädie der medizinischen Universität Graz unter der Leitung von Univ. Prof. Dr. A. Leithner und OA Dr. W. Maurer-Ertl organisiert und durchgeführt.

3. Wie ist der Ablauf der klinischen Studie?

Im Zuge einer Routinekontrolle, werden zunächst aktuelle Röntgenbilder angefertigt Dabei besteht eine Strahlenbelastung von 1mSv. Diese werden in weiterer Folge vermessen. Als nächster Schritt ist studienbedingt eine Blutabnahme geplant. Dabei werden 2 mal 6ml Blut abgenommen. Das entspricht ungefähr 1 Teelöffel. In einem Labor werden dann die Metallionenkonzentrationen in ihrem Blut gemessen. Danach folgt ein Vergleich bzw. eine statistische Auswertung der Daten.

4. Was sind die Risiken für Sie durch die Teilnahme an dieser Studie

Grundsätzlich bestehen keine voraussehbaren zusätzlichen Risiken durch die Teilnahme an dieser Studie, außer solchen, die normalerweise mit Blutabnahmen und Röntgenkontrollen verbunden sind.

5. In welcher Weise werden die im Rahmen dieser klinischen Prüfung gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Prüfer/innen und deren Mitarbeiter/innen Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden („personenbezogene“ Daten). Weiters können Beauftragte von in- und ausländischen Gesundheitsbehörden, der zuständigen Ethikkommission Einsicht in diese Daten nehmen, um die Richtigkeit der Aufzeichnungen zu überprüfen. Diese Personen unterliegen einer gesetzlichen Verschwiegenheitspflicht.

Die Weitergabe der Daten im In- und Ausland erfolgt ausschließlich zu statistischen Zwecken in verschlüsselter (nur „indirekt personenbezogener“) oder anonymisierter Form, das heißt, Sie werden nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser klinischen Prüfung werden Sie nicht namentlich genannt.

Die Prüfer/innen und ihre Mitarbeiter/innen unterliegen im Umgang mit den Daten den Bestimmungen des österreichischen Datenschutzgesetzes 2000 in der jeweils geltenden Fassung.

Wenn Sie Ihre Einwilligung zurückziehen und damit Ihre Teilnahme vorzeitig beenden, werden keine neuen Daten mehr über Sie erhoben.

6. Können sie die Teilnahme an dieser Studie vorzeitig beenden?

Sie können ohne Angabe von Gründen jederzeit von der Teilnahme an dieser Studie zurücktreten ohne dass ihnen dadurch Nachteile in der weiteren Betreuung bzw. in der Nachkontrolle ihrer Prothese entstehen. Die Qualität der medizinischen Betreuung an der Klinik für Orthopädie ist in jedem Fall garantiert, unabhängig davon ob Sie an dieser Studie teilnehmen oder nicht.

Ich willige hiermit zur Teilnahme an der Studie
„Serum-Metallionenspiegel 5 Jahre nach einer totalen Hüftendoprothese mit Keramik-Metall-Gleitpaarung“
ein.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

Graz am …… ……..
Unterschrift Patient

Graz am …… ……..
Unterschrift verantwortlicher Arzt

7.2. CRF

Case Report Form

Serum-Metallionenspiegel 5 Jahre nach einer totalen Hüftendoprothese mit Keramik-Metall-Gleitpaarung

Vorname:

Nachname: Patientenetikette

Gebdatum:

Geschlecht: ☐ weiblich ☐ männlich

Initialen: _____ (Vorname Nachname)

Patientenfortlaufnummer: _____

Körpergröße (m): _____

Körpergewicht (kg): _____

Einschlusskriterien	**Ja**	**Nein**
• Alter 18-91	☐	☐
• Primäre Implantation einer Hüfttotalendoprothese	☐	☐
• Implantation zwischen 2008 – 2010	☐	☐
• Primäre oder sekundäre Coxarthrose	☐	☐

Ausschlusskriterien	**Ja**	**Nein**
• Patient wünscht nicht an der Studie teilzunehmen	☐	☐

Datum Studieneinschluss: ____ / _____ / _____ TT MM JJJJ

OP-Termin: ____/_____ / _____TT MM JJJJ

Hüftprothese: ☐ links ☐ rechts☐bds

Femurimplantat: Durchmesser Kopf: _____mm

Schaftgröße: _____

Durchmesser Pfanne: _____mm

Zusätzliche Implantate im Körper: ☐ ja ☐ nein

- TEP: Schulter: Bezeichnung laut OP-Bericht
  Hüfte: ☐MoM☐ Metall/Keramik ☐PE/Keramik
  ☐Keramik/Keramik
  Durchmesser der Implantate: _____
  Knie: Bezeichnung laut OP-Bericht
- Sonstige:

_____

_____

7.3. Harris Hip score

PAIN

- ❑ None (44)
- ❑ Slight (40)
- ❑ Mild (30)
- ❑ Moderate (20)
- ❑ Marked (10)
- ❑ Totally Disabled (0)

FUNCTION

Limp

- ❑ None (11)
- ❑ Slight (8)
- ❑ Moderate (5)
- ❑ Severe (0)
- ❑ Unable to walk (0)

Support

- ❑ None (11)
- ❑ Stick long walks (7)
- ❑ Stick full time (5)
- ❑ Crutch (3)
- ❑ 2 Sticks (2)
- ❑ 2 Crutches (0)
- ❑ Unable to walk (0)

Distance walked

- ❑ Unlimited (11)
- ❑ 600 metres (8)
- ❑ 200-300 metres (5)
- ❑ Indoors only (2)
- ❑ Bed and chair (0)

ACTIVITIES

Stairs

- ❑ Normally (4)
- ❑ Normally with banister (2)
- ❑ Any method (1)
- ❑ Not able (0)

Socks/Tie shoes

- ❑ With ease (4)
- ❑ With difficulty (2)
- ❑ Unable (0)

Sitting

- ❑ Any chair, one hour (5)
- ❑ High chair, half hour (3)
- ❑ Unable to sit half hour [any chair] (0)

Public Transport

- ❑ Able to enter (1)
- ❑ Unable to enter (0)

ABSENCE OF DEFORMITY

Requires absence of all four below:

- ❑ Yes (fixed adduction <10°, fixed internal rotation [in extension] <10°, leg length discrepancy <3.2cm and fixed flexion >30°)
- ❑ If less than all of above

RANGE OF MOTION

Flexion _____

Abduction _____

Adduction _____

External rotation _____

Internal rotation _____

Total degrees _____

ROM SCORE

- ❑ 210°-300° (5)
- ❑ 160°-209° (4)
- ❑ 100-159° (3)
- ❑ 60°-99° (2)
- ❑ 30-59° (1)
- ❑ 0°-29° (0)

CUMULATIVE SCORE

Pain (max 44)	_____
Function (max 33)	_____
Activities (max 14)	_____
Absence of deformity (max 4)	_____
Range of motion (max 5)	_____

Total HHS (max 100) **_____**

7.4. WOMAC Score

Dieser Score besteht aus 24 Fragen (5 Schmerz, 2 Steifigkeit und 17 körperliche Funktion). Insgesamt sind somit 240 Punkte möglich, 0 Punkte gilt als bestes, 240 Punkte als schlechtestes Ergebnis.

Schmerzfragen:

Die folgenden Fragen beziehen sich auf die Stärke der Schmerzen, die Sie in ihre Hüfte haben. Bitte geben Sie für jede Frage die Stärke der Schmerzen an, die Sie in den letzten 2 Tagen verspürt haben (Bitte kreuzen Sie das zutreffende Kästchen an).

Wie starke Schmerzen haben Sie beim

1. Gehen auf ebenem Boden

0	1	2	3	4	5	6	7	8	9	10

keine Schmerzen extreme Schmerzen

2. Treppen hinauf oder hinuntersteigen

0	1	2	3	4	5	6	7	8	9	10

keine Schmerzen extreme Schmerzen

3. Nachts im Bett

0	1	2	3	4	5	6	7	8	9	10

keine Schmerzen extreme Schmerzen

4. Sitzen oder Liegen

0	1	2	3	4	5	6	7	8	9	10

keine Schmerzen extreme Schmerzen

5. Aufrecht stehen

0	1	2	3	4	5	6	7	8	9	10

keine Schmerzen extreme Schmerzen

Fragen zur Steifigkeit:

Die folgenden Fragen beziehen sich auf die Steifigkeit (nicht die Schmerzen) ihrer Hüfte. Steifigkeit ist ein Gefühl von Einschränkung oder Langsamkeit in der Beweglichkeit, wenn Sie ihre Gelenke bewegen. Bitte geben Sie für jede Frage die Stärke der Steifigkeit an, die Sie in den letzten 2 Tagen verspürt haben (Bitte kreuzen Sie die zutreffenden Kästchen an).

6. Wie stark ist die Steifigkeit gerade nach dem Erwachen am Morgen?

0	1	2	3	4	5	6	7	8	9	10

keine Steifigkeit extreme Steifigkeit

7. Wie stark ist ihre Steifigkeit nach Sitzen, Liegen oder Ausruhen im späteren Verlauf des Tages?

0	1	2	3	4	5	6	7	8	9	10

keine Steifigkeit extreme Steifigkeit

Fragen zur körperlichen Tätigkeit:

Die folgenden Fragen beziehen sich auf Ihre körperliche Tätigkeit. Damit ist Ihre Fähigkeit gemeint, sich im Alltag zu bewegen und sich um sich selbst zu kümmern. Bitte geben Sie für jede der folgenden Aktivitäten den Schwierigkeitsgrad an, den Sie in den letzten 2 Tagen wegen Beschwerden an ihrer Hüfte gespürt haben (Bitte kreuzen Sie die zutreffenden Kästchen an).

8. Wie groß sind ihre Schwierigkeiten beim Treppen hinuntersteigen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

9. Wie groß sind ihre Schwierigkeiten beim Treppe hinaufsteigen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

10. Wie groß sind ihre Schwierigkeiten beim Aufstehen vom Sitzen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

11. Wie groß sind ihre Schwierigkeiten beim Stehen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

12. Wie groß sind ihre Schwierigkeiten beim sich zum Boden Bücken?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

13. Wie groß sind ihre Schwierigkeiten beim Gehen auf ebenem Boden?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

14. Wie groß sind ihre Schwierigkeiten beim Ein und Aussteigen in ein Auto?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

15. Wie groß sind ihre Schwierigkeiten beim Einkaufen Gehen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

16. Wie groß sind ihre Schwierigkeiten beim Socken/Strümpfe anziehen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

17. Wie groß sind ihre Schwierigkeiten beim Aufstehen aus dem Bett?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

18. Wie groß sind ihre Schwierigkeiten beim Socken/Strümpfe ausziehen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

19. Wie groß sind ihre Schwierigkeiten beim Liegen im Bett?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

20. Wie groß sind ihre Schwierigkeiten beim ins Bad/aus dem Bad steigen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

21. Wie groß sind ihre Schwierigkeiten beim Sitzen?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

22. Wie groß sind ihre Schwierigkeiten beim sich auf die Toilette Setzen/Aufstehen von der Toilette?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

23. Wie groß sind ihre Schwierigkeiten bei anstrengenden Hausarbeiten?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

24. Wie groß sind ihre Schwierigkeiten bei leichten Hausarbeiten?

0	1	2	3	4	5	6	7	8	9	10

keine Schwierigkeiten extreme Schwierigkeiten

Messergebnisse Metallionen

Datum	Kobalt (µg/dl)	Chrom(µg/dl)

Radiologische Auswertung

· Beinlängenausgleich: ☐ li: _____cm ☐re: _____cm

	Datum	Inklination	Reelle Inklination	Stem-shaft-angle	Stem-neck-alignment	Arcofcover (mm)	Becken-schiefstand
PräOP							
PostOP							

Adverse Events (Clicking, Squeaking, Revision):

_____

_____

_____

_____

_____

_____

_____

_____

_____