Hip Revision Surgery

Identification of Genetic Markers and Evaluation of Novel Treatment Strategies

ANDERS BRÜGGEMANN
Total hip arthroplasty (THA) is, despite its overall good outcome, for some patients followed by hip revision surgery. This seems in parts to be because of genetic susceptibility to revision surgery. The most common reason for revision surgery is aseptic loosening followed by periprosthetic joint infection and dislocation. Cups made of porous tantalum (TM cups) were thought to be favorable in revision surgery to address aseptic loosening, but they seem to confer an increased risk of dislocation. The effectiveness and biocompatibility in vivo of TM cups have not been researched. Dual mobility cups (DMCs) with two articulating surfaces are proposed to prevent dislocation to a higher degree than standard polyethylene liners.

Our hypotheses were that TM cups are superior to their historical treatment alternative in terms of re-revision rates; that the combination of DMC cemented into TM cups would decrease the risk for dislocation after revision surgery; that tantalum ion liberation is marginal after the use of TM cups; and that certain risk genes are associated with an increased risk for revision surgery after total joint arthroplasty.

Studies I&II were register-based cohort studies comparing the implant survival of TM cups and conventional acetabular reinforcement rings (study I), and the combination of TM cups/DMC with TM cups/standard polyethylene liners (study II). We found that TM cups perform equally well as reinforcement rings, but that the two implants differ in their failure mechanisms. Cementing a DMC into TM cups adequately addressed the issue of recurrent dislocation. In study III we investigated whether tantalum ion liberation does occur after implantation of a TM cups and how this affects patients’ immunological response by comparison of three groups: primary non-tantalum THA, primary tantalum THA and revision tantalum THA. We found the highest concentration of tantalum ions in the revision cases, yet tantalum ions were not associated with an immunological response, and we found no signs of alteration in the investigated lymphocyte subsets. Study IV aimed to identify possible risk genes for revision surgery after total hip or knee replacement by a genome wide association study. We found six significant risk genes for the endpoint revision surgery for any reason, and three for the endpoint revision due to aseptic loosening. We found a variety of suggestive risk genes within the region coding for the ABO-system.

In conclusion, the novel treatment options TM cups and DMC show good results in hip revision surgery, but longer follow-up is warranted. The use of porous tantalum seems not to be associated with the immunological activation that can be observed in metallosis. The risk for revision surgery is associated with certain risk genes.

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Till min familj: Tack och förlåt!
This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


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## Abbreviations

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<th>Definition</th>
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<tr>
<td>ALVAL</td>
<td>Aseptic Lymphocyte-dominated Vasculitis-Associated Lesions</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>DMC</td>
<td>Dual Mobility Cup</td>
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<td>GWAS</td>
<td>Genome-Wide Association Study</td>
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<td>HHS</td>
<td>Harris Hip Score</td>
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<td>HOOS</td>
<td>Hip disability and Osteoarthritis Outcome Score</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>MARR</td>
<td>Müller Acetabular Reinforcement Ring</td>
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<tr>
<td>MoM</td>
<td>Metall-On-Metall</td>
</tr>
<tr>
<td>NPR</td>
<td>National Patient Register</td>
</tr>
<tr>
<td>OA</td>
<td>OsteoArthritis</td>
</tr>
<tr>
<td>PE</td>
<td>PolyEthylene</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient Reported Outcome Measures</td>
</tr>
<tr>
<td>SHAR</td>
<td>Swedish Hip Arthroplasty Register</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
</tr>
<tr>
<td>STR</td>
<td>Swedish Twin Register</td>
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<tr>
<td>THA</td>
<td>Total Hip Arthroplasty</td>
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<tr>
<td>TJA</td>
<td>Total Joint Arthroplasty</td>
</tr>
<tr>
<td>TKA</td>
<td>Total Knee Arthroplasty</td>
</tr>
<tr>
<td>TM</td>
<td>Trabecular Metal</td>
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Introduction

Total Hip Arthroplasty

Total hip arthroplasty (THA) has since its introduction become one of the most frequently performed surgeries worldwide. In Sweden alone, more than 18,000 primary THA were performed in 2018. The underlying causes for primary THA vary, with osteoarthritis (OA) as the most common diagnosis in all age groups, followed by fractures of the hip and secondary OA (SHAR 2018). The vast majority of patients treated with THA are satisfied with the procedure, and after their surgery they score significantly higher in patient reported outcome measurements (PROM) (Galea et al. 2019).

Hip Revision Surgery

Despite its overall good outcome, THA is for some patients followed by revision surgery. Labek et al. (2011) described that the mean revision rate after THA is 1.29 per 100 observed component years. This accumulates to a revision rate of 12.9% after 10 years. More than 1,500 revision surgeries are performed annually in Sweden alone (Swedish Hip Arthroplasty Register 2016), and the revision burden is estimated to be greater in other countries (Kurtz et al. 2007). Projections predict an increase in hip revision surgery that would increase the long term (20-30 years) revision rate in Sweden from 20% in 2015 to 23-26% in 2050 (Pabinger et al. 2018). The effects on the individual in terms of physical, mental and social health as well as the overall costs of treatment, rehabilitation and loss of income weigh heavily (Burns and Bourne 2006).

The main reason for revision surgery after THA is aseptic loosening, followed by revisions due to periprosthetic joint infections and recurrent dislocation (SHAR 2018). The underlying causes for revision surgery vary with time after the index procedure: Early revisions are mostly performed due to recurrent dislocations or infection. After approximately 5 years the most common cause for revision is aseptic loosening of either the cup or the stem component, or both (Ulrich et al. 2008, Delaunay et al. 2013).
Genetics of OA, THA and Prosthetic Loosening

Primary OA of the hip is an inheritable trait. In a study by Spencer et al., the relative risk of developing OA – measured both radiologically and clinically – when a family history of THA was present was 3.5 when compared to matched controls (2005). Weldingh et al. established a higher risk for undergoing THA when patients’ mothers had OA (2019). A Danish twin study suggested that “Family factors of genes and shared environment are highly significant and account for 68 % of the variation in the population liability to total hip arthroplasty” (Skousgaard et al. 2015).

Given the established heritability of OA, effort was made to identify gene loci associated with OA (Evangelou et al. 2013). OA could be linked to genetic variants in single nucleotide polymorphisms (SNPs) at close to 100 genetic risk loci (Chapman et al. 1999, Ingvarsson et al. 2001, Southam et al. 2004, Zeggini et al. 2012, Hoaglund 2013, Greenfield 2014, Tachmazidou et al. 2019). Studies indicate that genes encoding for proteins that are part of the inflammatory response might be correlated with the development of OA (Moxley et al. 2010, Kaarvatn et al. 2013). In summary, both within-family studies, twin-pair studies and genome-wide association studies (GWAS) confirm that OA is to some extent inheritable and associated with identified risk loci in various genes.

The risk of prosthetic loosening is also assumed to be associated with certain SNP and thereby to some extent inheritable. In contrast to the epidemiological endeavors made to investigate the heritability of OA, heritability of implant loosening is not investigated in within-family or twin-pair studies. Candidate-driven genetic studies have however shown that genes coding for different proteins, cytokines and receptors that are involved in both bone formation and inflammation are connected to the risk of progression of osteolysis, a hallmark of failed THA. SNPs coding for inflammatory cytokines (tumor necrosis factor (TNF)α, interleukin (IL) 1, 2, 6), receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) pathway, mannose-binding lectin (MBL), matrix metalloproteinases (MMP), and transforming growth factor (TGF) β1, amongst others, are associated with THA-failure due to osteolysis and loosening (Wilkinson et al. 2003, Kolundžić et al. 2006, Malik et al. 2006, Malik et al. 2007, Malik et al. 2007, Gordon et al. 2008, Gallo et al. 2009, Greenfield 2014). Hitherto, only two GWAS have been conducted to search for risk SNP in revision surgery: MacInnes et al. investigated two cohorts from Norway (779 cases and 1,845 controls) and the UK (317 cases and 573 controls) but failed to identify risk SNPs that reached GWAS-significance (2019). Koks et al. (2019) also identified mere suggestive, but not significant, SNPs associated with the risk for revision surgery in their study on 423 arthroplasty-treated patients.
Revision Surgery for Aseptic Loosening

The majority of all revision surgery addresses the acetabular component, the leading cause being aseptic loosening (SHAR 2018). Hence, this thesis focuses on cup revision either in combination with stem revision or without.

At Uppsala University Hospital patients with cup loosening are nowadays routinely treated with insertion of Trabecular Metal (TM) cups. This method was first introduced at our department in 2006 since it was believed to be more effective than historical treatment strategies such as the Müller acetabular reinforcement ring (MARR), either with or without bone grafting. TM cups are made of porous tantalum, which resembles cancellous bone by its mechanical properties. The porosity of up to 80 % enables bone ingrowth (Levine et al. 2006). On a macroscopic and biomechanical level, elasticity combined with high friction enables good primary and secondary stability, even in situations with more pronounced bone loss. Yet, no comparative studies comparing the TM cup with its historical treatment alternative are to be found. MARRs proved to be fairly successful in revision surgery but the technique has its challenges and pitfalls. Stability relies on contact with viable bone. This necessitates bone grafting in many cases, a technique that has proven to be demanding (van Haaren et al. 2007). In situations where osteolysis leaves only 50% or less viable bone contact, MARRs proved not to be a satisfactory concept, and alternative strategies such as Burch-Schneider reinforcement cages and other devices had to be used (Flecher et al. 2008).

The TM cup seems to offer advantages in revision surgery, mainly owing to its superior capability of osseointegration (Bobyn et al. 1999, Kremers et al. 2012, Batuyong et al. 2014). When the studies presented in this thesis were conceived, available studies on TM cups used in revision surgery mostly report satisfactory or good results in the short or medium term, but they lacked a comparison between this novel type of implant and historically used concepts such as the MARR (Unger et al. 2005, Borland et al. 2012, Batuyong et al. 2014).

Revision Surgery for Recurrent Dislocation

Dislocation is one of the major causes for revision surgery and occurs as a result from multifactorial causes: implant-, patient- and surgery-related factors influence the risk for dislocation subsequent to THA. Studies have – amongst others - identified cup malposition, smaller head sizes, a history of spinal fusion and the posterolateral approach as factors increasing the risk for dislocation (Alberton et al. 2002, Zijlstra et al. 2017, Gausden et al. 2018). The key to approaching the unstable THA in a revision setting subsequent to recurrent dislocation is a thorough analysis of all of the risk factors. Implant-related
causes can generally be attributed to implant malpositioning, inadequate restoration of the preoperative biomechanics, soft tissue laxity, or combinations of these factors. The tradition has been to address every single one of these issues, which in the case of malpositioned cups meant revising this component. Cup revisions are mostly combined with an increase in neck length and sometimes head diameter. The method of inserting a posterior lip augmentation device was first described by Olerud and Karlström (1985) and was seemingly associated with a low risk of recurrent dislocation. However, such augmentation devices shape an artificial containment at the cost of reduced range of motion and the risk of impingement. Constrained liners, that might be fairly effective in terms of preventing dislocation, lead to dissociation of the liner/cup interface, breakage and extensive wear (Fricka et al. 2006).

At Uppsala University Hospital patients who undergo revision surgery due to dislocations are treated with a dual mobility cup (DMC). In DMCs the cobalt-chrome femoral head is locked inside a polyethylene liner that articulates freely in the outer, cemented metal shell. The inner articulation surface stands for the greater part of the total range of motion, whilst the outer articulation only is utilized for movements in the final degrees of the range of motion (De Martino et al. 2014). This results in a large range of motion, a large jumping distance, and consequently a reduced risk of dislocation (Grazioli et al. 2012, Abdel 2018). The use of such implants therefore reduced the need for constrained liners, trochanteric osteotomy, soft tissue reconstructions, or insertion of augmentation devices. Indeed, register-based analyses indicate that DMCs are an efficient treatment alternative in cases of cup revision due to dislocation (Hailer et al. 2012). However, register analyses can only investigate surgical endpoints such as re-revision, whereas dislocations and subsequent closed reductions are not registered. Given this, there is a lack of information on how DMCs used in revision surgery perform with respect to the endpoint dislocation.

Metal Ion Liberation Following THA

Following the rise and fall of metal-on-metal (MoM) THA, well-deserved focus has been directed towards the occurrence of metal ion liberation not only after MoM-THA but even after the use of conventional metal-on-polyethylene THA (International Consortium of Investigative Journalists (ICIJ) 2018). Metal debris causes localized soft tissue reactions (aseptic lymphocyte-dominated vasculitis-associated lesions/ALVAL) but can even lead to toxic systemic levels of metal ions (Willert et al. 2005, Wyles et al. 2017). While the effects of metal ion liberation are well investigated for both cobalt and chromium, the two main components in most prostheses, systematic studies investigating tantalum ion liberation after THA are not to be found. ALVAL is mediated through activation of macrophages as a general foreign body response,
B cell activation and organization in lymphoid organs, as well as T cell activation in a similar manner as seen in type IV hypersensitivity (Mittal et al. 2013). The latter is in its turn initiated by HLA-DR$^+$ T cells. Previous studies could establish a correlation between HLA-DR$^+$ T cells and metal ion concentrations after MoM-THA (Hailer NP 2016).

Tantalum is thought to be well tolerated in terms of biological and immunological responses (Balla et al. 2010). Scientific studies concerning elevated tantalum-ions as well as immunological responses in humans in a mid-term follow-up are hard to find (Levine et al. 2006): Tantalum has been investigated in bulk form to evaluate biocompatibility and bone ingrowth, but the effect of tantalum particles has not been researched. Apart from one case report (Babis et al. 2014), there are no studies investigating the effect of tantalum ion liberation, even though tantalum cups have been implanted in more than half a million individuals worldwide.

Research Questions

1. Are Trabecular Metal cups superior to their historical treatment alternatives Müller acetabular reinforcement rings?

2. Can cementing a dual mobility cup into a Trabecular Metal cup reduce the risk of dislocation after hip revision surgery in comparison with standard polyethylene liners in combination with Trabecular Metal cups?

3. Does liberation of tantalum ions occur after total hip arthroplasty with tantalum implants and how is the immune system affected?

4. Do certain single nucleotide polymorphisms associated with a higher risk of revision surgery after arthroplasty surgery exist?
Hypotheses

Our primary hypotheses were:

1. Patients treated with a Trabecular Metal cup in hip revision surgery have a low risk of re-revision when compared to the Müller acetabular reinforcement ring.

2. Patients treated with a dual mobility cup cemented into a Trabecular Metal cup in hip revision surgery have a lower risk of both re-revision and recurrent dislocation than those treated with a polyethylene liner in combination with a Trabecular Metal cup.

3. Liberation of tantalum ions is marginal and does not influence patients’ T-cell mediated response.

4. Certain single nucleotide polymorphisms are associated with a higher risk for revision surgery following total joint arthroplasty.
Methods

Ethics
The research described in this thesis was conducted in accordance with the Helsinki declaration. Approval was requested and granted by the local ethics committee (concerning studies I&II: Etikprövningsnämnden Uppsala, entry no. 2014/108, date of issue April 16, 2014 and entry no. 2014/108/3, and April 19, 2017, study III: Etikprövningsnämnden Uppsala, entry no. 2011/297/4, date of issue January 30, 2018, study IV: Etikprövningsnämnden Uppsala, entry no. 2013/475, date of issue December 11, 2013). For studies II and III, all identified patients received written information about the study and were asked to participate. If the patient chose to participate, an informed consent form was signed. For the register-based parts of studies I, II and IV included in this thesis, written consent from each individual is not requested by the Swedish Patient Law.

Methodological Considerations
All presented studies are to some extent register-based observational cohort studies. Owing to the Swedish personal identification number and the Swedish Hip Arthroplasty Registers (SHAR) completeness of 98.3%, follow-up is close to complete for all register data. For study I, we cross-matched our study population with the SHAR to ensure that no re-revision performed at other Swedish units went unnoticed. Patients’ charts, either from our unit or from the respective external department (whenever the patient came via a referral clinic), were assessed for all patients in study II to ensure that dislocations treated with closed reduction were included in our analysis. Study participants in study III were either identified in the local hip arthroplasty register (“Primary Non-Tantalum”) after uncemented primary THA, or recruited as participants in a randomized controlled trial at our department (ClinicalTrials.gov-Identifier: NCT01630941) that was initiated to investigate the effect of an osteoclast inhibitor after THA (“Primary Tantalum”), or recruited from the cohort in study II (“Revision Tantalum”). For study IV, data from the Swedish Twin Register (STR) with information on more than 60,000 twins was matched on the personal identification number with the National Patient Register (NPR) to gather information on the endpoints of interest.
All data was collected in Excel spreadsheets, imported into the statistical software R (R Core Team 2016) and analyzed using the packages Gmisc, Hmisc, rms, matchit, survival, survminer and ggplot2 along with their dependencies. If not stated otherwise, any p-value<0.05 was considered statistically significant with the exception of study IV, in which a p-value<5*10^{-8} was deemed significant.

Radiography

In order to determine acetabular defects prior to the index procedures in studies I&II, we obtained standard anteroposterior (AP) radiographs of the pelvis. Two independent observers (Anders Brüggemann and resident Erik Fredlund) classified the radiographs along the classification proposed by Paprosky et al. (1994): It consists of three grades with roman numerals and sub-categories for type II and III defects. Type I defects contain mild cases of loose implants with minimal loss of bone stock, marginal migration and intact walls and columns of the acetabulum (see Figure 1). Type II A defects indicate destruction of the superior wall with cranial migration of the implant, type II B defects show superolateral migration and type II C defects include destruction of the medial wall and migration medially. If severe bone loss is present and superior migration of the hip center exceeds three cm, Paprosky classifies these cases as type III (Figure 2). For type III A defects, moderate destruction of the medial wall and posterior column are observed, for type III B, both medial wall and posterior column show severe destruction.
Figure 1. Illustration of acetabular defects as classified by Paprosky. From Telleria and Gee (2013).

The crude agreement percentage between the two observers was 75%, Cohen’s weighted kappa was thus estimated to be 0.9. This value is considered as “almost perfect agreement” according to the suggestions of Landis and Koch (1977). Whenever the two observers failed to reach an agreement, consensus was made under the guidance of the main supervisor (Nils Hailer).

Figure 2. Preoperatively assessed radiographs showing a Paprosky type I (left picture), a Paprosky type IIA of the right hip (center picture), and a Paprosky type IIIB defect of the right hip (right picture).
Implant Survival of TM Cups after Hip Revision Surgery

For study I, we identified all patients who had received either a TM cup or a MARR in our prospective local hip arthroplasty register and checked their charts for re-revision and/or date of death to estimate and compare implant survival and the risk of re-revision. We identified and included all patients that underwent hip revision surgery with a TM cup (during 2008 – 2012) or a MARR (1998 – 2012). Such procedures were termed the “index procedure”. Bone loss prior to the index procedure was assessed by analyzing radiographs obtained preoperatively according to the above described Paprosky-classification.

We cross-matched our data with the SHAR to investigate if subsequent re-revision of the device implanted at the index procedure took place, at what time point the re-revision was performed, and for what reasons. Dates of death were collected for all deceased patients. This enabled unadjusted component survival analysis according to Kaplan-Meier. Mantel-Haenszel’s log-rank test was used to estimate differences in survival between groups. We compared the respective treatment options with re-revision for aseptic loosening as the primary endpoint and re-revision for any reason as the secondary endpoint.

DMC Cemented into TM Cups

All patients receiving a TM cup in hip revision surgery during 2008 – 2016 at our department were included in study II, hence there was an overlap with the population in study I (see Flowchart 1). We split this cohort of 184 patients into two subgroups that were treated either with a DMC cemented into the TM cup (“DMC group”, see Figure 3) or with a polyethylene (PE) liner, either cemented or snap-fitted into the TM cup (“PE group”). Acetabular defects were assessed on radiographs taken prior to the index procedure as described above. We collected all patients’ charts from our unit as well as from the referring department when applicable. This gave information on demographic data as well as all surgery-related information and enabled complete follow-up with respect to the endpoints dislocation, re-revision due to instability, and re-revision for any reason. Dates of death were collected for all deceased individuals. We used the Kaplan-Meier method to estimate implant-survival and assessed difference in survival by Mantel-Haenszel’s log-rank test.
Flowchart 1. Description of the overlap of the study populations in studies I-III.

We invited all patients who were alive at the time study II was conceived to a follow-up at our department including physical examination in order to determine hip function using the Harris hip score (HHS), radiographic imaging to detect asymptomatic loosening or osteolysis, blood sample analysis searching for elevated tantalum-ions, as well as questionnaires, i.e. the hip disability and osteoarthritis outcome score (HOOS) and EQ5D.

Figure 3. Postoperative AP pelvis radiograph after revision surgery with a DMC cemented into a TM cup in the patients’ right hip.
Subsequent to the publication of study II, questions rose as to whether the difference in survival between the DMC- and the PE-group actually are due to the DMC: One might argue that the method of fixation matters, since cementing enables one to achieve a more accurate positioning of the cup as well as an anatomic restoration of the center of rotation. Hence, not the DMC itself, but the cementation would yield a difference in outcomes. In order to evaluate this, propensity score matching (PSM) was used to identify patients experiencing a dislocation, which were then matched to a cohort by the nearest-neighbor principle on the variables DMC/PE, gender, acetabular defect size and age group on a 2:1 ratio, meaning two controls were matched on every case. These subgroups were then further analyzed regarding standardized difference of the means (SDM) for all included variables to assess quality of matching and compared to one other regarding anteversion and abduction of the implant on AP and lateral radiographs as well as restoration of the center of rotation on AP radiographs, expressed as the difference in vertical distance between the operated side vs the reference side.

Since DMCs are assumed to potentially accelerate osteolysis and loosening, we also conducted a preliminary study on revision rates in all patients treated with a DMC during revision surgery at our department with a minimal follow-up of 8 years. These patients’ medical charts were reviewed to identify subsequent dislocations and/or re-revision, along with the underlying cause.

Tantalum Ion Liberation

All patients in study III identified as outlined above were scheduled for a follow-up at our department. Two blood samples were taken and either analyzed at our local laboratory regarding lymphocyte subsets or sent to an accredited external laboratory (ALS, Luleå, Sweden) for the analysis of ion concentrations of tantalum, chromium (Cr), cobalt (Co), and nickel (Ni). Standard AP and lateral radiographs were taken to search for any signs of osteolysis, loosening or migration of the implant, and the HHS was used to assess hip function. Since data were severely skewed they were presented as medians with 95%-Confidence Intervals (95%CI) and non-parametric tests were used for comparison between groups: the Wilcoxon-Mann-Whitney for n=2 groups, the Kruskal-Wallis test for n>2 groups, and Dunn’s test was used as a post-hoc test after the Kruskal-Wallis test. The correlations between metal ion concentration and previously described subtypes of lymphocytes associated with the development of ALVAL were estimated by the method described by Spearman. Furthermore, correlation between metal ion levels and time since surgery was estimated. For Co, Cr, and Ni, the analysis was limited to a comparison between the Primary Non-Tantalum and the Primary Tantalum group, since these metals were not measured in the Revision Tantalum group.
Risk Genes for Prosthetic Loosening

In order to investigate the effect of certain SNPs on the risk for revision surgery, we crossmatched 63,010 Swedish twins from the STR with the NPR on the personal identification number unique to each Swedish citizen. In doing so, we acquired data on demographics via the STR (sex, age, zygosity, self-reported BMI) as well as dates, diagnoses and procedure codes related to total joint arthroplasty (TJA) from the NPR. For a subset of 16,879 twins, genetic data were available. After quality control, these data were analyzed using Illuminas OmniExpress and Psych arrays. The Haplotype Reference Consortium was used as a reference for data imputation. Hereafter, post-imputation quality control was secured by filtering on impute2imputation >0.7. This left 4,548,648 variants in 16,879 study participants and of these, 1,130 had undergone arthroplasty of the knee (519 individuals) and/or hip (685) joint and composed our cohort. Ninety-four study participants were revised due to any reason after TJA and were thus considered as cases for our primary outcome: 32 patients underwent revision TKA and 64 revision THA, hence, two individuals were revised in both the hip and knee joint. Of the 94 revised individuals, 75 underwent revision surgery due to aseptic loosening and these were considered cases for our secondary outcome. Since members of our study cohort were siblings, Cox regression models with a robust sandwich estimator were fitted to account for the relatedness in our data. For this study, only p-values <5*10^-8 were considered statistically significant.
Results

Study I

Study Population

In study I, 111 patients were treated with a TM cup of various designs (see Table 1), and 96 patients received a MARR (see Flowchart 2). Median age was 71 (35–95) years and the acetabular defect sizes were distributed to type I in 39 cases, IIA in 22, IIB in 27, IIC in 43, IIIA in 32, and IIIB in 37 cases (see Figure 4). Mean follow-up differed between the two groups due to the fact that the TM cup replaced the MARR as our standard treatment option in 2008 (Figure 5): TM cups were followed for mean 4.9 (2.1 – 6.9) years, MARR for mean 12 (2.3 – 17) years.

Figure 4. Distribution of the acetabular defect sizes as classified by Paprosky in total counts for the MARR group in light red and the TM group in light blue.
Table 1. Different properties of the TM cups used.

<table>
<thead>
<tr>
<th>Cup</th>
<th>Method of fixation cup</th>
<th>Method of fixation liner</th>
<th>Coated or all-Tantalum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuum</td>
<td>Uncemented press-fit</td>
<td>Snap-fit</td>
<td>Coated</td>
</tr>
<tr>
<td>Trilogy TM</td>
<td>Uncemented press-fit</td>
<td>Snap-fit</td>
<td>Coated</td>
</tr>
<tr>
<td>TM Modular</td>
<td>Uncemented press-fit</td>
<td>Snap-fit</td>
<td>Coated</td>
</tr>
<tr>
<td>TM Revision Shell</td>
<td>Uncemented press-fit</td>
<td>Free cementation</td>
<td>All-Tantalum</td>
</tr>
</tbody>
</table>

Flowchart 2. Inclusion of the study population for study I.

318 revision surgeries identified in the local arthroplasty register

186 TM cups

75 patients excluded:
- double entries
- bilateral observations
- primary arthroplasty

111 patients available for follow-up

132 MARR

36 patients excluded:
- double entries
- bilateral observations
- primary arthroplasty

96 patients available for follow-up
Findings

When investigating implant survival with re-revision for any reason as the endpoint, the estimates in both groups were similar (6-year-survival: 87% [CI: 81–94] for TM cups and 95% [CI: 90–99] for MARR, \( p = 0.06 \)), but the respective mechanisms of failure differed between groups. Whilst the majority of patients treated with a TM cup had to undergo early re-revision due to instability (10/111) after a mean of 0.5 years, most re-revisions in the MARR-group were performed due to aseptic loosening (8/96) after a mean of 5.5 years. In the TM group, 9/10 patients undergoing re-revision due to instability were treated with an uncemented snap-fit liner at index surgery. A subgroup analysis revealed that none of the 25 patients treated with a DMC cemented into a TM cup was revised due to instability, yet two of them underwent revision surgery due to aseptic loosening.

When choosing re-revision due to aseptic loosening as the endpoint, unadjusted implant survival six years after index surgery was estimated at 97% (95%CI: 94–100) for TM cups and 96% (CI: 92–100) for MARR (\( p = 0.6 \)). Due to the scarcity of events, fitting multivariable Cox regression models gave inflated confidence intervals. However, competing risk regression for the endpoint re-revision for any reason showed a hazard ratio (HR) of 0.1 (95%CI: 0.01 – 0.74, \( p =0.03 \)) for the MARR. Operation time was longer (165 vs 130 minutes, \( p =0.003 \)) and blood loss showed a tendency to be larger (1100 vs 600...

Figure 5. Total counts of revision on the y-axis using the TM cup (light blue) or MARR (light red) per year (1998 to 2012), given on the x-axis.
ml, $p=0.05$) in the MARR group; yet, data were missing for the majority of the cases in the MARR group. This difference between the MARR and the TM cups can in parts be explained by the fact that the majority of MARR (76%) were implanted after bone grafting, whilst only 29% of the TM cups were combined with bone grafting.

Thus, even though TM cups seem to present with certain advantages due to the operative technique and show satisfying results in terms of stable fixation, the issue of recurrent dislocation merited further investigation.

Study II

Study Population

The finding of study I was that the majority of re-revisions of patients who had received a TM shell was performed due to instability. This inspired study II in which we followed all patients receiving a TM cup during 2008 – 2016, and specifically investigated whether the combination of a TM shell with a DMC reduces instability. This enlarged our cohort from the 111 cases in study I to 184 patients in study II (see Flowchart 3). Altogether, there were 94 females and 90 males with a mean age of 67 years (35 – 88). Sixty-nine patients received a DMC cemented into a TM cup at index surgery, 115 patients were treated with a standard PE liner, either cemented or snap-fitted. There were differences between groups with regards to the acetabular defect size and follow-up time: A higher proportion of type III defects was found in the DMC group and mean follow-up was longer for the PE group (Figure 6). Out of the 184 included patients, 20 were deceased at follow-up and 50 patients could or would not participate in the clinical follow-up, leaving 114 patients for clinical follow-up. Eighty-four of these completed follow-up at our department, enabling us to determine blood levels of tantalum.
Flowchart 3. Inclusion of the study population for study II.

- **184 revision surgeries with a TM cup**
  - (111 of these included in study I)

- **69 DMC**
  - 5 patients deceased
  - 13 patients excluded due to severe comorbidity
  - 7 patients declined participation
  - 44 patients available for clinical follow-up
    - 25 patients completed follow-up at our department
    - 13 patients completed follow-up at another clinic
    - 6 solely filled in EQ5D and HOOS

- **115 PE liner**
  - 15 patients deceased
  - 24 patients excluded due to severe comorbidity
  - 6 patients declined participation
  - 70 patients available for clinical follow-up
    - 59 patients completed follow-up at our department
    - 2 patients completed follow-up at another clinic
    - 9 solely filled in EQ5D and HOOS
Figure 6. Distribution of the acetabular defect sizes as classified by Paprosky in total counts for the DMC group in light red and the PE group in light blue.

Findings

Due to our chart analysis, we were able to identify four patients that experienced a dislocation but were not re-revised for that reason. These would hence not have been detected by a simple register study: One patient in the DMC group experienced a dislocation, but the patient’s general health prohibited further re-revision, and the implant remained dislocated. In the PE group there were 14 patients experiencing at least one dislocation. Apart from the eleven patients re-revised for instability which would have been detected in the register, three patients would have went unnoticed: One patient remained stable after one closed reduction, the other two were re-revised for other reasons than instability (one infection, one aseptic loosening). Dislocation-free survival after four years was thus estimated to be 99% (95%CI: 96 – 100) in the DMC group, whereas it was 88% (95%CI: 82 – 94, \(p=0.01\)) in the PE group. Exploratory Cox multivariable regression resulted in a HR for dislocation of 0.10 (95%CI: 0.01 - 0.8, \(p=0.03\)) for the DMC group (Figure 7). Standardized difference in means after propensity score matching showed overall good balance (Figure 8). When comparing the dislocated patients with their matched controls, we found no statistically significant differences in cup positioning as expressed by anteversion and abduction or in restoration of the center of rotation (Table 2). We were thus unable to confirm that malpositioning of the cup
or cranialization of the center of rotation would be the underlying causes leading to dislocation in the patients treated with standard PE liners.

Table 2. Radiographic characteristics of the hips of dislocated patients and their matched controls not experiencing dislocation after index revision are given as means with standard deviation (SD).

<table>
<thead>
<tr>
<th>Matched Controls</th>
<th>Dislocated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cranialization of the center of rotation [mm]</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-7 (15)</td>
</tr>
<tr>
<td><strong>Abduction angle [degrees]</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>46 (7)</td>
</tr>
<tr>
<td><strong>Anteversion angle [degrees]</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

Figure 7. Forest plot over hazard ratios for the risk of dislocation for the respective variable included in the analysis: 1st column identifies the variable, 2nd column gives the levels within said variable, 3rd gives the estimated HR with 95%CI and 5th column shows the respective p-value.
When investigating the endpoint re-revision (as reported to the register), we found two re-revisions in the DMC group, both due to loosening at the interface between the TM cup and the host bone, but no loosening between the DMC and the TM cup. Eleven out of 15 re-revisions in the PE group were performed due to instability, the remaining indications were aseptic loosening (two cases), infection (one case), and one patient was re-revised due to persistent pain from a penetrating screw. For the endpoint re-revision due to dislocation survival for the DMC group after 4 years was 100%, whereas it was 89% (95% CI: 84 – 95, \( p = 0.006 \)) in the PE group. With re-revision for any reason as the endpoint, 4-year-survival within the DMC group was 96% (95%CI: 90 – 100), as opposed to 87% (95%CI: 81 – 93, \( p = 0.03 \)) for the PE group. With re-revision due to aseptic loosening as the endpoint, implant survival was similarly good in both groups with no statistically significant difference.

Results from our hitherto unpublished work on patients receiving a DMC during hip revision surgery with a minimum 8-year follow-up do not confirm the assumption that these patients would be at a higher risk for re-revision due to aseptic loosening. Of 151 patients included in this unpublished study, only seven underwent subsequent re-revision during the follow-up. Three patients were revised due to infection, three due to aseptic loosening, and one due to
dislocation. The estimated 10-year survival was 93% (95%CI: 88 – 98, see figure 9).

![Unadjusted survival curve for all patients receiving a DMC at revision surgery with follow-up longer than 8 years: the shaded area indicating 95%CI and the ticks indicating censoring.](image.png)

Figure 9. Unadjusted survival curve for all patients receiving a DMC at revision surgery with follow-up longer than 8 years: the shaded area indicating 95%CI and the ticks indicating censoring.

Tantalum ion levels were similar in the two treatment groups: 0.1 μl/L (95%CI: 0.05 – 0.2) in the DMC group and 0.1 μg/L (95%CI: 0.05 – 0.2) in the PE group ($p=0.9$). PROM as estimated by EQ5D, HOOS and HHS were satisfactory to good, with no clinically relevant difference between groups.

**Study III**

**Study Population**

The elevated tantalum serum levels in study II were difficult to interpret since there are no systemic studies on tantalum ion liberation to be found. Furthermore, any immunological alteration in patients treated with THA could both be related to tantalum ions or to other metal ions (Cr, Co, Ni). We therefore evaluated metal ion concentrations and immunological response as expressed by lymphocyte subsets in three different groups of THA patients in study III (Table 3): Patients receiving a cemented tantalum-free primary THA (Lubinus cup in combination with the SPII® stem, “Primary Non-Tantalum”), patients
receiving an uncemented primary THA with a tantalum coated cup (Continuum®, in combination with Links CFP stem, “Primary Tantalum”) and revised patients with uncemented all-tantalum implants (TMARS®) or tantalum-coated cups (Continuum®, “Revision Tantalum”). While Tantalum was measured in all patients, Cr, Co and Ni was only assessed in the primary cases.

Table 3. Demographics for patients treated with a cemented cup without tantalum during primary arthroplasty (“Primary Non-Tantalum”), patients with an uncemented tantalum cup during primary arthroplasty (“Primary Tantalum”), and patients treated with an uncemented tantalum revision shell during hip revision surgery (“Revision Tantalum”) in totals or means with 95%-Confidence Intervals (95%CI).

<table>
<thead>
<tr>
<th></th>
<th>Primary Non-Tantalum</th>
<th>Primary Tantalum</th>
<th>Revision Tantalum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>30</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>9</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>Side (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>19</td>
<td>16</td>
<td>48</td>
</tr>
<tr>
<td>Left</td>
<td>11</td>
<td>14</td>
<td>36</td>
</tr>
<tr>
<td>Diagnosis at surgery (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary OA</td>
<td>9</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Femoral Neck Fracture</td>
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<td></td>
</tr>
<tr>
<td>Loosening</td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Dislocation</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95%-CI)</td>
<td>25.3 (23.2 - 27.3)</td>
<td>26.0 (24.6 - 27.2)</td>
<td>26.6 (25.7 - 27.5)</td>
</tr>
<tr>
<td>Follow-up time [y]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95%-CI)</td>
<td>2.8 (2.2 - 3.3)</td>
<td>4.4 (4.1 - 4.7)</td>
<td>4.4 (3.8 - 5.0)</td>
</tr>
</tbody>
</table>

Findings

We found higher concentrations of tantalum ions in the Revision Tantalum group (0.091 µg/L, 95%CI 0.083 - 0.112 µg/L) than in the Primary Non-Tantalum (0.05 µg/L, 95%CI 0.05 - 0.05) and the Primary Tantalum groups (0.051 µg/L, 95%CI 0.050 - 0.055, p < 0.0001 for comparison between all three groups). A weak negative correlation between tantalum concentrations and the percentage of HLA-DR+/CD8+ T cells (ρ = -0.22, 95%CI -0.35 – (-0.05), p=0.01) was found, but not between tantalum concentrations and the percentage of HLA-DR+/CD4+ T cells (ρ = -0.11, 95%CI -0.27 – 0.06, p = 0.24). Time since surgery did not influence tantalum concentrations (ρ =0.07, 95%CI -0.12 – 0.26, p=0.42). Even though there were some differences between groups
with regards to total white blood cell counts and lymphocyte subsets, all values were within the reported normal intervals (Figure 10).

The HHS was generally good, with the Primary Tantalum group scoring best (100, 95%CI 96 - 100), and the Revision Tantalum group ranking significantly worse (86, 95%CI 78 – 90, \( p<0.0001 \)). Radiographs did not present with signs of osteolysis or loosening.

![Graph showing differences in means between the pooled group of patients with a tantalum implant and the Primary Non-Tantalum group.](image)

**Figure 10.** Differences in means between the pooled group of patients with a tantalum implant (either Primary Tantalum or Revision Tantalum group) and the Primary Non-Tantalum group (the reference) with 95%CI. Note the different scaling of the x-axis.

Except for tantalum concentrations, there were no statistically significant differences between the Primary Non-Tantalum and the Primary Tantalum groups with respect to metal ion concentrations. The estimated medians for the Primary Non-Tantalum group were 0.50 µg/L for Cr (IQR: 0.02), 0.11 g/L (IQR: 0.06) for Co, and 0.50 µg/L (IQR: 0.14) for Ni. For the Primary Tantalum group, the corresponding values were 0.50 µg/L for Cr (IQR: 0, \( p=0.6 \)), 0.12 g/L (IQR: 0.09, \( p=0.1 \)) for Co, and 0.51 µg/L (IQR: 0.17, \( p=0.3 \)) for Ni (Figure 11).
Figure 11. Boxplots for the metal ion concentration Cr, Co, Ni, from left to right: y-axis giving the logarithm of the investigated metal for the Primary Non-Tantalum group in light red and the Primary Tantalum group in light blue, upper and lower hinges indicating the 3rd and 1st quantile, whiskers indicating ±/+ * 1.5IQR and dots indicating outliers.

When investigating the possible effects of metal ion liberation from the metals Co, Cr, and Ni on the percentages of HLA-DR⁺/CD8⁺ T cells or HLA-DR⁺/CD4⁺ T cell, no statistically or clinically significant correlations could be detected (Figure 12). However, a statistically significant, yet only moderate positive correlation between higher Ni concentration and time since surgery was established ($\rho=0.31$, 95% CI 0.06 - 0.54, $p=0.01$).
Study IV

Study Population

In order to identify possible genomic loci associated with an increased risk for revision surgery subsequent to TJA, we conducted a GWAS on a data set from the STR. The study cohort consisted of both hip and knee arthroplasty treated patients who were either revised for any reason (n=94 individuals) or who needed no further surgical intervention (n=1,036). Seventy-five of the 94 individuals undergoing revision surgery did so due to aseptic loosening. The reasons underlying primary surgery varied for both hip and knee arthroplasty, but the foremost common reason was primary OA in both groups (84% for...
hip arthroplasty and 93% for knee arthroplasty). There were no baseline differences in demographics between the revised cases and controls (Table 4).

Table 4. Demographics for the study population in totals or means with standard deviation (SD). Missing information on zygosity in one individual amongst the controls. Note that two patients were revised in both the hip and knee joint, hence the total number of revision surgeries is 96.

<table>
<thead>
<tr>
<th></th>
<th>Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=1,036)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>481</td>
</tr>
<tr>
<td>Female</td>
<td>555</td>
</tr>
<tr>
<td><strong>Zygosity</strong></td>
<td></td>
</tr>
<tr>
<td>Monozygotic</td>
<td>245</td>
</tr>
<tr>
<td>Dizygotic, same sex</td>
<td>399</td>
</tr>
<tr>
<td>Dizygotic, opposite sex</td>
<td>391</td>
</tr>
<tr>
<td><strong>Deceased</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>122</td>
</tr>
<tr>
<td><strong>TJR</strong></td>
<td></td>
</tr>
<tr>
<td>THA</td>
<td>613</td>
</tr>
<tr>
<td>TKA</td>
<td>479</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>74 (9)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>23 (3)</td>
</tr>
</tbody>
</table>

**Findings**

When investigating revision for any reason, six risk loci were identified with genome-wide statistically significant $p$-values of $1.7 \times 10^{-10} – 2.6 \times 10^{-8}$. Four of these were located on Chromosome 3 coding for the taurine-transporter $SLC6A6$ (sodium-dependent taurine and beta-alanine transporter), with hazard ratios for revision surgery ranging from 2.97 - 3.11 (Figure 13, Table 5). The fifth locus was located on chromosome 1, coding for calmodulin-binding transcription activator 1 ($CAMTA1$, HR 2.34, 95%CI 1.74 – 3.13, $p=1.45 \times 10^{-08}$), and the sixth (rs13081679, HR 2.86, 95%CI 1.97 – 4.14, 2.63*10$^{-08}$), was located in an intron region on chromosome 3. Furthermore, 28 of the 60 SNPs with the lowest $p$-values were located within the gene region coding for the $ABO$-system.

When investigating our secondary outcome, revision due to aseptic loosening, three SNPs were GWAS-significant: rs17309567 within the SLC6A6-gene presented as the leading SNP with a HR of 3.35 (95%CI: 2.31-4.86,
p=1.69e-10), followed by two SNPs within the region coding for the ABO-system: rs7853989 (HR: 3.46; 95%CI 2.33-5.13, p=6.91e-10), and 9:136126631 (HR: 2.82; 95%CI 1.95-4.07, p=3.35e-08, Table 6, Figure 14). Amongst the leading 30 SNPs associated with the risk of revision due to aseptic loosening, 27 were located within the region coding for the ABO-system.

Figure 13. Cumulative implant survival with revision surgery for any reason as the endpoint on the y-axis over time on the x-axis for the six GWAS-significant SNPs. Red indicates homozygosity for the risk-allele, green heterozygosity, and blue homozygosity for the major allele.

Table 5. The ten SNPs associated with revision for any reason with the lowest p-values with their gene (where applicable), rs-number (SNP), their chromosome (CHR), basepair (BP), number of included patients in total (N) and in cases (NEvent), hazard ratios (HR) with lower (LCL) and upper (UCL) levels of the 95%-CI as well as the corresponding p-value.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>CHR</th>
<th>BP</th>
<th>N</th>
<th>NEvent</th>
<th>HR</th>
<th>LCL</th>
<th>UCL</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC6A6</td>
<td>rs62233562</td>
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<td>14505533</td>
<td>1130</td>
<td>94</td>
<td>3.11</td>
<td>2.19</td>
<td>4.4</td>
<td>1.74*10^-10</td>
</tr>
<tr>
<td>SLC6A6</td>
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<td>3</td>
<td>14506680</td>
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<td>3.11</td>
<td>2.19</td>
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<td>SLC6A6</td>
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<td>4.14</td>
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<td>2.65</td>
<td>1.84</td>
<td>3.83</td>
<td>1.61*10^-07</td>
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</table>
Figure 14. Cumulative implant survival with revision surgery due to aseptic loosening as the endpoint on the y-axis over time on the x-axis for the three GWAS-significant SNPs. Red indicates homozygosity for the risk-allele, green heterozygosity, and blue homozygosity for the major allele.

Table 6. The ten SNPs with the lowest p-values associated with the risk for revision due to aseptic loosening with their gene (where applicable), rs-number (SNP), their chromosome (CHR), base pair (BP), number of included patients in total (N) and in cases (NEvent), hazard ratios (HR) adjusted for with lower (LCL) and upper (UCL) levels of the 95%-CI as well as the corresponding p-value.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>CHR</th>
<th>BP</th>
<th>N</th>
<th>NEvent</th>
<th>HR</th>
<th>LCL</th>
<th>UCL</th>
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<tbody>
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<td>3.35</td>
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Discussion

Hip revision surgery is necessary in more than 20% of all patients treated with THA in the long-term (Pabinger et al. 2018) and is - given the increasing demand for primary THA - associated with great costs for the health care system. In terms of improvement of quality of life, results after hip revision surgery are comparable to those after primary THA (Robinson et al. 1999), but show higher failure rates than primary THA (SHAR 2018).

Studies on hip revision surgery are in general of evidence level IV or V, since they are often case series from a single center. Numerous studies have reported generally good outcomes of TM cups in the setting of hip revision surgery, but they solely report on pro- or retrospectively followed cohorts treated with this type of implant without any comparison group (Unger et al. 2005, Flecher et al. 2008, Lakstein et al. 2009, Batuyong et al. 2014, Konan et al. 2016). Such studies are prone to statistical weaknesses since they yield a power problem due to sample size limitations. Furthermore, retrospective cohort studies are often hampered by incomplete follow-up, such that the occurrence of relevant endpoints could be missed.

Strictly register-based studies, on the other hand, have larger sample sizes, they are often reliable concerning completeness of the investigated endpoints, and usually allow for comparisons of different implants or concepts. A study on data derived from the SHAR analyzed the outcome of TM cups in revision settings and compared it to two other cups. No difference in survival was detected when investigating reoperation or re-revision as the endpoint (Mohaddes et al. 2015). However, register studies are limited in that they lack relevant information on important confounders. For instance, acetabular defect sizes as a proxy measurement of the complexity of the case are not reported to the register. Furthermore, not all endpoints of interest are registered in national registers: Dislocations treated with closed reduction cannot be studied within the setting of register-based studies. Skyttä et al. (2011) identified in their large register-based study re-revision due to recurrent dislocation as a major concern after the use of TM cups, but they did not analyze dislocations treated with closed reduction.

About two years after the publication of study I Matharu et al. presented a propensity score matched comparison between TM and non-TM cups from the same manufacturer in revision surgery (2018). Still, this study only investigated the potential benefit of coating with tantalum, not different types of implants such as the TM cup versus MARR, Burch-Schneider-rings or Ganz-
rings. In addition to this, that study was unable to include acetabular defect sizes as a proxy measurement for case complexity in their matching process. Another study, published in 2018, compared the outcomes in patients treated with Burch-Schneider rings and TM cups: Acetabular defect sizes were graded according to the American Association of Orthopedic Surgeons classification and no difference in implant survival or complication rates were found (Lopez et al. 2018).

Attempts to compare the methods at hand via a systematic review were made (Beckmann et al. 2014), but for obvious reasons, the results must be interpreted with great caution: In this study, both the American Association of Orthopedic Surgeons classification and the Paprosky classification were used to determine acetabular bone loss which gives a somewhat heterogenous picture of the acetabular defect size as these two classifications are not interchangeable. Even though aseptic loosening is to be considered a late complication and follow-up duration was shorter for patients receiving a TM cup than those receiving a reinforcement ring of various designs (Müller, Ganz, Burch-Schneider), a yearly failure rate was calculated as a measurement for treatment success and interpreted as favorable for the TM cup.

Thus, to avoid these methodological pitfalls, the designs of some of the studies in this thesis are a combination of register-based data with clinically important information on the severity of cases by analyzing preoperatively taken radiographs (studies I&II). Furthermore, for study II we gathered information on dislocations via analysis of patients’ medical charts. This enabled comparisons between groups as well as investigating not only re-revision but even dislocation as an endpoint in our survival analysis.

As seen in study I, TM cups seem to provide stable fixation during revision surgery, since the risk of re-revision due to aseptic loosening is low. This is in accordance with the findings of other studies (Mohaddes et al. 2015, Konan et al. 2016). On the other hand, restoring the center of rotation seems to be difficult, at least whenever an un cemented snap-fit liner is used. Dislocation after the use of TM cups in hip revision surgery has been identified as a frequent complication by other authors (Skyttä et al. 2011). In our material, dislocation rates seemed not to be correlated with either femoral head size, surgical approach, occurrence of stem revision at index surgery, or acetabular defect size. We do however believe that one might find correlations in a larger study sample with greater power, since other studies were able to identify these factors as being associated with the risk of dislocation (Alberton et al. 2002, Khatod et al. 2015).

Addressing the pending risk of dislocation after hip revision surgery with a TM cup by cementation of a DMC indeed almost eliminated the risk of dislocation. Due to scarcity of events, confidence intervals in our Cox regression models were inflated, but still indicated that the DMC is protective of dislocation. This is in accordance with previous studies showing that the DMC re-
roduces the risk of subsequent re-revision surgery due to instability after revision arthroplasty (Hailer et al. 2012, Mohaddes et al. 2017), and some studies suggest that DMCs also reduce the risk of dislocation treated with closed re-
duction after revision surgery (Wegrzyn et al. 2015). We could verify that this also stands true when DMCs are combined with TM cups. Long-term follow-
up is of course warranted as the risk of aseptic loosening in these cases could be higher than thus far detected.

Little is known about the liberation of tantalum ions and its potential harm to patients’ health. Our established median tantalum ion level of 0.09 µg/L in study III can only be related to the reported reference level of 0.008 – 0.01 µg/L in a healthy, implant-free population (Rodushkin et al. 2004). There are hitherto no studies reporting serum concentrations in humans exposed to tantalum except for a case report by Babis et al. (2014): The authors reported tantalum serum concentration after failed revision arthroplasty with heavy metal debris. Their measured concentration of 20 µg/L is extreme, still, the reported patient did not present with any symptoms caused by tantalum ion liberation other than local skin pigmentation. While tantalum is considered to be highly biocompatible (Balla et al. 2010), Co, Cr, and Ni can cause local tissue reactions and even systemic symptoms (Wyles et al. 2017). Previous studies on metallosis and ALVAL have identified the T-cell response mechanism as an important key player in the development of ALVAL. Hence, we focused our study on this particular mechanism. We found no signs of activation of the T-cell response after the use of tantalum implants such as can be observed in ALVAL. Neither were we able to detect a statistically significant response to the trace metals Co, Cr, Ni. Furthermore, we found no difference between lymphocyte subsets in patients treated with a tantalum-free implant when compared with the patients receiving tantalum-implants. We thus found no reason to believe that stable tantalum-implants would pose a hazard to patients’ health in the same manner MoM-THA have proven to do.

Since OA, the underlying cause of most TJA, is to a great extent inheritable (Skousgaard et al. 2015) and recent GWAS have identified several risk SNPs associated with the phenotype OA (Tachmazidou et al. 2019), the idea that even the risk of undergoing revision surgery is affected by genetics is only logical. Unfortunately, since revision surgery is an endpoint with a lower incidence and hence of lower interest for the broader public, larger datasets with reliable information on important variables influencing the risk of revision surgery have not yet been established. One GWAS on the endpoint osteolysis, a hallmark of failed TJA, was conducted, but could not identify GWAS-significant risk SNPs (MacInnes et al. 2019). Koks et al. (2019) tried to identify SNPs associated with a higher risk for revision surgery, but could also not establish any association with GWAS-significance.

In our study, six hitherto unknown risk SNPs associated with a higher risk for revision surgery for any reason were identified, four of them coding for a
taurine transporter (SLCA6A). This particular transporter is thoroughly investigated in an animal model where knockout mice lacking this taurine transporter presented with lower body mass index and decreased exercise capacity as well as - expectedly – a massive reduction in intracellular taurine concentrations (Warskulat et al. 2007). It is unclear how the SNPs identified in our study influence SLCA6A, i.e., one cannot tell whether individuals homozygotic for the risk allele would present higher or lower intracellular taurine concentrations than those homozygotic for the major allele. Assuming that the risk for revision surgery is affected by genetics in a similar way as OA, one would expect that the identified risk alleles cause an upregulation of intracellular taurine concentrations and thus a higher BMI, but this is thus far mere an assumption.

Apart from the GWAS-significant loci in the analysis of our primary outcome, the risk loci within the ABO-system identified in the analysis of our secondary outcome are interesting. Early epidemiological studies identified patients with different blood groups as susceptible to certain diseases and traits which in many cases could be confirmed by later GWAS (Liumbruno and Franchini 2013). The ABO-system affects the variability in certain cancer forms (Amundadottir et al. 2009) and is associated with a variation in IL-6 serum levels (Naitza et al. 2012). Patients with blood group A show a higher incidence of gastric cancer than those with blood group O and present with a higher risk for *H. pylori* infections than non-A blood group patients (Liumbruno and Franchini 2013). Most notably, one retrospective cohort study found a higher risk for developing venous thromboembolism after THA in patients with the blood group AB, even when controlling for possible confounders (Newman et al. 2017).

It should be noted that we were unable to adjust our analysis for possible confounders of importance. We included age at primary surgery and sex as well as the principal components 1-4 in our analysis, but lack information on all other patient- and surgery-related risk factors. Potentially, the higher risk for revision surgery attributed to a certain SNP is solely due to the fact that, by pure chance, all patients homozygotic for the risk allele were diabetic patients with extreme obesity. The risk-increase caused by these patient-related risk factors would then be interpreted as caused by the identified SNP. Furthermore, as with all complex and multifactorial traits, one would not expect a GWAS to explain the total variance in susceptibility for revision surgery, but only a small portion (Manolio et al. 2009). The greatest part of the variance in susceptibility for revision surgery must still be assumed to origin from the surgeon, the implant, and the patients’ risk profile.
Strengths and Weaknesses

Obviously, there are several limitations to the studies presented. For all four studies we face the common problems in register-based studies of underreporting, missing and incomplete data as well as unmeasured confounders. For instance, Lindgren et al. (2014) in their study on 45,531 patients with 49,219 THAs reported to the SHAR found that only 67% of all patients undergoing any reoperation due to periprosthetic joint infection were correctly reported to the SHAR. Study IV is especially prone to be biased by this underreporting: For studies I&II, analysis of patients’ medical charts assured that re-revisions and dislocation were detected with a high certainty, but study IV completely relies on correct coding of the performed surgery and completeness in reporting. MacInnes et al. had in their GWAS on a Norwegian cohort reliable data on the implants used and the study populations demographics and were thus able to match cases and controls on these important confounders (2019).

Moreover, few events in terms of low revision rates in studies I, II and IV inflated confidence intervals and enlarged estimation uncertainty. Systematic reviews and meta-analyses like the one conducted by Beckmann et al. (2014) surpass this issue by aggregating data from all available studies investigating the implant and outcome at hand. Meta-analyses are, on the other hand, vulnerable to various decision-making steps during the process of study-inclusion and acquisition of the included data, the method of analyzing these data and, finally, the interpretation of the aggregated data (Gurevitch et al. 2018).

The approach using a historical comparison group in study I adds possible confounders that we cannot control for: Since 1998 we changed various aspects of our treatment algorithms such as postoperative restrictions, use of tranexamic acid, and choice of antibiotic therapy. Study II suffered a relatively large loss to clinical follow-up and this might influence our results regarding PROM and HHS (Murray et al. 1997). Studies I, II and III presented with some heterogeneity within and between groups. Most notably, the investigated cohorts receiving TM cups consisted of various cup designs and two different methods of fixation of the liner within the cup. For studies II and III, tantalum concentrations were only measured in stable cases; It would have been of interest to estimate the levels in loose cases prior to the re-revision in the same matter Babis et al. did (2014). For study III, not all measurements were available in all groups: We lack information on concentrations for Co, Cr, Ni in the Revision Tantalum group and the Blood Donor group was not investigated regarding WBC and HLA-DR+ cells. Regrettably, the setting of our study did not allow to analyze any time trend by repeated measurements, nor could we capture other important factors influencing patients’ immunological response such as comorbidity. Furthermore, we can only draw conclusion as to the effect of tantalum ions on the T-cell response mechanism but cannot speculate whether tantalum ions could be harmful to patients’ health in other ways. For
instance, tantalum could theoretically accumulate in a specific organ system and cause local damage or be cancerogenic in general.

We decided to analyze revision arthroplasty subsequent to both total knee and total hip arthroplasty as our outcome measurement in study IV and one might argue that the two are not completely comparable as an entity. Additionally, laterality is not recorded in the NPR and we were unable to analyze which side was revised in bilateral cases. We lack information on important confounders for study IV such as patient- and surgery-related risk factors: BMI, comorbidities, approach, head-diameter, certain implants such as MoM-THA have proven to increase the risk for revision surgery. These have been identified as independent risk factors for revision surgery and might thus influence our estimates in any direction. This weakness might very well explain why we were able to detect significant SNPs whilst other GWAS were unable to do so (MacInnes et al. 2019). Yet, even the setting of a later GWAS did not allow for controlling for surgery- and patient related factors in their study on a total of 97 cases and 289 controls and they also failed to identify genome-wide significant SNPs (Koks et al. 2019).

There are, however, certain strengths to our work: The cohort sizes for studies I and II are to be considered relatively large in the field of hip revision surgery and they do present with a historical comparison group. Owing to the setting of these two studies, we have reliable data on the acetabular defect sizes present at index surgery. Furthermore, study II identified not only re-revision due to instability, which is the register-based endpoint, but additionally dislocation treated with closed reduction, an endpoint that is not reported to arthroplasty registers. Study III is the first to report tantalum ion concentrations in a larger cohort after the use of TM cups as well as its potential associations with patients’ T-cell responses. Study IV is the first GWAS to identify genetic loci associated with the risk of revision surgery with genome-wide statistical significance.
Hip revision surgery remains a challenge. TM cups seem to be a reliable treatment option even in cases with severe loss of bone stock, but one must consider the risk of dislocation. In particular, the use of TM cups with un cemented snap-fit liners should be restricted to the relatively simpler cases, i.e. Paprosky type I defects that lack other known risk factors for dislocation such as longer necks, small head diameter, posterior approach. The use of TM cups presents with specific advantages in comparison to the MARR in terms of reduced operational time and blood loss since bone-grafting and supportive screw implantation usually is unnecessary.

The combination of DMCs cemented into TM cups reduces the risk for dislocation in comparison to conventional liners within TM cups. This novel combination should thus be considered in order to prevent a dreaded and for the patient dramatic and painful complication.

Tantalum ion liberation seems to occur to an acceptable degree after the use of TM cups since the estimated median of tantalum ion concentrations even for the revision group was less than twice the detection value. Further long-term studies of these implants are warranted. In particular, measurement of tantalum concentrations in patients with loose implants would be of interest since it seems more likely to then be able to detect alterations in the T-cell response. Accordingly, an analysis of other cells and even proteins involved in the development of metallosis and ALVAL should be systematically investigated in patients with TM cups.

Certain risk genes are associated with an increased risk of undergoing revision surgery after TJA. This might in the near future enable caregivers to estimate patients’ susceptibility to undergo revision surgery even before the primary TJA is performed. Given our findings of two significant and multiple suggestive SNP within the ABO-region, carrying certain blood groups might be considered as a risk increasing factor, and TJA might thus be avoided as far as possible in these patients. A future large-scale GWAS with the possibility to control for important confounders investigating more specific outcomes such as the risk of revision after cemented vs un cemented THA is warranted: Potentially, the presence or absence of different risk genes could guide which method of fixation to choose. Being homozygotic for a risk gene associated with revision after cemented THA might direct the choice of implant towards an uncemented design. Some
materials (e.g. porous tantalum) that do not provoke an immunological re-
response might be favorable in individuals presenting with risk genes for
aseptic loosening and even this could influence the choice of implants.
Future Studies

The most pressing issue meriting further investigation is the connection between the ABO-system and revision surgery. In order to illuminate this matter, we plan to conduct a nationwide study in which we include all patients treated with a THA from the SHAR and crossmatch these on their personal identification number with the respective councils’ blood banks which have information on the blood groups. In doing so, we would be able to estimate the risk of revision for the different blood groups. This could then even be replicated for all patients treated with a TKA, since the SHAR and the Swedish Knee Arthroplasty Register since January 1st, 2020, have been fused into the Swedish Arthroplasty Register.

We are currently gathering genetic data from all patients undergoing any TJA related surgery willing to participate. In doing so, we will be able to conduct the aforementioned studies investigating different types of implants in a larger cohort. Still, GWAS are usually unable to explain all of the observed heritability in more complex traits such as revision surgery (Manolio et al. 2009). Hence, to estimate to what extend the risk for revision surgery is inheritable, one has to rely on other methods. Heritability can be estimated via structural equation modelling where so-called ACE-models are built to analyze twins, siblings, or other relatives. “ACE” is an acronym where the “A” stands for additive genetic effects, “C” for environmental factors shared by the individuals and “E” for environmental factors unique for each individual. Estimating heritability using twin pairs is undisputedly the simplest way to adjust for many confounders since monozygotic twins share 100% and dizygotic share 50% of their genome with their twin whilst sharing 100% of the C-term according to the assumptions underlying ACE-modelling. However, even first-degree relatives (non-twin) to any given index patient share approximately 50% of their genome, second-degree relatives share 25%. A preliminary study with data from the STR analyzing only twins revealed a power problem for these estimates. Hence, we intend to include all patients within the SHAR and crossmatch them with the Swedish Multigeneration Register to estimate the total heritability as well as probandwise concordances.

And finally, even though DMCs perform well in revision surgery, there are some concerns for possible negative effects of the two articulation surfaces in the long term. In theory, the greater the articulating surface, the greater the wear. One study (Tabori-Jensen et al. 2017) fanned the flame of worry show-
ing considerable wear rates after the use of a specific DMC (Saturne®, Amplitude), different from the one investigated in this thesis. DMCs have been used routinely for the past decade at our institution both in primary and revision THA, yet we have so far not experienced any apparent problems with osteolysis or aseptic loosening because of high wear rates. In order to confirm our experience, we intend to follow all patients with more than 8 years follow-up radiologically and clinically to assess wear rate, osteolysis, implant migration and PROM.
Höftproteskirurgi är ett väldigt framgångsrikt kirurgiskt ingrepp och förbättrar livskvalité samtidigt som den minskar smärta hos den drabbade patienten. Tyvärr behöver ca 10 % av alla patienter genomgå en omoperation av höftleden, oftast eftersom protesen lossnar, men den konstgjorda leden kan även hoppa ur led (luxation).

Vid omoperation av höften har under de senaste två decennierna två relativt nya implantat använts: cupar gjorda av poröst tantalum som ska minska risken för lossning och cupar med två artikulationsytor, så kallade dubbelcupar, som ska minska risken för luxation. Dessa två implantat är dock ej undersökta i jämförande studier. Likaså är det inte känt huruvida tantalum genom frisättning av joner kan påverka patienternas immunsystem. Vidare finns det antaganden att risken för att behöva genomgå omoperation ska vara ärtligt bevingad.

Denna avhandling undersökte i sina fyra delarbeten om cupar gjorda av tantalum visar en bättre överlevnad än de historiska behandlingsalternativen; om dubbelcupar visar det bättre utfallet avseende risken för luxation i jämförelse med standardcupar; om frisättning av tantaljoner förekommer efter användning av tantalumcupar och hur detta påverkar patienternas immunologi; om risken för reoperation är associerad med vissa riskgener.

Implantatöverlevnad analyserades med hjälp av överlevnadskurvor. Tantalumcupar uppmättes och deras medianvärden jämfördes mellan olika grupper av patienter som opererades med proteser som innehöll tantalum och de som opererades med konventionella proteser. Därutöver relaterades tantalumjoner till särskilda markörer inom immunsystemet. För att hitta riskgener för omoperationer jämfördes genomet hos individer som genomgick reoperation efter protesinsättning med de som inte gjorde det.

lossning av implantaten. Många riskgener som var nära statistisk signifikans befann sig inom genen som kodar för ABO-grupperingen.

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A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title “Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine”.)