Uncemented total hip arthroplasty. Wear is the problem

Smeekes, C.

Uncemented Total Hip Arthroplasty

Christiaan Smeekes

UNCEMENTED TOTAL HIP ARTHROPLASTY

Wear is the problem

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UNCEMENTED TOTAL HIP ARTHROPLASTY

Wear is the problem

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Contents

1 Introduction and research questions

The drive to improve outcome for symptomatic disabling pain in patients with destroyed hip joints initiated innovations to replace this joint with artificial articulations. Due to poor results of these early " medical devices" of the 19th century, ever since then, research into new technologies has been explored to push improvement of new implants in order to increase quality of life for these disabled patients. One of the first pioneers in the field of implants was Professor Themistocles Glück in Germany. In 1891 he used ivory implants to replace femoral heads. Later on, mould techniques were tried with bearings of glass and stainless steel [1,2]. However, these implants were not able to bear the forces applied during motion and ambulation of the patients and thus failed soon after their implantation. These failures also gave insight in the complex biomechanics and kinematics and stimulated research into newer materials. In 1953 George McKee and Watson Farrar used the first Metal on Metal (MoM) bearing prosthesis. This prosthesis used a cobalt-chromium-molybdenum femoral and acetabular component. Around the same time Sir John Charnley developed a new type of hip prosthesis that strongly resembles the design of the current Total Hip Replacement (THR) design. It consists of a polyethylene acetabular component and a femoral stem with a metal head. A layer of bone cement is used to fix the acetabular and femoral component to the bone [3].The high rate of component loosening of the MoM prosthesis and the superior results of the hip prosthesis with a polyethylene acetabular component in the 1970's resulted in abandoning the use of these MoM prosthesis. Although some studies with limited number in probably selected cases, showed that this prosthesis had a good survival rate of 74% in 28 years [4]. Whilst others found high failure rates of the MoM after 14 years, with a survival of 37,5% in 20 years [5]. The inventions of Charnley (metal head on poly) and McKee-Farrar (metal on metal) are regarded as the ancestors of the modern Total Hip Arthroplasty (THA) used in the clinic today. Nowadays, total hip arthroplasty is considered the most efficient and cost effective surgical intervention of the 20th century [6].

In 2015 more than 28.000 THA's were performed in the Netherlands [7]. Worldwide the number of THA's performed is estimated at about a million a year [8]. One of the most important characteristics of a hip prosthesis is alleviation of pain for the patient, leading to better mobility, in combination with excellent implant survival of at least 95% survival at 10 years for the best performing designs. Even more, these excellent results are present without a "maintenance service". Nevertheless, these high total hip survival rates are not present in the younger (< 55 years population), therefore new techniques were developed to improve the survival of existing implants. A big change in hip arthroplasty was the introduction of cementless THA next to the classical Charnley like designs which were implanted with bone cement. Interestingly suddenly articles appeared in the 80s

on the so called "cement disease" which by some is claimed to be "invented" by the manufacturer in order to promote cementless THR designs[9]. The cement disease would cause osteolysis around the hip implant, which is most probable related to the stem design and quality of the polyethylene and not to the cement as such [10,11]. The latter is substantiated by the high survival rates of the cemented Exeter and SP stems in registry studies at present [12,13]. Even more, another theoretical advantage of cementless designs was the preservation of bone stock and easier revisions of the hip [14], however this advantage turned out to be the opposite (i.e. extensive revions with bone loss of the Lord stems) [15]. On the other hand, the cementless acetabular component is the most frequently used fixation in the Netherlands and Denmark (64%) [7,18], though it is not proven to have a better survival than the cemented acetabular component in young patients [16].

The introduction of arthroplasty registries by different countries enabled to have real world data collection with subsequent survival of implants in real world settings and not only in a well-controlled research setting. Registries in Denmark, Finland, England, Norway, New Zealand and Australia, Sweden and The Netherlands show that for all patients the survival rate of 10 years of these implants was 93%-95% [12,13,17-20]. Due to this good survival rate of the THA, the procedure is slightly more often used in younger patients in the last two decades (i.e. in the Dutch arthroplasty the percentage of patients younger than 60 years increased from 15% in 2007 to 18% in 2015 and in the Swedish registry we find an increase of 8% in these years) [7,12]. This younger age group of patients is more mobile and active, which increases the demand on the implant in terms of a higher range of motion and wear rates, with subsequent negative effect on survival. Bayliss et al show an increased revision rate of almost 35% in this younger patient population versus 1-6% in patients which underwent THA older than 70 years of age [21]. The survival of cementless THA in younger patients, aged 55-65 years, was 87%-96% [12,13,17-20]. The search for implants with a more durable concept and subsequent improved survival rate continued with the introduction of ceramic on ceramic bearings, although with high variation in results [22]. The theoretical advantage of low wear properties of this type of bearing with subsequent increased survival rate was not always shown [23-25]. For that matter complications like fracture of the components [26] as well as squeaking noises were reported [27]. These lower survival rates in the younger patient population compared to the older patients and the shortcomings of the ceramic on ceramic led to the revival of the MoM bearing surface. The theoretical advantages were a lower wear rate, lower dislocation rate and a larger range of motion [28-30]. These new implant characteristics were especially designed for the young and active patients, which would potentially be in need for a durable articulation with a larger range of mo-

tion than the classical total hip arthroplasty. First the resurfacing design prosthesis was reintroduced, after high failure rates in the past with older designs [31,32]. The good early results at short and mid-term follow-up of the newer resurfacing designs like the Birmingham hip resurfacing arthroplasty [33-35], opened the way to use a large diameter MoM design also for the classic THR design because of the earlier mentioned theoretical advantages [28-30]. However short after a worldwide introduction of the MoM implants complications were seen in patients with MoM resurfacing and MoM THA. Complications such as high metal ion levels in the blood[36], development of cystic and solid masses in the periarticular region[37], reaction of the tissue around the hip prosthesis[38] and most important a lower survival of the implants: National Registries showed a survival rate of 72%-89% after ten years[12,13,17-20,39].

AIM OF THE THESIS

This thesis evaluates two total hip implant designs used in the younger aged patient population; (1) a cementless THR with a conventional ceramic on polyethylene (CoP) bearing and (2) a THR with a MoM bearing. An analysis into outcome and failure mechanisms on both designs was performed with focus on:

- **The clinical outcome and survival of a conventional CoP THA cohort with the 24-year follow-up and an analysis into factors associated with clinical and radiographic outcome**
- **The clinical evaluation of a large head MoM THA cohort. Analysis of failure of the MoM THA in relation to anatomical reconstruction of the hip**
- **The failure mechanisms of the MoM THA as visualised at MRI images**
- **The reproducibility of the histological scoring system of peri-articulair tissue reactions of failed MoM THA.**

OUTLINE OF THE THESIS

The **second chapter** presents the long-term results of a conventional Cementless CoP bearing (Spotorno CLS) total hip replacement system and an analysis of the factors associated with clinical and radiographic outcome and failure. This system uses a CoP bearing, which is one of the most used combination for an articulation at this moment. In **chapter three** a THR with a MoM bearing will be evaluated with focus on clinical outcome, incidence of postoperative pain and presence of pseudotumors. Revisions of these implants are evaluated using, radiographs, metal

ion levels as well as functional outcome and quality of life after the MoM THA. In **chapter four** we investigate the effect of MoM THR position (inclination and anteversion angle of the cup) and preoperative anatomic position (i.e. anatomical reconstruction of the hip) and are evaluated with respect to serum cobalt levels.

In MoM THA a high number of patients develop cystic and solid masses in the periarticular region. In **chapter five** a description of the occurrence of pseudotumors in symptomatic and asymptomatic patients with MoM THA with different pseudotumor grading systems and the relation with the clinical outcome is analysed. In the **sixth chapter** scoring classifications for periprosthetic tissues around failed MoM THA's are evaluated with the aseptic lymphocyte vasculitis-associated lesion (ALVAL) scores and the modified Oxford ALVAL score.

[1] Smith-Petersen MN (1948) The classic: evolution of mould arthroplasty of the hip joint. J Bone Joint Surg
[2] Wiles P (1957) The surgery of the osteoarthritic hip. hip Br J Surg 417 doi:45:488-97
[3] Charnley J (1961) Arthroplasty of the hip. A new operation. Lancet 7187:1129-32.
[4] Brown SR, Davies WA, DeHeer DH, Swanson AB (2002) Long-term survival of McKee-Farrar total hip prostheses. Clin Orthop Relat Res 402:157-63.
[5] August AC, Aldam CH, Pynsent PB (1986) The McKee-Farrar hip arthroplasty. A long-term study. J Bone Joint Surg Br 4:520-7.
[6] Learmonth ID, Young C, Rorabeck C (2007) The operation of the century: total hip replacement. Lancet 9597:1508-19. doi:S0140-6736(07)60457-7 [pii];10.1016/S0140-6736(07)60457-7 [doi]
[7] The Dutch Arthroplasty Register (LROI). Annual report 2017. (2017) http://www lroi-rapportage nl/
[8] Kurtz SM, Roder C, Lau E. (2010) International survey of primary and revision total hip replacement. Paper #365. Presented at the 56th Annual Meeting of the Orthopaedic Research Society.
[9] Makela KT, Matilainen M, Pulkkinen P, Fenstad AM, Havelin L, Engesaeter L, et al. (2014) Failure rate of cemented and uncemented total hip replacements: register study of combined Nordic database of four nations. BMJ:f7592.
[10] McCombe P, Williams SA (2004) A comparison of polyethylene wear rates between cemented and cementless cups. A prospective, randomised trial. J Bone Joint Surg Br 3:344-9.
[11] Wilkinson JM, Hamer AJ, Stockley I, Eastell R (2005) Polyethylene wear rate and osteolysis: critical threshold versus continuous dose-response relationship. J Orthop Res 3:520-5. doi:S0736-0266(04)00253-0 [pii];10.1016/j.orthres.2004.11.005 [doi]
[12] Swedish Hip Arthroplasty Register. Annual Report 2014 (2015) https://shpr registercentrum se/shar-in-english/shar-in-english/p/ryouZwaoe
[13] Norwegian Arthroplasty Register. Annual report 2016. (2015) http://nrlweb ihelse net/eng/default htm
[14] Ritter MA, Thong AE (2004) The role of cemented sockets in 2004: is there one? J Arthroplasty 4 Suppl 1:92-4. doi:S088354030400124X [pii]
[15] Malchau H, Herberts P, Wang YX, Karrholm J, Romanus B (1996) Long-term clinical and radiological results of the Lord total hip prosthesis. A prospective study. J Bone Joint Surg Br 6:884-91.
[16] Toossi N, Adeli B, Timperley AJ, Haddad FS, Maltenfort M, Parvizi J (2013) Acetabular components in total hip arthroplasty: is there evidence that cementless fixation is better? J Bone Joint Surg Am 2:168-74. doi:1537036 [pii];10.2106/JBJS.K.01652 [doi]
[17] National Joint Registery for England, Wales and North Ireland. Annual report 2016. (2014) http://www njrcentre org uk/njrcentre/Reports,PublicationsandMinutes/tabid/85/Default aspx
[18] The Danish Hip Arhtroplasty Register. Annual report 2016. (2015) http://danskhofteallo-plastikregister dk/en/publications/annual-reports/
[19] Australian Orthopedic Association National Joint Replacement Registery. Annual Report 2016. (2015) https://aoanjrr sahmri com/annual-reports-2016
[20] New Zealand Joint Registry. Annual report 2015. (2017) http://nzoa org nz/nz-joint-registry
[21] Bayliss LE, Culliford D, Monk AP, Glyn-Jones S, Prieto-Alhambra D, Judge A, et al. (2017) The effect of patient age at intervention on risk of implant revision after total

replacement of the hip or knee: a population-based cohort study. Lancet 10077:1424-30. doi:S0140-6736(17)30059-4 [pii];10.1016/S0140-6736(17)30059-4 [doi]

[22] Nieuwenhuijse MJ, Nelissen RG, Schoones JW, Sedrakyan A (2014) Appraisal of evidence base for introduction of new implants in hip and knee replacement: a systematic review of five widely used device technologies. BMJ:g5133.

[23] Hamadouche M, Boutin P, Daussange J, Bolander ME, Sedel L (2002) Alumina-on-alumina total hip arthroplasty: a minimum 18.5-year follow-up study. J Bone Joint Surg Am 1:69-77.

[24] Lerouge S, Huk O, Yahia L, Witvoet J, Sedel L (1997) Ceramic-ceramic and metal-polyethylene total hip replacements: comparison of pseudomembranes after loosening. J Bone Joint Surg Br 1:135-9.

[25] Migaud H, Putman S, Kern G, Isida R, Girard J, Ramdane N, et al. (2016) Do the Reasons for Ceramic-on-ceramic Revisions Differ From Other Bearings in Total Hip Arthroplasty? Clin Orthop Relat Res 10:2190-9. doi:10.1007/s11999-016-4917-x [doi];10.1007/s11999-016-4917-x [pii]

[26] Allain J, Roudot-Thoraval F, Delecrin J, Anract P, Migaud H, Goutallier D (2003) Revision total hip arthroplasty performed after fracture of a ceramic femoral head. A multicenter survivorship study. J Bone Joint Surg Am 5:825-30.

[27] Baek SH, Kim WK, Kim JY, Kim SY (2015) Do alumina matrix composite bearings decrease hip noises and bearing fractures at a minimum of 5 years after THA? Clin Orthop Relat Res 12:3796-802. doi:10.1007/s11999-015-4428-1 [doi];10.1007/s11999-015-4428-1 [pii]

[28] Anissian HL, Stark A, Gustafson A, Good V, Clarke IC (1999) Metal-on-metal bearing in hip prosthesis generates 100-fold less wear debris than metal-on-polyethylene. Acta Orthop Scand 6:578-82.

[29] Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH (2005) Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 1:11-9. doi:S0883540304003924 [pii];10.1016/j.arth.2004.07.008 [doi]

[30] Goldsmith AA, Dowson D, Isaac GH, Lancaster JG (2000) A comparative joint simulator study of the wear of metal-on-metal and alternative material combinations in hip replacements. Proc Inst Mech Eng H 1:39-47.

[31] de Waal Malefijt MC, Huiskes R (1993) A clinical, radiological and biomechanical study of the TARA hip prosthesis. Arch Orthop Trauma Surg 5:220-5.

[32] Duijsens AW, Keizer S, Vliet-Vlieland T, Nelissen RG (2005) Resurfacing hip prostheses revisited: failure analysis during a 16-year follow-up. Int Orthop 4:224-8. doi:10.1007/s00264-005-0652-8 [doi]

[33] Back DL, Dalziel R, Young D, Shimmin A (2005) Early results of primary Birmingham hip resurfacings. An independent prospective study of the first 230 hips. J Bone Joint Surg Br 3:324-9.

[34] Baker RP, Pollard TC, Eastaugh-Waring SJ, Bannister GC (2011) A medium-term comparison of hybrid hip replacement and Birmingham hip resurfacing in active young patients. J Bone Joint Surg Br 2:158-63. doi:93-B/2/158 [pii];10.1302/0301-620X.93B2.25625 [doi]

[35] Daniel J, Pynsent PB, McMinn DJ (2004) Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis. J Bone Joint Surg Br 2:177-84.

[36] Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. (2011) Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br 10:1308-13. doi:93-B/10/1308 [pii];10.1302/0301-620X.93B10.26249 [doi]

[37] Hauptfleisch J, Pandit H, Grammatopoulos G, Gill HS, Murray DW, Ostlere S (2012) A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. Skeletal Radiol 2:149-55. doi:10.1007/s00256-011-1329-6 [doi]

[38] Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, et al. (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 1:28-36. doi:87/1/28 [pii];10.2106/JBJS.A.02039pp [doi]

[39] Seppanen M, Karvonen M, Virolainen P, Remes V, Pulkkinen P, Eskelinen A, et al. (2016) Poor 10-year survivorship of hip resurfacing arthroplasty. Acta Orthop 6:554-9. doi:10.1080/17453674.2016.1246316 [doi]

2 Long-term results of total hip arthroplasty with the CementLess Spotorno (CLS) system

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ABSTRACT

Background/objective: This study presents the long-term results of the Cementless Sportorno (CLS) total hip arthroplasty system and an analysis of factors associated with clinical and radiographic outcome.

Methods: We studied a series of 120 consecutive CLS arthroplasties in a young patient group (mean age at surgery: 55.9 ± 5.9 years). The Merle d'Aubigné-Postel score, polyethylene (PE) wear, and radiographic status were recorded during follow-up. Survival analyses, repeated-measures analysis of variance, and a nested case-control study were used for statistical evaluation.

Results: After a mean follow-up of 14.6 years (range, 0.1 to 24.2, including revisions and lost to follow-up), 24 revisions had been performed, 16 of which for aseptic cup loosening. Kaplan-Meier survival analysis showed a 24-years survival of 72.8% (95% CI, 63.0%-82.6%) with revision for any reason as endpoint, and 80.1% (95% CI, 70.9%-89.3%) for revision for aseptic cup loosening. Mean final Merle d'Aubigné-Postel score was 16.1 points (range, 7- 18). Mean PE wear at final follow-up was 2.3 mm (range, 0.6-6.8 mm). A higher rate of PE wear was associated with better clinical scores but also with revision for cup loosening. Factors associated with more PE wear were: younger age at surgery; 32 - mm head; longer follow-up; and steeper inclination angle.

Conclusions: Beyond 10 years, the CLS stem is reliable, but the high revision rate for aseptic cup loosening is concerning, specifically with better performing (cementless) alternatives available.

INTRODUCTION

Total hip arthroplasty (THA) improves the quality of life in patients with osteoarthritis and is regarded as the most efficient and cost-effective surgical procedure [1]. Long-term follow-up evaluation of different designs of THA implants is important, especially since patients are increasingly undergoing surgery at a younger age, and life expectancy is increasing. By gathering this information, the optimal implant for a patient may be selected and suboptimal choices, as has been shown for e.g. metal-on-metal bearings can be avoided [2].

In this study, we present the long-term results (>20 years) of the Cementless Spotorno (CLS) THA system, and an analysis of factors associated with clinical and radiographic outcome.

METHODS

Between 1989 and 1997 a consecutive series of 120 CLS THA procedures were performed in 96 relatively young patients at our institution (Meander Medical Centre). In a previous study, we reported the results of 102 THA's in 81 patients, with follow-up until 2007 and a 15-year survival of 78.4% (95% CI: 63.9%-92.9%) for revision for any reason [3].

In the current study, we report the results of all 120 THA's, with additional follow-up until January 2014, now including 24-years survival analyses.

Patients

Baseline inclusion criteria were: age ≤66 years at surgery, primary THA for osteoarthritis, rheumatoid arthritis, or femoral head osteonecrosis, and a femur suitable for the CLS stem [3,4]. Baseline exclusion criteria were: malignancies in the 5 years prior to index THA, no informed consent, and neurovascular compromised lower limb. Only patients who did not have a revision procedure were invited for additional long-term follow-up evaluation in the period between June 2012 and January 2014.

The Institutional Review Board approved all stages of the study. Informed consent was provided by all patients.

Implants and procedure

The CLS system consists of a cementless, collarless 3-D tapered wedge titanium press-fit femoral stem, and a cementless titanium-alloy expanding acetabular cup. The neck-shaft angle of 145° was the only available size at the time of implantation.

A 28- or 32-mm Biolox ceramic head (CeramTec), was used in all hips. For more information on the CLS implant, we refer to our previous article [3].

2 orthopaedic surgeons (H.G.W. Vermeer and A.F.W. Barnaart) performed the THA using a posterolateral surgical approach. Standard antibiotic and antithrombotic prophylaxis consisting of cefazolin (3 doses of 1g each, starting 30 minutes before surgery) and warfarin (for 6 weeks after surgery) was used. Heterotopic ossification prophylaxis (indomethacin for 5 days after surgery) was used for men and for patients who had previous hip surgery. Patients received standard postoperative care, including pain medication and physical therapy. Full weight-bearing was permitted immediately after surgery.

Clinical and radiological evaluation

Patients were invited for a pre-operative visit and for post-operative follow-up visits on a regular basis. For the additional long-term follow-up visit for the current study, patient addresses were acquired using the hospital information system. If patients had moved, contact information was updated via the general practitioner. For deceased patients, the general practitioner was asked whether the patient had undergone revision surgery in another hospital.

Patients were clinically evaluated according to the Merle d'Aubigné-Postel score, as modified by Charnley [5,6]. This score consists of 3 items; hip pain, hip motion, and walking ability. The scores for each item range from 0 points (maximum symptoms) to 6 points (no symptoms). Additionally, patients were assessed with the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score at the additional long-term follow-up visit between 2012 and 2014 [7].

Preoperative radiographs were used to evaluate acetabular center-edge angle according to Wiberg [8], and mean neck shaft angle. On all postoperative radiographs, inclination angle of the acetabular component, the degree of linear wear of PE wear, and the angle of PE wear were measured according to Livermore et al [9]. Measurements were performed by an independent and blinded investigator (C.S.), using the software package AGFA orthopaedic-Tools Version 2.06.

Statistical methods

Descriptive analyses were performed on baseline data and final outcomes. The results were expressed as means with standard deviations or medians with ranges where relevant.

To assess THA survival, we used Kaplan Meier survival analyses with aseptic cup loosening, revision for any reason and aseptic stem loosening as endpoints, respectively. Cox regression analyses were performed to assess factors associated with THA survival (with regards to aseptic cup loosening).

Repeated-measures analyses of variance were conducted to study the associations of baseline data (demographics, THA characteristics, baseline clinical scores) and PE wear with Merle d'Aubigné-Postel scores during follow-up. Additional repeated measures analyses were performed to study the associations of baseline data (demographics, THA characteristics, baseline clinical scores) with PE wear in follow-up. A random effect per THA was included to account for repeated measures.

Lastly, a nested case-control study was performed to evaluate factors associated with early revision (<15 years) for aseptic cup loosening. Cases were defined as patients who had a primary revision for aseptic cup loosening within 15 years; controls where all patients who did not have a primary revision for aseptic cup loosening in this period. Unpaired t-tests were applied to compare continuous data between these groups, and chi-square tests for categorical data.

21 patients received bilateral CLS THA. We assessed each THA separately. In the case of a bilateral procedure, we assumed that this paired structure would not have a substantial influence on the assessed outcomes.

RESULTS

Preoperative Evaluation

At baseline, the total patient group comprised 96 patients (120 hips). There were 59 CLS arthroplasties in female patients (49.2%). Indications were: osteoarthritis in 105 hips, rheumatoid arthritis in 10 and osteonecrosis of the femoral head in 5. Mean age at surgery was 55.9 ± 5.9 years. Mean body mass index (BMI) was 26.4 ± 3.4 kg/m^2. Mean preoperative total Merle d'Aubigné-Postel score was 8.8 ± 2.2 points, with the following category scores: 1.6 ± 1.0 points for pain, 2.8 ± 1.2 for walking and 4.5 ± 1.0 for motion. Demographics, prosthesis and anatomical baseline characteristics are summarized in Table 1.

Revisions, complications and survival analysis

Finally, after a mean follow-up of 14.6 years (range 0.1 - 24.2, including revisions and lost to follow-up), a total of 22 patients (24 THA's) underwent revision surgery (10 procedures additional to the original study). Overall, 28 patients were deceased (32 THA's) and 6 (7 THA's) were lost to follow-up for other reasons, leaving 45 (57 THA's) available for additional follow-up evaluation at our outpatient clinic. Because of poor physical condition, 2 (3 THA's) of these patients were visited at home for evaluation.

Table 1

Baseline (Preoperative) Patient Characteristics

	All patients (n=120)	Cases (n=16)*	Controls (n=69)*	Mean difference	95% CI	P-value
Gender (No.)						
Male	61 (50.8%)	6 (37.5%)	36 (52.2%)			
Female	59 (49.2%)	10 (62.5%)	33 (47.8%)			0.29
Age at surgery (years)†	55.9 ± 5.9	54.0 ± 6.1	56.7 ± 5.0	2.7	-5.2-0.3	0.07
BMI (kg/M^2)†	26.4 ± 3.4	26.6 ± 4.4	26.4 ± 3.1	-0.2	-1.6-2.1	0.05
Hip†						
Neck shaft angle (deg.)	133.5 ± 8.1	136.8 ± 6.1	132.8 ± 8.3	-4	-1.8-9.9	0.17
Center-edge angle of Wiberg (deg.)	35.1 ± 8.3	39.1 ± 10.1	34.5 ± 7.8	-4.6	-2.1-10.1	0.19
Component size (mm)						
Cup	53.8 ± 2.6	52.9 ± 3.2	54.0 ± 2.4	1.1	-2.5-0.5	0.17
Stem	10.4 ± 2.0	9.8 ± 1.7	10.6 ± 2.0	0.8	-1.8-0.3	0.15
Head size (no.)						
28mm	20	1	12			
32mm	100	15	57			0.73
Merle d'aubigné-postel score (points)†						
Pain	1.6 ± 1.0	1.2 (1.0)	1.7 (0.9)	0.4	-0.1-0.9	0.11
Motion	4.5 ± 1.0	4.8 (0.7)	4.4 (1.0)	-0.4	-0.9-0.1	0.13
Walking	2.8 ± 1.2	2.6 (1.1)	3.0 (1.1)	0.3	-0.3-0.9	0.28
Total	8.8 ± 2.2	8.7 (2.4)	9.0 (2.1)	0.3	-0.9-1.5	0.57

*Cases = patients who had a revision procedure due to aseptic loosening of the acetabular component within 15 years of follow-up; Controls = all patients without a revision within 15 years postoperatively.

†Values are given as means ± standard deviations in parentheses.

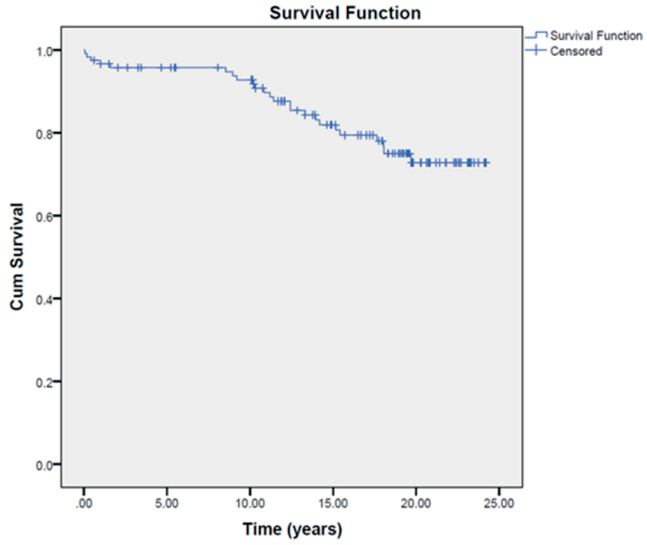
BMI = body mass index; CI = confidence interval

Of the total of 24 revisions, 16 were for aseptic loosening of the acetabular component. Furthermore, 2 patients had a fracture of segments of the cementless expansion cup during follow-up. There was 1 perioperative femoral fracture and 1 stem with early distal migration (subsidence), both leading to early revision (<6 months). There were 3 stems with aseptic loosening, requiring revision. And 1 patient with rheumatoid arthritis had a hematogenous infection after 186 months, leading to 2-stage revision arthroplasty.

Kaplan-Meier survival analysis showed a 24-years survival of 72.8% (95% CI: 63.0%-82.6%), with revision for any reason as endpoint (Fig. 1). With revision due to aseptic cup loosening as endpoint, 24-years survival was 80.1% (95% CI: 70.9%-89.3%) (Fig. 2). Survival was 95.1% (95% CI: 90.0%-100.0%) for revision for aseptic loosening of the femoral component.

Final evaluation

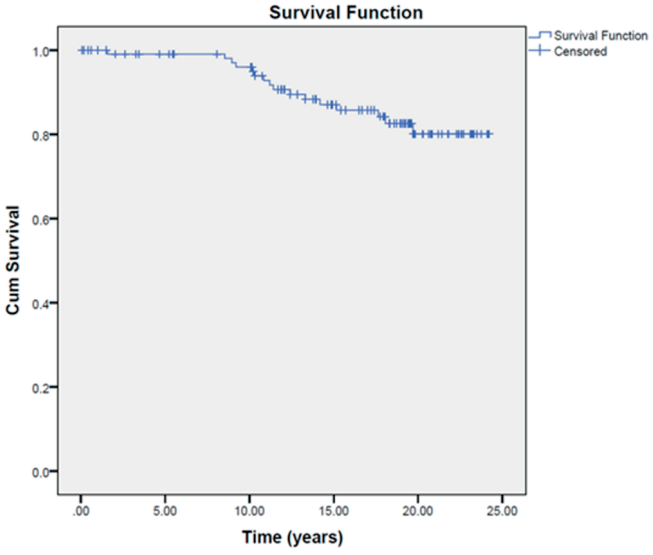
Merle d'Aubigné-Postel was 16.1 points (range 7 - 18) after a mean follow-up of 14.6 ± 7.2 years (either evaluated in 2014, or earlier, including lost to follow-up and last evaluation before eventual revision surgery). As an additional follow-up measure to the previous study, the WOMAC score was assessed for the 57 THA's evaluated in 2013-2014. Mean WOMAC scores were 2.4 ± 3.4 points for pain, 1.5



Number at risk at each time point

Remaining	120	102	94	67	28	0
Cum. Event	0	5	8	18	24	24

Figure 1. Kaplan-Meier survival analyses with revision for any reason as end-point.



Number at risk at each time point

Remaining	120	102	94	67	28	0
Cum. Event	0	1	4	12	16	16

Figure 2. Kaplan-Meier survival analyses with revision for aseptic cup loosening as end-point.

± 1.9 for stiffness and 12.4 ± 13.9 for physical function. The mean total WOMAC was 16.2 ± 18.3 points. Mean PE-wear was 2.3 ± 1.0 mm at final follow-up. Mean PE wear rate was 0.15 ± 0.08 mm/year (Table 2).

Table 2

Results at final follow-up, before an eventual revision procedure, for all patiens, cases, and controls*

	All patients (n=120)	Cases (n=16)*	Controls (n=69)*	Mean difference	95% CI	P-value
Duration of follow up (months)†	762.5 ± 374.2	623.4 ± 235.0	815.4 ± 370.1			
Merle d'aubigné-postel score (points)†						
Pain	5.4 ± 1.0	4.9 ± 1.2	5.5 ± 1.0	0.6	-1.1-0.2	0.16
Motion	5.5 ± 0.9	5.9 ± 0.3	5.4 ± 1.0	-0.5	0.0-1.3	**0.04**
Walk	5.2 ± 1.4	4.8 ± 1.2	5.3 ± 1.4	0.5	-1.2-0.5	0.45
Total	16.1 ± 2.6	15.7 ± 2.2	16.3 ± 2.6	0.6	-1.9-1.6	0.9
Analyses of Radiographs		(n=15)	(n=65)			
Total polyethylene wear† (mm)	2.3 ± 1.0	2.7 ± 1.1	2.3 ± 1.0	-0.4	-0.9-0.2	0.22
Polyethylene wear rate† (mm/yr)	0.15 ± 0.08	0.24 ± 0.09	0.12 ± 0.05	-0.12	-0.16--0.8	**< 0.001**
Wear angle† (deg)	-17.3 ± 26.1	-17.8 ± 12.9	-19.0 ± 27.4	-1.2	-15.8-13.3	0.87
Inclination angle† (deg)	48.1 ± 8.9	48.0 ± 10.0	49.0 ± 7.0	1.0	-3.4-5.3	0.67

*Cases = patients who had a revision procedure due to aseptic loosening of the acetabular component within 15 years of follow-up, and Controls = all patients without a revision within 15 years postoperatively.

†Values are given as means ± the standard deviations.

CI = confidence interval.

Cox regression survival analyses were used to calculate the associations of baseline patient and prosthetic characteristics with prosthesis survival, with revision for aseptic cup loosening as end point. We found associations of the following variables with an increased risk of revision arthroplasty: male sex, a higher BMI, a younger age at surgery, a smaller acetabular component size, and a larger femoral head component size (32 vs. 28 mm) (Table 3). However, the observed hazard ratios were not statistically significant. For clinical baseline scores, a higher (better) baseline Merle d'Aubigné-Postel motion score was associated with revision for aseptic cup loosening in our data (hazard ratio = 1.80; 95% CI, 0.92 - 3.30; p=0.09) (Table 3).

In a repeated-measures analysis of variance, we assessed the associations of baseline patient and prosthesis characteristics and PE wear during follow-up (accounting for interaction between wear and follow-up), with total Merle d'Aubigné-Postel scores. Age at surgery, femoral head component size, and angle of inclination were removed from this analysis because their associated p values were >0.25, with minimal estimated effects on the clinical score. Multivariately, BMI had a statistically significant negative association with final clinical score (-0.11 per additional BMI point, p = 0.04; 95% CI, -0.22 to -0.01). There were significant positive associations of larger acetabulum component size and more PE wear, with better follow-up scores (Table 4).

Table 3

Cox regression survival analyses of the effects (depicted as hazard ratios) of baseline parameters on the risk of revision for aseptic loosening of the acetabular component

	Hazard ratio	95% CI	p value
Patient charactaristics			
Gender (male vs. female)	1.53	0.55-4.21	0.41
BMI (kg/M^2)	1.04	0.88-1.24	0.64
Age at surgery (per 1-year increase)	0.94	0.88-1.01	0.11
Age at surgery (per 10-year increase	0.56	0.28-1.13	0.11
Merle d'Aubigné-Postel score			
Pain	0.66	0.36-1.18	0.16
Motion	1.8	0.92-3.3	0.09
Walking	0.81	0.53-1.25	0.35
Total	0.96	0.77-1.20	0.7
Prosthesis component sizes			
Cup (mm)	0.89	0.74-1.08	0.22
Head size (32 vs. 28 mm)	2.84	0.37-21.63	0.31

BMI = body mass index; CI = confidence interval

A second repeated-measures analysis of variance was performed, to assess associations of baseline demographics and prosthesis characteristics with PE wear in follow-up. From this model, BMI, gender and acetabulum component size were removed, because their associated p values were >0.25, with minimal estimated effects on PE wear. In the final multivariate model, there were significant negative associations (less PE wear) for older age at surgery and 28-mm head component size (vs. 32 mm). There were positive associations (more PE wear) with higher angle of PE wear (not significant), longer duration of follow-up, and steeper inclination angle (Table 4).

Nested case-control study

For the nested-case control study (cases: revisions for aseptic cup loosening within 15 years), 85 patients (69 controls and 16 cases) were available. At baseline, no statistically significant differences were found between cases and controls with respect to demographics or preoperative radiological findings (Table 1).

At the time of final follow-up, there was a significantly higher Merle d'Aubigné-Postel score for motion in the cases (better motion) (Table 2). There was no statistically significant difference in the total amount of PE wear between both groups, but the wear rate was significantly higher in the cases: 0.24 ± 0.09 mm/year vs. 0.12 ± 0.05 mm/year in controls, leading to a mean difference of 0.12 mm/year, p<0.001 (Table 2).

Table 4

Repeated-measures analysis of variance of effects of relevant parameters associated with Merle d'Aubigné-Postel score and polyethylene wear during follow-up

Merle d'Aubigné-Postel score	Effect size	95% CI	p value
BMI (kg/M^2)	-0.11	-0.22- -0.01	**0.04**
Gender (male vs. female)	-0.69	-1.5-0.11	0.09
Cup component size (mm)	0.21	0.06-0.36	**0.01**
Time after surgery (years)	-0.003	-0.05-0.05	0.89
Amount of polyethylene wear (mm)	0.75	0.36-1.13	**<0.001**
Polyethylene wear			
Age at surgery (1-yr. increase)	-0.03	-0.05- -0.014	**0.001**
Wear angle	0.001	-0.0004-0.004	0.108
Head size (28 vs. 32 mm)	-0.53	-0.80- -0.25	**<0.001**
Inclination angle	0.013	-0.003-0.022	**0.008**
Duration of follow up (years)†	0.09	0.08-0.098	**<0.001**

BMI = body mass index; CI = confidence interval

DISCUSSION

In this long-term follow-up study of the Cementless Spotorno total hip system, 24 years survival was worrying, with 72.8% (95% CI, 63.0%-82.6%) for revision for any reason. Aseptic loosening of the cup was the main reason for revision, with a 24-years survival of 80.1% (95% CI, 70.9%-89.3%). We found no baseline parameters with a significant association with survival (Cox-regression analyses), but a greater age at surgery had a clinically relevant positive association with prosthesis survival in our data (not significant). A better motion score preoperatively had a clinically relevant negative association with prosthesis survival (not significant). Patients who had a revision within 15 years for aseptic cup loosening, had a higher rate of PE wear during follow-up, which was associated with a younger age at surgery, larger head component size, steeper cup inclination angle and longer duration of follow-up.

With regards to the long-term (>20 years) CLS cup survival, we found only 1 other study in peer-reviewed English language literature, by Terré [10], reporting a cumulative survival rate of 79% at 21 years. For long-term survival (>20 years) in other cementless cups, better results have been reported: e.g. Ihle et al [11] reported a 83% probability of survival of the titanium-coated RM cup at 20 years, and Loughead et al [12] reported a 88% survival (Kaplan-Meier) at 23 years with the porous coated anatomic cup (PCA) (Howmedica). Della Valle et al [13] published

reasonable results with the Zimmer Harris-Galante I cup, with 96% survival for aseptic cup loosening after a minimum of 20 years. Although long-term results for cementless cups seem somewhat better in these other studies, it has to be taken into account that in most studies, patient age at surgery is generally higher compared to our study population. Regarding registry studies, we found no comparable durations of follow-up, with the longest reported follow-up periods of 14 years in the Australian registry and 10 years in the Swedish registry [14,15].

For the CLS stem, we found an excellent long-term survival of 95.1% (95% CI, 90.0%-100.0%) for revision for aseptic loosening at 24 years, even with this young patient group. This is in concordance with other long-term studies of the CLS stem. For example, Biemond et al [16] reported a 93.5% survival with 18.4 years of follow-up, Evola et al [17] reported 91.5% survivorship at a minimum of 21 years of follow-up, and Streit et al [18] 86% with 22 years of follow-up. Our results are also comparable with those of other reliable cementless stems in young patients. For example, for the Taperloc, 90% survival has been reported at 25 years [19], and for the Zweymuller Alloclassic 96% at 20 years [20]. For cemented stems, Bedard et al [21] reported results after a minimum of 20 years of follow-up in a systematic review. In 6 studies, survivorship for aseptic loosening in patients older than 50 years of age ranged from 86% to 98% at 20 years. And in 4 studies assessing 25 years of follow-up, revision rates for aseptic loosening in patients younger than 50 years were reported between 68% and 94%.

In our study, patients with an early revision for aseptic cup loosening had a higher PE wear rate during follow-up. Assessing the association of baseline parameters with PE wear, we found that younger age at surgery was associated with more PE wear, which might be due to more physical activity. This might also be an explanation for the relatively high revision rate for cup loosening in this relatively young patient group. There were also positive associations (more wear) with a higher angle of PE wear (not significant), longer duration of follow-up, steeper inclination angle of the cup, and 32-mm head component size (vs. 28-mm).

Assessing the associations of baseline parameters and PE wear with clinical scores in follow-up, we found that patients with a higher baseline BMI had worse clinical scores, corroborating our previous study [3]. There were also positive associations for higher PE wear and larger cup size conferring better clinical scores in follow-up. Of course, it has to be taken into account that our results represented first generation polyethylene. The wear rate of 0.15 mm/year is unacceptably high nowadays, but it is comparable with other conventional liners [22].

The current study shows, that in a relatively young patient group, the long-term survival of CLS Spotorno stems is excellent. However, the high rate of PE wear and aseptic loosening of the CLS Spotorno cups is concerning. A 72.8% 24-years sur-

vival is undesirable and inferior compared to other cementless and cemented cups. Further evaluation is needed to assess the reasons for these failure rates, including implant design, surgical technique and our relatively young patient group, but in the intervening time, we would advise to be cautious with the use of this particular cementless cup. Based on these experiences, we abandoned the use of the CLS cup at our institution.

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H.G.W. Vermeer, MD, one of the two operating surgeons.

Disclosures
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[1] Learmonth ID, Young C, Rorabeck C (2007) The operation of the century: total hip replacement. Lancet 9597:1508-19. doi:S0140-6736(07)60457-7 [pii];10.1016/S0140-6736(07)60457-7 [doi]

[2] Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW (2012) Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 9822:1199-204. doi:S0140-6736(12)60353-5 [pii];10.1016/S0140-6736(12)60353-5 [doi]

[3] de Witte PB, Brand R, Vermeer HG, van der Heide HJ, Barnaart AF (2011) Mid-term results of total hip arthroplasty with the CementLess Spotorno (CLS) system. J Bone Joint Surg Am 13:1249-55. doi:10.2106/JBJS.I.01792 [doi]

[4] Spotorno L, Romagnoli S, Ivaldo N, Grappiolo G, Bibbiani E, Blaha DJ, et al. (1993) The CLS system. Theoretical concept and results. Acta Orthop Belg:144-8.

[5] Charnley J (1972) The long-term results of low-friction arthroplasty of the hip performed as a primary intervention. J Bone Joint Surg Br 1:61-76.

[6] D'AUBIGNE RM, POSTEL M (1954) Function al results of hip arthroplasty with acrylic prosthesis. J Bone Joint Surg Am 3:451-75.

[7] Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW, et al. (2004) Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis 1:36-42.

[8] Rott Z (1967) [The CE-angle (Wiberg) and its measuring]. Z Orthop Ihre Grenzgeb 3:461-3.

[9] Livermore J, Ilstrup D, Morrey B (1990) Effect of femoral head size on wear of the polyethylene acetabular component. J Bone Joint Surg Am 4:518-28.

[10] Terre RA (2010) Estimated survival probability of the Spotorno total hip arthroplasty after a 15- to 21-year follow-up: one surgeon's results. Hip Int:S70-S78. doi:43CBC329-7027-4A79-9593-9DC0EE3C975E [pii];10.5301/HIP.2010.1610 [doi]

[11] Ihle M, Mai S, Pfluger D, Siebert W (2008) The results of the titanium-coated RM acetabular component at 20 years: a long-term follow-up of an uncemented primary total hip replacement. J Bone Joint Surg Br 10:1284-90. doi:90-B/10/1284 [pii];10.1302/0301-620X.90B10.20274 [doi]

[12] Loughead JM, O'Connor PA, Charron K, Rorabeck CH, Bourne RB (2012) Twenty-three-year outcome of the porous coated anatomic total hip replacement: a concise follow-up of a previous report. J Bone Joint Surg Am 2:151-5. doi:10.2106/JBJS.J.01553 [doi]

[13] Della Valle CJ, Mesko NW, Quigley L, Rosenberg AG, Jacobs JJ, Galante JO (2009) Primary total hip arthroplasty with a porous-coated acetabular component. A concise follow-up, at a minimum of twenty years, of previous reports. J Bone Joint Surg Am 5:1130-5. doi:91/5/1130 [pii];10.2106/JBJS.H.00168 [doi]

[14] Australian Orthopedic Association. Hip and Knee arthroplasty. 2015.

[15] Göran Garellick, Johan Kärrholm, Cecilia Rogmark, Ola Rolfson, Peter Herberts. Swedish Hip Arthroplasty Register 2013.

[16] Biemond JE, Venkatesan S, van Hellemondt GG (2015) Survivorship of the cementless Spotorno femoral component in patients under 50 years of age at a mean follow-up of 18.4 years. Bone Joint J 2:160-3. doi:97-B/2/160 [pii];10.1302/0301-620X.97B2.34926 [doi]

[17] Evola FR, Evola G, Graceffa A, Sessa A, Pavone V, Costarella L, et al. (2014) Performance of the CLS Spotorno uncemented stem in the third decade after implantation. Bone Joint J 4:455-61. doi:96-B/4/455 [pii];10.1302/0301-620X.96B4.32607 [doi]

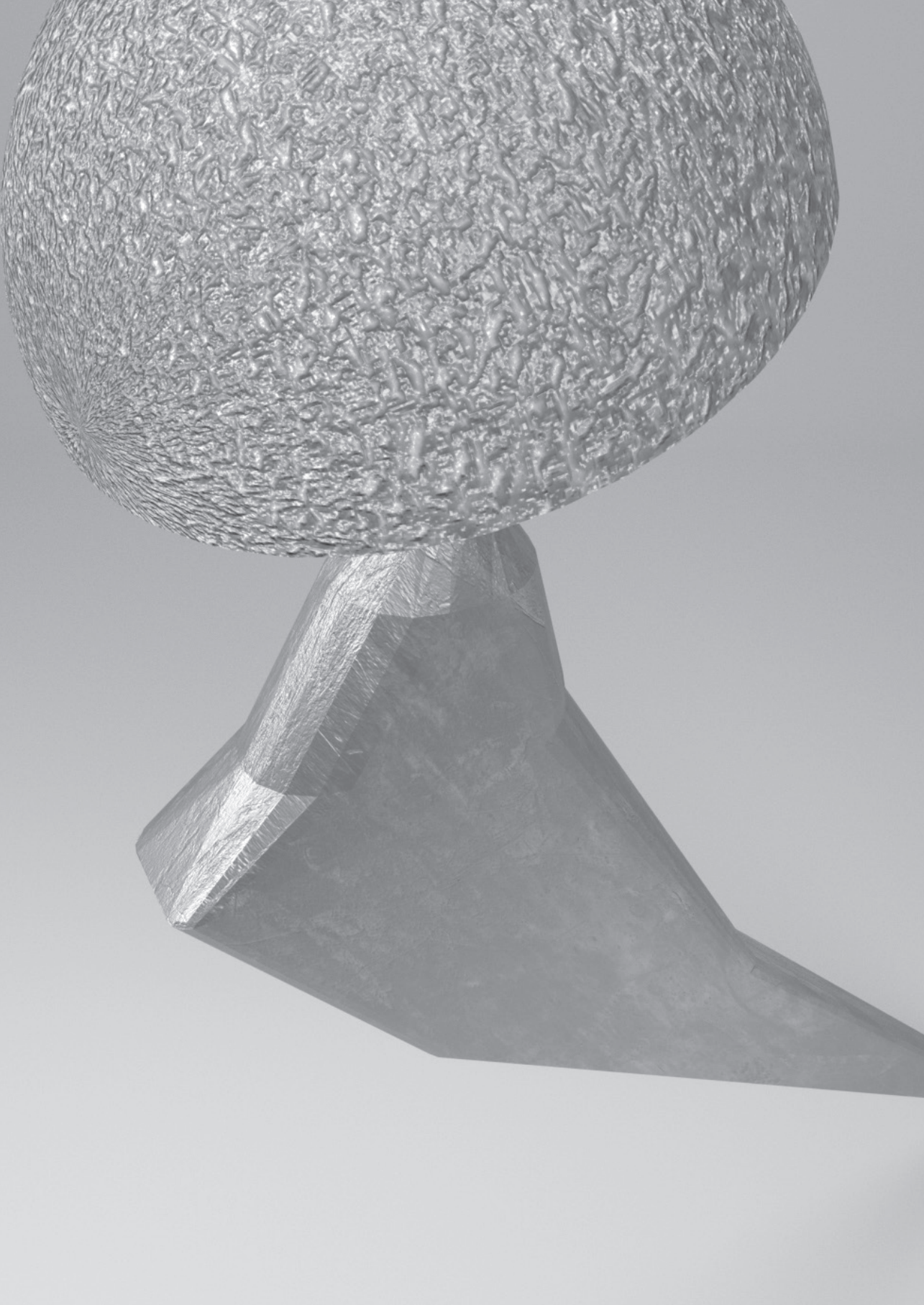
[18] Streit MR, Innmann MM, Merle C, Bruckner T, Aldinger PR, Gotterbarm T (2013) Long-term (20- to 25-year) results of an uncemented tapered titanium femoral component and factors affecting survivorship. Clin Orthop Relat Res 10:3262-9. doi:10.1007/s11999-013-3033-4 [doi]

[19] McLaughlin JR, Lee KR (2015) Total Hip Arthroplasty With an Uncemented Tapered Femoral Component in Patients Younger Than 50 Years of Age: A Minimum 20-Year Follow-Up Study. J Arthroplasty doi:S0883-5403(15)01107-9 [pii];10.1016/j.arth.2015.12.026 [doi]

[20] Kolb A, Grubl A, Schneckener CD, Chiari C, Kaider A, Lass R, et al. (2012) Cementless total hip arthroplasty with the rectangular titanium Zweymuller stem: a concise follow-up, at a minimum of twenty years, of previous reports. J Bone Joint Surg Am 18:1681-4. doi:1356713 [pii];10.2106/JBJS.K.01574 [doi]

[21] Bedard NA, Callaghan JJ, Stefl MD, Liu SS (2015) Systematic review of literature of cemented femoral components: what is the durability at minimum 20 years followup? Clin Orthop Relat Res 2:563-71. doi:10.1007/s11999-014-3876-3 [doi]

[22] Kurtz SM, Gawel HA, Patel JD (2011) History and systematic review of wear and osteolysis outcomes for first-generation highly crosslinked polyethylene. Clin Orthop Relat Res 8:2262-77. doi:10.1007/s11999-011-1872-4 [doi]



3 Large fixed-size metal-on-metal total hip arthroplasty: higher serum metal ion levels in patients with pain

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ABSTRACT

Purpose

Recently, concerns have arisen about metal-on-metal (MoM) total hip arthroplasty (THA). Therefore, the purpose of this cross-sectional cohort-study was to describe the incidence of pain, pseudotumors, revisions and the relation between elevated metal ion levels, functional outcome and quality of life after MoM THA.

Methods

In 351 patients, 377 MoM THA with a fixed-size 38-mm head were evaluated with a mean follow-up of 30 months (range 11-58). Evaluation included pain, serum metal ions, patient-reported questionnaires (Short Form-36 [SF-36], Hip disability and Osteoarthritis Outcome Score [HOOS] and the Oxford Hip Score [OHS]) and radiological imaging. Sixteen patients did not participate in the screening.

Results

One hundred and eighteen (35%) patients reported pain and showed significantly higher cobalt and chromium levels compared to patients without pain. Median serum cobalt levels were 4.4 μg/l (Interquartile range (IQR) 6.6) and chromium levels were 3.6 μg/l (IQR 4.8). Patients with cobalt levels of ≤5 μg/l reported significantly better outcome on the SF-36 and HOOS. Fifty-seven pseudotumors were identified in 227 THA's. A revision rate of 19% was observed.

Conclusion

In conclusion, 35% of the patients experienced pain after MoM THA. These patients showed significantly higher serum metal ion levels. The patient-reported questionnaires indicated significantly better outcome in patients with cobalt levels ≤5 μg/l.

INTRODUCTION

Total hip arthroplasty (THA) improves the quality of life and is regarded the most efficient and cost-effective surgical procedure in history [1]. Due to these successes, THA is performed in increasingly younger, more mobile and active patients. These developments increase the demand on the implant in terms of a higher range of motion and wear rates, with subsequent negative effect on the survival. Long-term implant failure necessitates the constant need for advancements in implant design [2]. The revival of the metal-on-metal (MoM) bearing surface for THA was driven by potentially better wear properties, a lower dislocation rate and a larger range of motion due to a larger femoral head component [3,4]. However, recent studies show that the larger range of motion is not clinically relevant [5].

Early results indicated favourable short-term and mid-term outcome of the resurfacing MoM THA and the 28-mm head MoM THA [6,7]. However, serious concerns have since arisen about the association of MoM THA and elevated cobalt and chromium serum ion levels, pseudotumors and systemic toxicological effects [8,9]. Furthermore, the early revision rates of MoM THA are reported to be higher than conventional THA by some authors [10,11]. However, others reported excellent results and low revision rates following MoM THA [12]. Next to the technical results, patient-reported functionality of the lower extremity and quality of life following THA have become increasingly relevant [13].

Currently, we are not aware of any study presenting the clinical outcome and revision rate of a 38-mm fixed-size head MoM prosthesis. Additionally, the relation of quality of life and metal ions with the use of validated questionnaires is unknown.

The purpose of this consecutive cross-sectional study was to evaluate the patient-reported pain, presence of pseudotumors, revision rate at short-term follow-up and the association between elevated levels of serum metal ions, patient-reported functionality and quality of life following large fixed-size head MoM THA.

METHODS

Patients

Between February 2008 and January 2011, a consecutive cohort of 377 uncemented MoM THA with a 38-mm fixed-size head were performed in 351 patients at the Meander Medical Centre. All patients were prospectively evaluated following a pre-defined prospective screening protocol. Sixteen patients with unilateral surgery (16 THA) did not participate in the screening; see Fig 1. Three hundred

and thirty-five patients with 361 THA's were available for further analyses. Patient demographics and indications for surgery were presented in Table 1. This study has been approved by the institutional medical ethical review board.

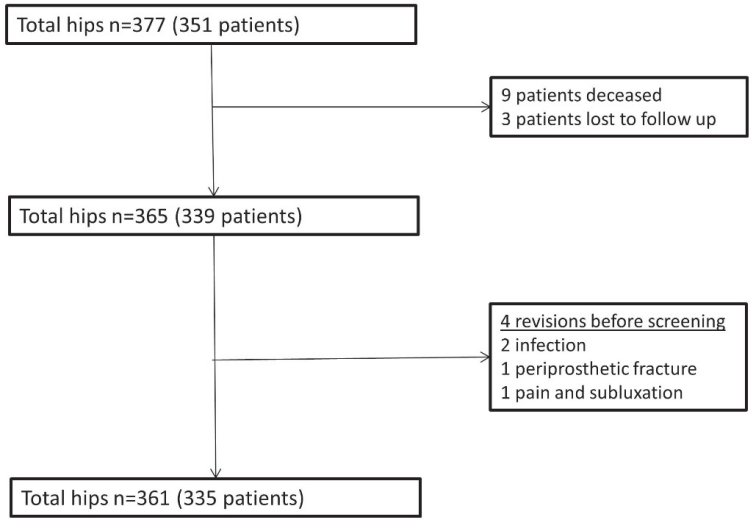

Figure 1 Study flow-chart
(THA, total hip arthroplasty)
Three patients (3 THA) where lost to follow up. One patient moved to another part of the country and the burden of visiting our outdoor patient clinic was too high because of her physical condition. We contacted the patient by phone and she did not report any complaints of the hip. One patient refused screening. One patient was untraceable. Four patients (4 THA) underwent revision surgery before the start of the prospective screening protocol.

Surgical technique and rehabilitation

A total of nine experienced surgeons implanted the MoM THA through a posterolateral approach using a standardized procedure. The cobalt and chromium bearing couple consisting of monoblock acetabular cup with a 38-mm fixed-size head design was implanted in all cases (M2a-38; Biomet, Warsaw, IN, USA). The cup size ranges from 48 mm to 64 mm. No additional screws were used for fixation. All patients received a press-fit titanium femoral stem (Taperloc; Biomet, Warsaw, IN, USA).

On the first day after surgery, a standardised rehabilitation program was started. During admission, patients were instructed to mobilise full weight-bearing with crutches by a physical therapists. After discharge, patients were treated by an outpatient clinic-based physical therapist for approximately three to six months.

Table 1 Baseline demographics

N=335 patients	**Mean**	**Range**
Age at surgery (years)	63	41 - 88
Follow up (months)	30	11 - 58
BMI (kg/m^2)	28	18 - 43
	Count	**%**
Females	204	61
Unilateral	309	92
Left	164	45
N=361 MoM THA	**Count**	**%**
*Idiopathic osteoarthritis (total)**	334	92.5
Unilateral	290	
Bilateral (M2a)	22	
Secondary osteoarthritis (total)	11	3.0
Unilateral*	9	
Bilateral (M2a)**	1	
Non-union /necrosis after femoral neck fracture (total)	10	2.7
Unilateral	10	
Bilateral (M2a)	0	
*Osteonecrosis (total)****	6	1.8
Unilateral	3	
Bilateral (M2a)	2	

(BMI body mass index,SLE systemic lupus erythematosus, THA totalhHipaArthroplasty, MoM metal onmMetal)

34 patients had a THA with a MoM bearing on the contralateral side

**In four patients osteoarthritis after trauma/surgery >10 years ago, in three patients osteoarthritis after dysplasia, in one patient osteoarthritis after septic arthritis and in one patient the osteoarthritis developed after Perthes disease.*

***One patient developed a bilateral osteoarthritis caused by SLE*

****in one patient the indication was osteoarthritis of the left hip and osteonecrosis of the right hip*

Prospective screening protocol

Patients received a standardized outpatient consultation. This included physical examination, patient-reported questionnaires, blood analyses for metal ions, radiographs of the hip and pelvis and magnetic resonance imaging (MRI).

Pain was defined as either the presence or absence of any pain in the hip area reported by the patient. Patients completed the Hip disability and Osteoarthritis

Outcome Score questionnaire (HOOS) [14], the outcome of which is divided into the subscales: pain, other symptoms, function in daily living (FDL), function in sport and recreation and hip-related quality of life (QOL), the Short-Form 36 questionnaire (SF-36) [15] which outcome is divided in eight subscales: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and general mental health (MH), and the Oxford Hip Score questionnaire (OHS) [16].

Cobalt and chromium ion levels were determined in the serum with the use of an AAnalyst 800 Atomic Absorption Spectrophotometer (Perkin Elmer, Waltham, MA, USA). The blood samples were collected in a metal-free container. Cobalt serum levels larger as 5 μg/l were defined as elevated in MoM THA [17].

A contrast-enhanced MRI of the hip region with metal artefact reducing sequences (MARS) was performed in patients with osteolysis on the X-ray, elevated serum metal ion levels above 5 μg/l or pain. Patients without these criteria received routine annual follow-up; see Fig. 2. A total of 209 MRI scans were performed evaluating 227 THA's. Four patients allegeable for MRI evaluation refused the investigation due of claustrophobia or reported only mild complaints. 27 patients requested MRI evaluation for both the possible short- term and long-term consequences of MoM THA. A 1.5-T MRI unit (Achieva; Philips Healthcare, Best, the Netherlands) was used to obtain the MARS sequences. The contrast agent used was Dotarem (Guerbet, Paris, France). All MRI scans were evaluated by a senior musculoskeletal radiologist (B.H.). For description of the pseudotumors, the Anderson classification[18] and the Hauptfleisch classification [19] were used.

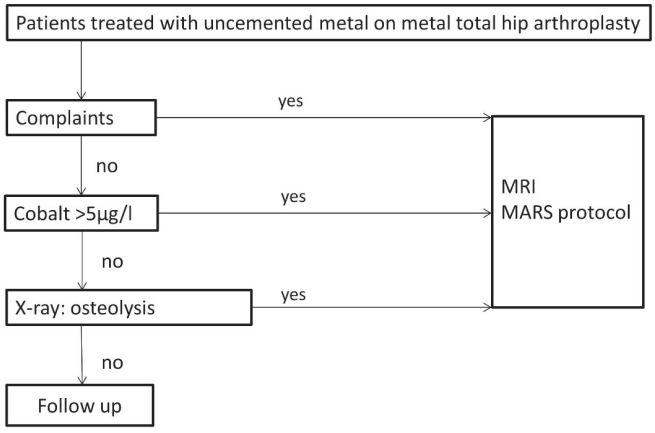

Figure 2 Screening flow-chart of the pre defined protocol
(MRI, Magnetic Resonance imaging; MARS, Metal Artifact Reduction Sequence)

Statistical analysis

Normally distributed variables are expressed as the mean with ranges and non-parametric distributed variables are expressed as median with the interquartile range (IQR), unless otherwise stated. SPSS statistics 20 (IBM Corporation, Armonk, NY, USA) was used for the analyses with a two-tailed significance level of $p<0.05$.

In case of a non-parametric distribution the Mann-Whitney U-test was used to compared the cobalt and chromium levels in patients with pain to patients without pain. Furthermore the outcome of the patient-reported questionnaires between patients with a cobalt serum level of ≤5.0 μg/l and patients with a cobalt level >5.0 μg/l were analysed with a multiple logistic regression model corrected for age, gender and BMI.

RESULTS

One hundred and eighteen (35%) of the total of 335 patients reported pain at the hip area related to the MoM THA. Fifty-two patients had bilateral MoM THA surgery, of which 26 patients had bilateral fixed-size 38-mm head. Four patients with bilateral surgery reported pain at one side only. The cobalt and chromium metal ion levels of all patients are shown in Table 2. Sixty-six patients underwent revision surgery of 67 THA with a median serum cobalt level of 10.1 μg/l (IQR 10.5) and a median serum chromium level of 6.8 μg/l (IQR 7.7).

In unilateral MoM THA, patients with hip pain (n=87) had a median cobalt level of 6.8 μg/l (IQR 8.4) and patients who did not report pain (n=182) had a median cobalt level of 2.9 μg/l (IQR 4.5) ($p<0.001$, Mann-Whitney U test). The median chromium level in patients with pain (n=87) was 4.9 μg/l (IQR 4.3) and the median chromium level in the group of patients without pain (n=182) was 2.8 μg/l (IQR 4.5) ($p=0.002$, Mann-Whitney U test); see Fig. 3.

Patients with cobalt ≤5 μg/l (n=140) had significantly higher scores compared to patients with cobalt >5 μg/l (n=93) on the HOOS domains ($p<0.05$ on all domains, multiple logistic regression), see Fig. 4. On the SF-36, patients with cobalt ≤5 μg/l (n=140) scored 77 (range 11-100) and patients with cobalt >5 μg/l (n=91)) scored 71 (range 19-99) (multiple logistic regression $p=0.027$). For all domains see Fig. 5. The mean OHS for patients with a cobalt ≤5 μg/l (n=141) is 47 (range 8-56) compared to 44 (range 12-56) for patients (n=93) with a cobalt >5 μg/l ($p=0.057$, multiple logistic regression).

Table 2 Serum metal ion levels of all patients and pseudotumor classifications

Groups	Patients	Implants*	Cobalt in µg/l (IQR)	Chromium in µg/l (IQR)	Number of pseudotumors	Hauptfleisch classification			Anderson classification				
						1	2	3	A	B	C1	C2	C3
Total	335	361	4.4 (6.6)	3.6 (4.8)		26	28	3	170	0	9	43	5
No pain	221	235	3.5 (5.1)	3.0 (4.8)									
Cobalt ≤5µg/l	145	152	2.1 (2.0)	2.1 (2.1)	7	3	3	1	22	0	0	7	0
Cobalt >5µg/l	76	83	8.2 (6.5)	7.4 (4.4)	15	7	7	1	63	0	3	10	2
Pain	118	126	7.1 (9.3)	5.2 (6.5)									
Cobalt ≤5µg/l	41	42	2.5 (2.3)	2.0 (2.8)	5	2	3	0	35	0	0	5	0
Cobalt >5 µg/l	77	84	10.8 (9.0)	6.3 (7.5)	30	14	15	1	50	0	6	21	3

(IQR, Inter Quartile Range)

MRI MARS Sequences:

T1W coronal plane with TE 16 ms, TR 450-650 ms SL 2.5 mm, FOV 36x37.1 and BW 435 HZ/pixel.
T2W coronal plane with TE 80 ms, TR 3500-7000 ms SL 2.5 mm, FOV 36x45 and BW 435 HZ/pixel.
STIR coronal plane with TE 40 ms, TR shortest ms SL 3.5 mm, FOV 36x45 and BW 435.5 HZ/pixel.

Anderson classification	**Description**
A Normal	Normal post-op appearances including seromas and small haematomas
B Infection	Fluid-filled cavity with high signal T2 wall; inflammatory changes in soft tissues; ± bone marrow oedema
C1 Mild MoM	Periprosthetic soft tissue mass with no hyperintense T2W fluid signal or fluid-filled peri-prosthetic cavity; either less than 5 cm maximum diameter
C2 Moderate MoM	Periprosthetic soft tissue mass/fluid-filled cavity greater than 5 cm diameter or C1 lesion with either of following: (1) muscle atrophy or edema in any muscle other than short externa rotators or (2) bone marrow edema: hyperintense on STIR
C3 Severe MoM	Any of the following: (1) fluid-filled cavity extending through deep fasci, (2) a tendon avulsion, (3) intermediate T1W soft tissue cortical or marrow signal, (4) fracture

Hauptfleisch classification	**Description**
1	Thin-walled cystic mass (cyst wall <3 mm)
2	Thick-walled cystic mass (cyst wall > 3mm, but less than the diameter of the cystic component)
3	A predominantly solid mass

*four patients with bilateral surgery reported pain only on one side

Pseudotumors

Two hundred and twenty-seven MoM THA's were evaluated with MRI. In total, 57 (25 %) pseudotumors were diagnosed and classified, see Table 2. Most of the pseudotumors were diagnosed as type C2 of the Anderson classification (n=43) and type 1 and 2 of the Hauptfleisch classification (n=26 and n=28, respectively). Seven (24 %) pseudotumors were diagnosed on patient-requested MRI scans. In these patients, no periprosthetic osteolysis at conventional radiographs, elevated serum levels or pain was present at follow-up.

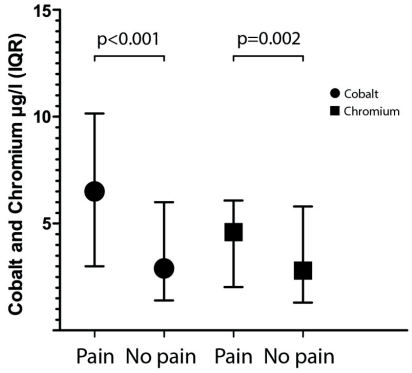

Figure 3 Serum cobalt and chromium levels
(MoM, metal on metal; THA, total hip arthroplasty; IQR, inter quartile range)
Median (IQR) serum cobalt and chromium levels in patients with complaints compared to patients without complaints with unilateral MoM THA.

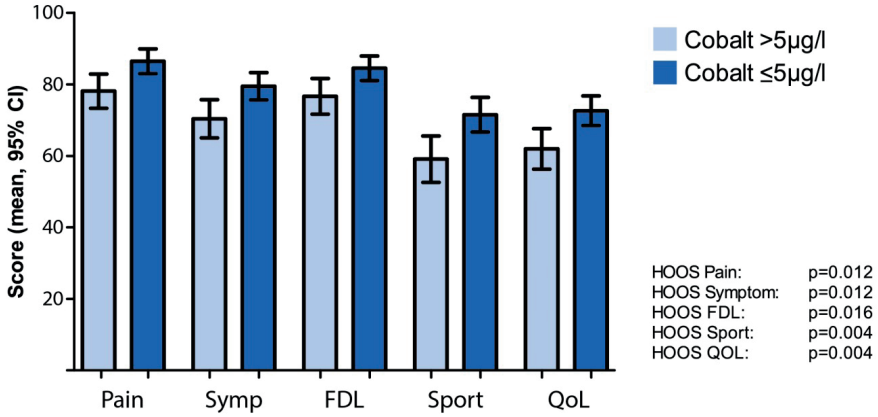

Figure 4 The Hip disability and Osteoarthritis Outcome Score questionnaire
(FDL, Function in Daily Living; QoL, Quality of Life; HOOS, Hip disability and Osteoarthritis Outcome Score; Symp, Symptom; MoM, metal on metal)
The HOOS of patients who underwent unilateral MoM surgery with serum cobalt levels of ≤5 µg/l compared to patients with serum cobalt levels of >5 µg/l.

Revisions

A total of 70 patients with 71 MoM THA's (19 %) underwent revision surgery. The mean time from implantation to revision was 31 months (range 0.2-50 months). Fifty-one (72 %) revisions were performed because of MoM-related problems; see Table 3. In all these revisions, the acetabular component and the modular head was revised, except for one patient in whom both components were revised. Serum cobalt and chromium levels decreased after revision.

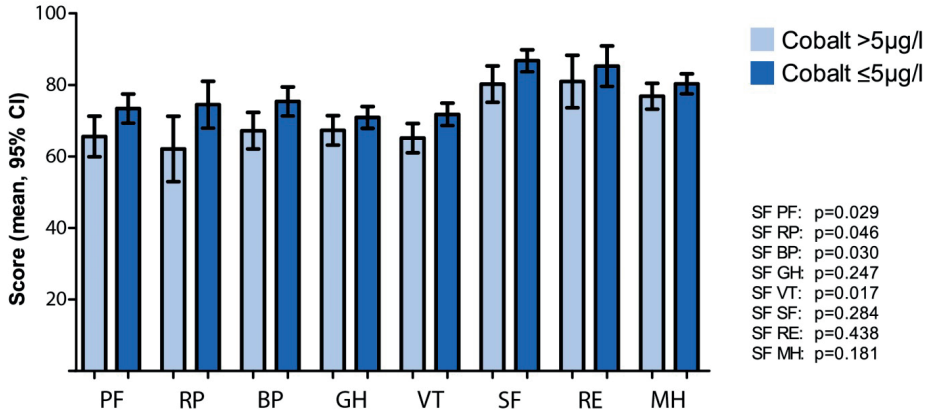

Figure 5 The Short Form 36 questionnaire
(SF-36, Short-Form 36; PF, physical functioning; RP, role limitations due to physical health problems; BP, bodily pain; GH, general health perceptions; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; GH, general mental health; MoM, metal on metal)
Scores on the Short Form 36 questionnaire of patients who underwent unilateral MoM surgery with serum cobalt levels of ≤5 µg/l compared to patients with serum cobalt levels of >5 µg/l.

Four patients underwent revision surgery before the implementation of the screening protocol. Two of these patients underwent revision surgery of both components because of an infection: one because of a periprosthetic fracture type Vancouver B and one patient underwent an acetabular cup revision because of clinical instability. Since the implementation of the screening protocol, two additional patients underwent revision surgery at another institution: one because of pain and loosening of the femoral component and elevated levels of cobalt and chromium,

Table 3 Reasons for revision

Reasons for revision	Number (%)
MoM related:	
Pain and cobalt levels >5 µg/l and pseudotumor	28 (39)
Pain and cobalt levels >5 µg/l	16 (23)
Pain or cobalt levels >5 µg/l and pseudotumor	7 (10)
Non MoM related:	
Component loosening	10 (14)
Pain and instability and/or fractures	5 (7)
Infection	3 (4)
Other	2 (3)
Total	**71 (100)**

(MoM, metal on metal)

and the other patient because of pain, elevated levels of cobalt and chromium and a pseudotumor.

DISCUSSION

A high number of patients reported pain after MoM THA. These patients showed significantly higher serum cobalt and chromium ion levels than patients without pain. Furthermore, patients with a cobalt level ≤5 μg/l reported significantly better outcome on the SF-36 and HOOS questionnaire. The incidence of pseudotumors was 25 % and the revision rate was 19 %.

In the current study 35 % of the patients reported pain from the THA region. The incidence of patient-reported pain is up to 28 % for MoM THA in previous literature [8,20]. This is in contrast to conventional THA, where only up to 10% of the patients reported pain after surgery [21]. Furthermore, patients who reported pain also had significant elevated serum cobalt and chromium levels compared to patients without pain. The association between high metal ion levels and pain in the hip area was previously described by Hart et al. [22]. Of the 153 patients with elevated serum levels of cobalt >5 μg/l, 50% reported pain about the THA region. Also, patients with a cobalt ≤5 μg/l showed significantly higher scores on the SF-36 and HOOS questionnaire compared to patients with a cobalt >5 μg/l. Compared to previous studies reporting patient assessments of THA, the outcome of patients with cobalt ≤5 μg/l is in six of the eight domains slightly higher [13]. Patients with cobalt >5 μg/l scored on six of the eight domains slightly lower, in one domain the group had the same outcome and on one domain the group scored slightly higher [13]. The HOOS questionnaire showed a slightly better score in all domains for patients with cobalt ≤5 μg/l and a slightly lower score on three domains and comparable scores in the other domains in patients with cobalt >5 μg/l [23].

The overall incidence of pseudotumors was 25 % in the current cohort. This finding is similar to preceding studies [8,24]. Furthermore, in the patients without any risk factors or symptoms we observed seven (24 %) “silent” pseudotumors. Previously, the reported incidence of pseudotumors demonstrated in patients without hip pain and cobalt levels ≤5 μg/l is up to 27 % [8,24]. Toxic reactions on the local metal wear debris from the MoM articulation are thought to be a cause for pseudotumor. Also cell-mediated hypersensitivity reactions are associated with metal wear debris [25]. A combination of these factors may be the underlying cause for the higher incidence of reported pain in patients with elevated serum ion levels [22,26].

We observed a revision rate (19 %) of the large fixed-size head MoM THA at a mean follow-up of 2.5 years. The main reason for revision (39 %) was the presence of a pseudotumor in combination with pain and elevated metal ion levels. In the patients who underwent a revision a high percentage of aseptic loosening of the acetabular component was found, possibly induced by metal wear debris osteolysis [25]. Fabi et al. found [10] revision rates of 56 % for aseptic loosening of the MoM THA, performed within three years. This high short-term failure rate and reported complication rate in MoM THA have also been found by others [8,11]. This is the first study describing the outcome of a MoM THA with a fixed-size 38-mm head. Only the Australian register described this type of prosthesis with the same stem, head and cup couple. An outcome of 46 revisions of 471 implants with a percentage of revision in 10 years of 13.2 % is presented. The M2a and Taperloc combination has the most revisions after 10 years in the register [27]. In the Swedish register and the National Joint Registery for England, Wales and Northern Ireland no information of this particular system has been found. The predicted revision percentage of all uncemented MoM at ten years is 21.9% [28].

The failure of large fixed-size head MoM THA cannot be attributed to one single cause. It is more likely that an interaction of several factors lead to early failure of these large fixed-size head MoM THA's. The failure cascade starts with wear of the bearing and corrosion at the taper-head transition, as the tribolayer formation is essential for less wear. The absence of this tribolayer can be a factor in the failure mechanism of the MoM arthroplasty [29]. The tribolayer is a tribochemical reaction frequently found on MoM bearing surface. In vivo wear is reduced by an effective mix-film lubrication [29]. Also the taper-head transition of different metals can induce failure of the large diameter head MoM THA. In the current study, a cobalt-chromium head on a titanium trunnion was used, which might lead to galvanic corrosion [30]. Previously, a low release of titanium is found with a modular neck [31]. Possibly even a low release of titanium can induce galvanic corrosion. This leads to a high release of metal corrosion debris and therefore might accelerate wear as well. All these processes will increase local metal debris, which causes local soft tissue reaction and increased serum metal ion levels [8].

Some study limitations exists. Thirty-one patients did not complete the screening protocol throughout the follow-up. Twenty-seven patients requested MRI evaluation for the possible short- and long-term consequences of MoM THA. Four patients at risk for developing a pseudotumor refused MRI scanning. Since some variables were collected at baseline retrospectively, no pre-operative patient reported questionnaires were available. Even more, not all patients with unilateral MoM surgery did complete the questionnaires during the screening. However, the response rate was high (84 %) on the patient-reported questionnaires. Since vast

amounts of literature on THA and patient-reported questionnaires exists, those data served as reference. In this study the largest cohort of an MoM prosthesis with a 38-mm fixed-size head is presented. We are not aware of any other study that presents such a unique homogeneous cohort with this head and cup couple in combination with the same femoral component. It is of great importance that the orthopaedic community describes the outcome of MoM prosthesis as a group but also the outcomes of the individual systems to gather information of the weaknesses of the different systems.

In conclusion, the current study showed a high incidence of hip pain after MoM THA with a large 38-mm fixed-size femoral head. Patients with pain showed significantly elevated serum metal ions levels compared to patients without pain. Patients with a cobalt level ≤5 μg/l compared to patients with cobalt serum levels >5 μg/l had significantly better outcome on the patient-reported questionnaires. A high revision rate is reported at a mean of 2.5 years, the majority due to MoM induced problems.

ACKNOWLEDGEMENTS

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[1] Learmonth ID, Young C, Rorabeck C (2007) The operation of the century: total hip replacement. Lancet 9597:1508-19. doi:S0140-6736(07)60457-7 [pii];10.1016/S0140-6736(07)60457-7 [doi]

[2] Takenaga RK, Callaghan JJ, Bedard NA, Liu SS, Gao Y (2013) Which functional assessments predict long-term wear after total hip arthroplasty? Clin Orthop Relat Res 8:2586-94. doi:10.1007/s11999-013-2968-9 [doi]

[3] Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH (2005) Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 1:11-9. doi:S0883540304003924 [pii];10.1016/j.arth.2004.07.008 [doi]

[4] Goldsmith AA, Dowson D, Isaac GH, Lancaster JG (2000) A comparative joint simulator study of the wear of metal-on-metal and alternative material combinations in hip replacements. Proc Inst Mech Eng H 1:39-47.

[5] Zijlstra WP, van dA-S, I, Zee MJ, van Raay JJ (2011) No clinical difference between large metal-on-metal total hip arthroplasty and 28-mm-head total hip arthroplasty? Int Orthop 12:1771-6. doi:10.1007/s00264-011-1233-7 [doi]

[6] Back DL, Dalziel R, Young D, Shimmin A (2005) Early results of primary Birmingham hip resurfacings. An independent prospective study of the first 230 hips. J Bone Joint Surg Br 3:324-9.

[7] Innmann MM, Gotterbarm T, Kretzer JP, Merle C, Ewerbeck V, Weiss S, et al. (2014) Minimum ten-year results of a 28-mm metal-on-metal bearing in cementless total hip arthroplasty in patients fifty years of age and younger. Int Orthop 5:929-34. doi:10.1007/s00264-013-2228-3 [doi]

[8] Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC (2012) High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. J Bone Joint Surg Br 6:755-61. doi:94-B/6/755 [pii];10.1302/0301-620X.94B6.28373 [doi]

[9] Prentice JR, Clark MJ, Hoggard N, Morton AC, Tooth C, Paley MN, et al. (2013) Metal-on-Metal Hip Prostheses and Systemic Health: A Cross-Sectional Association Study 8 Years after Implantation. PLoS One 6:e66186. doi:10.1371/journal.pone.0066186 [doi];PONE-D-13-00138 [pii]

[10] Fabi D, Levine B, Paprosky W, Della VC, Sporer S, Klein G, et al. (2012) Metal-on-metal total hip arthroplasty: causes and high incidence of early failure. Orthopedics 7:e1009-e1016. doi:10.3928/01477447-20120621-12 [doi]

[11] Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW (2012) Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 9822:1199-204. doi:S0140-6736(12)60353-5 [pii];10.1016/S0140-6736(12)60353-5 [doi]

[12] Meding JB, Meding LK, Keating EM, Berend ME (2012) Low incidence of groin pain and early failure with large metal articulation total hip arthroplasty. Clin Orthop Relat Res 2:388-94. doi:10.1007/s11999-011-2069-6 [doi]

[13] Keurentjes JC, Blane D, Bartley M, Keurentjes JJ, Fiocco M, Nelissen RG (2013) Socio-economic position has no effect on improvement in health-related quality of life and patient satisfaction in total hip and knee replacement: a cohort study. PLoS One 3:e56785. doi:10.1371/journal.pone.0056785 [doi];PONE-D-12-27003 [pii]

[14] de Groot IB, Reijman M, Terwee CB, Bierma-Zeinstra S, Favejee MM, Roos E, et al. (2009) Validation of the Dutch version of the Hip disability and Osteoarthritis Outcome Score.

Osteoarthritis Cartilage 1:132. doi:S1063-4584(08)00173-8 [pii];10.1016/j.joca.2008.05.014 [doi]

[15] Ware JE, Jr., Keller SD, Hatoum HT, Kong SX (1999) The SF-36 Arthritis-Specific Health Index (ASHI): I. Development and cross-validation of scoring algorithms. Med Care 5 Suppl:MS40-MS50.

[16] Gosens T, Hoefnagels NH, de Vet RC, Dhert WJ, van Langelaan EJ, Bulstra SK, et al. (2005) The "Oxford Heup Score": the translation and validation of a questionnaire into Dutch to evaluate the results of total hip arthroplasty. Acta Orthop 2:204-11.

[17] Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. (2011) Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br 10:1308-13. doi:93-B/10/1308 [pii];10.1302/0301-620X.93B10.26249 [doi]

[18] Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF (2011) Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. Skeletal Radiol 3:303-7. doi:10.1007/s00256-010-1000-7 [doi]

[19] Hauptfleisch J, Pandit H, Grammatopoulos G, Gill HS, Murray DW, Ostlere S (2012) A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. Skeletal Radiol 2:149-55. doi:10.1007/s00256-011-1329-6 [doi]

[20] Lavigne M, Laffosse JM, Ganapathi M, Girard J, Vendittoli P (2011) Residual groin pain at a minimum of two years after metal-on-metal THA with a twenty-eight-millimeter femoral head, THA with a large-diameter femoral head, and hip resurfacing. J Bone Joint Surg Am:93-8. doi:93/Supplement_2/93 [pii];10.2106/JBJS.J.01711 [doi]

[21] Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H (2006) Chronic pain following total hip arthroplasty: a nationwide questionnaire study. Acta Anaesthesiol Scand 4:495-500. doi:AAS976 [pii];10.1111/j.1399-6576.2006.00976.x [doi]

[22] Hart AJ, Sabah S, Henckel J, Lewis A, Cobb J, Sampson B, et al. (2009) The painful metal-on-metal hip resurfacing. J Bone Joint Surg Br 6:738-44. doi:91-B/6/738 [pii];10.1302/0301-620X.91B6.21682 [doi]

[23] Nilsdotter AK, Lohmander LS, Klassbo M, Roos EM (2003) Hip disability and osteoarthritis outcome score (HOOS)--validity and responsiveness in total hip replacement. BMC Musculoskelet Disord:10. doi:10.1186/1471-2474-4-10 [doi]

[24] van der Weegen W, Smolders JM, Sijbesma T, Hoekstra HJ, Brakel K, van Susante JL (2012) High incidence of pseudotumours after hip resurfacing even in low risk patients; results from an intensified MRI screening protocol. Hip Int:0. doi:6CAD430F-1293-4F3B-B7A4-4E8841CA6DEF [pii];10.5301/hipint.5000004 [doi]

[25] Keegan GM, Learmonth ID, Case CP (2008) A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Rev Toxicol 8:645-74. doi:901626464 [pii];10.1080/10408440701845534 [doi]

[26] Zeng Y, Feng W, Li J, Lu L, Ma C, Zeng J, et al. (2014) A prospective study concerning the relationship between metal allergy and post-operative pain following total hip and knee arthroplasty. Int Orthop doi:10.1007/s00264-014-2367-1 [doi]

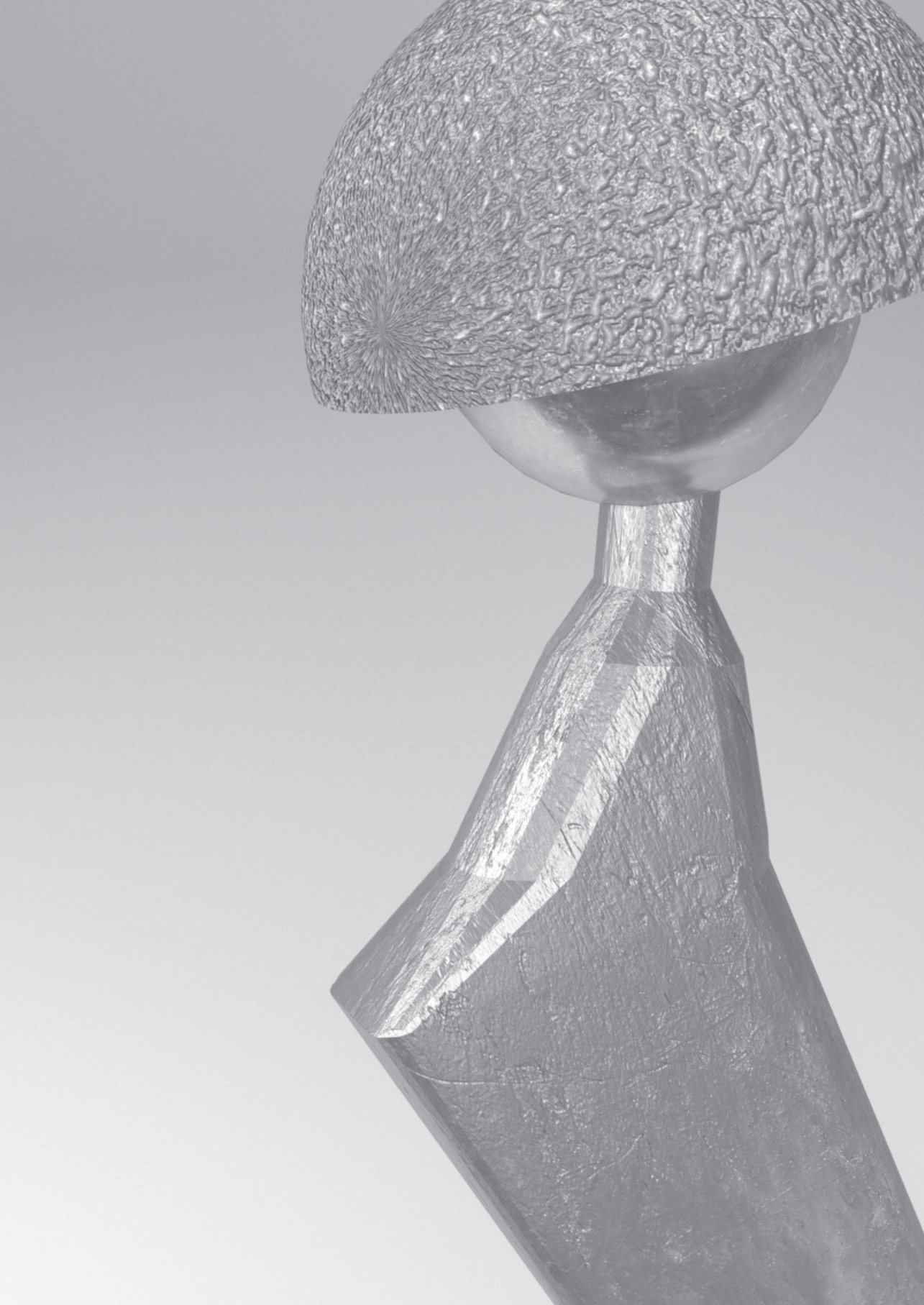
[27] Australian Orthopedic Association. Hip and Knee arthroplasty. 2012.

[28] National Joint Registery for England, Wales and North Ireland. 2014.

[29] Wimmer MA, Fischer A, Buscher R, Pourzal R, Sprecher C, Hauert R, et al. (2010) Wear mechanisms in metal-on-metal bearings: the importance of tribochemical reaction layers. J Orthop Res 4:436-43. doi:10.1002/jor.21020 [doi]

[30] Langton DJ, Sidaginamale R, Lord JK, Nargol AV, Joyce TJ (2012) Taper junction failure in large-diameter metal-on-metal bearings. Bone Joint Res 4:56-63. doi:10.1302/2046-3758.14.2000047 [doi];2000047 [pii]

[31] Kretzer JP, Jakubowitz E, Krachler M, Thomsen M, Heisel C (2009) Metal release and corrosion effects of modular neck total hip arthroplasty. Int Orthop 6:1531-6. doi:10.1007/s00264-009-0729-x [doi]



4 Inclination but not anatomical reconstruction is related with higher cobalt levels in MoM hip arthroplasty

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ABSTRACT

Background: Metal on Metal total hip arthroplasty is associated with elevated serum cobalt levels. In this study we investigate if there is a relation between the inclination and anteversion angle of the cup and the anatomical reconstruction of the hip on the serum cobalt levels.

Methods: Postoperative cobalt serum levels were measured in 250 patients with the M2a-38 cup and Taperloc stem combination. On standardized radiographs inclination and anteversion angle, lower limb length, lateral offset and center of rotation distance were evaluated. A difference of more than 5 millimeter compared to the preoperative situation was considered as a non-anatomical reconstruction.

Results: For every 10 degrees increase in inclination the cobalt level increased 14% (p=0.036). Women with the same cup inclination angle showed 34% higher cobalt levels than men (p=0.013). No relation was found between the anteversion angle, anatomical reconstruction and the serum cobalt levels.

Conclusions: A higher inclination of the cup leads to higher serum cobalt levels, but a non-anatomical reconstruction has no influence on serum cobalt levels.

INTRODUCTION

The constant need to improve implant survival led to the revival of Metal on Metal (MoM) bearings in total hip arthroplasty (THA). The advantages of this type of hard bearing prosthesis was a lower wear profile [1]. Moreover, the large femoral head component, allows for an increase in range of motion and a lower dislocation rate [2]. Contrary to expectations and early studies, a disproportionate high early failure rate on both resurfacing and stemmed large head prosthesis was recently found [3]. Different complications of MoM THA are mentioned in the literature such as pseudotumors, high serum and local metal ion levels and adverse tissue reaction [4-6].

The development of pseudotumors in patients with a MoM bearing prosthesis are related to elevated serum metal ions [7]. Furthermore, high local exposure of metal ions around the periprosthetic tissue can result in an aseptic lymphocyte dominated vasculitis-associated lesion (ALVAL) [4]. Another concern is that elevated levels of metal ions can induce systemic complications [8]. De Haan et. al. previously found higher levels of metal ions in patients with steeply-inclined acetabular components [9]. Some authors report the threshold value of 50 degrees for the maximal cup inclination while changes in anatomical reconstruction of the artificial hip expressed by deviation in lower limb length, lateral offset and change in anatomical center point of rotation are also likely to influence of release of metal ions [10].

Also other factors are known that lead to elevated metal ions levels in metal-on-metal hip arthroplasty. Insufficient and excessive cup anteversion is related to higher cobalt levels [11,12]. Also gender plays a role in cobalt serum levels [11,13,14].

In this study our primary objective is to investigate if there is a relation between the inclination and anteversion angle of the acetabular component and the serum cobalt levels. The secondary goal is to investigate the influence of the anatomical reconstruction of the hip on the serum cobalt levels.

METHODS

Between February 2008 and January 2011, a consecutive series of 377 uncemented primary MoM THA in 351 patients with a M2a-38 and Taperloc stem combination (Biomet, Warsaw, IN, USA) was performed at the Meander Medical Centre. The bearing couple consisting of a monoblock acetabular cup with a 38 mm fixed size head design and was implanted in all cases. All patients were subjected to a pre-

defined screening protocol after the first concerns of the MoM THA and the clinical results were reported [15].

For this radiological evaluation study, we selected from our cohort all unilateral MoM total hip arthroplasty patients. Indication for the operation was osteoarthritis and a standardized radiograph was available, on which the measurements could be performed.

A total of 250 patients with unilateral MoM hip arthroplasty with an M2a-38 and Taperloc stem combination (Biomet, Warsaw, IN, USA) were eligible for the analyses, for demographics see table 1. One hundred and one patients were excluded from the study. Sixteen patients (16 THA) did not complete the screening (9 patients (9 THA) deceased, 4 patients (4 THA) underwent revision surgery before the pre-defined screening and 3 patients (3 THA) were lost to follow up). 52 patients (78 THA) were excluded because of MoM THA on both sides. In 13 patients (13 THA) the radiograph was not reliable for measurements (teardrop not visible, osteonecrosis of the hip, 6 patients (6 THA) did not undergo a pre-operative radiograph at our institution, 12 patients (12 THA) were excluded because of a collum fracture (if there was no displacement of the fracture patient were included) or surgery in the past of the hip area (intertrochantic osteotomy). One patient (1 THA could not straighten his leg and in one patient (1 THA) the prosthesis had been removed because of an infection.

Table 1 Demographics

N=250 patients	**Mean**	**Standard deviation**
Age at surgery (years)	67.3	7.5
Follow up (months)*	29.6	9.9
BMI (kg/m^2)	27.6	4.4
Males	28.5	4.0
Females	27	4.6
Cupsize (mm)	54.7	3.6
	Count	**%**
Females	150	60.0
Left	164	65.6

This study has been approved by the institutional medical ethical review board and is registered under the number TWO 13-33.

Prospective Screening protocol

During the standardized outpatient visit patients were subjected to standard clinical investigations. These include physical examination, patient reported outcome measures (PROM)-questionnaires, blood analyses and hip radiographs. Blood samples were collected in a metal free container. Serum cobalt levels were determined with the use of an AAnalyst 800 Atomic Absorption Spectrophotometer (Perkin Elmer, Waltham, MA, USA). Cobalt serum levels above 5µg/l were used as cut off value for normal values in patients with a MoM implant [16].

Radiographic evaluation

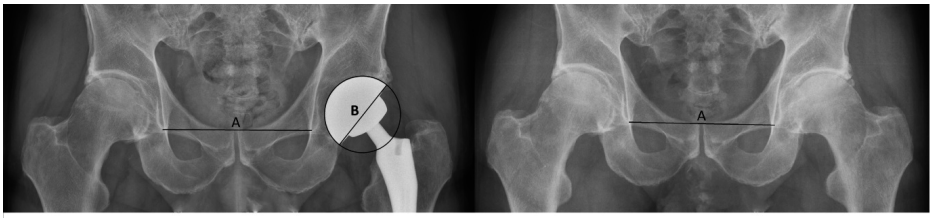
Pre-operative a standard posterior anterior (AP) radiograph was performed with the patient in supine position with both feet in 15-20 degrees internal rotation. Post-operative at six weeks a standard radiograph of the pelvis was made.

The calibration of the post-operative radiograph was performed with the size of the acetabular component. We used a PACS system of IMPAX with an orthopaedic-Tools AGFA 7 Healthcare NV, Mortsel, Belgium. A perfect matching circle was drawn around the outside of the acetabular component, for calibration. The calibration of the pre-operative radiograph was performed with the distance of the line between the most inferior point of the teardrop to the most inferior point of the teardrop on the contralateral side. The length of this line was measured on the calibrated post-operative radiograph. The pre-operative radiograph was calibrated using this line (fig.1).

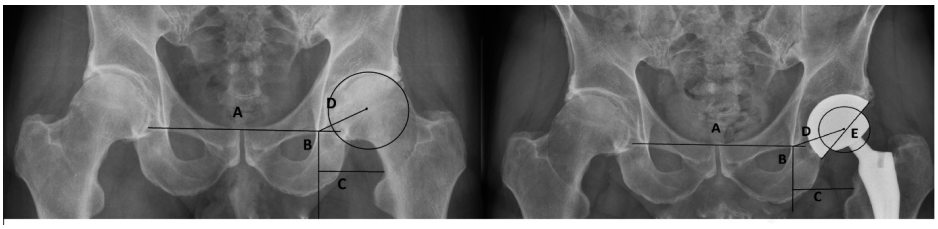
The lower limb length, lateral offset and center of rotation distance (CORD) were measured according to Patel on the pre-and post-operative calibrated radiographs (fig.2)[17]. Also the inclination angle of the acetabular cup was measured (fig.2). The anteversion was measured according the Woo and Morrey's method [18].

Difference in leg length, lateral offset and center of rotation distance of more than 5 millimeter compared to the preoperative situation were considered as a non-anatomical reconstruction. The groups were analyzed with a logistic regression analyses.

A part of the measurements (n=20) was repeated after two months to determine the intra observer reliability of the measurement of the radiograph on the same radiographs. To determine the reliability of the procedure we took 20 pictures of the same patients one year later in follow up. These cases were randomly chosen and the observer (CS) was blinded for the first measurement.



Description of figure 1: *Anteroposterior radiograph of the pelvis on which we demonstrate the technique for the calibration of the X-rays. On the left picture the post-operative X-ray is shown. First a perfect fitting circle is drawn around the acetabular component. With the diameter (B) the post-operative X-ray is calibrated. After calibration of the post-operative X-ray the interteardrop line (A) is drawn between the inferior aspect of the teardrops. The distance of the interteardrop line has been measured. On the right picture the pre-operative X-ray is showed, the size of the interteardrop line (A) is used to calibrate the pre-operative X-ray.*



Description of figure 2: *Left picture. Measurement performed on the pre-operative X-ray after calibration. First a line was drawn through the inferior aspect of the teardrop on both sides (A). A perpendicular line was drawn from the inferior aspect of the teardrop (B). On line B a line perpendicular was drawn till the superior part of the trochanter minor (C). Line B is called the Lower Limb Length and line C is the lateral offset. A perfect circle was drawn in the acetabulum. The center of this circle the center point of rotation. From this point a line is drawn to the superior aspect of the teardrop (D) this line is called the Center of Rotation Distance (CORD).*
Right picture. Measurements are performed on the post-operative X-ray after calibration. First a line was drawn through the inferior aspect of the teardrop (A). A perpendicular line was drawn from the inferior aspect of the teardrop (B). On line B a line perpendicular was drawn till the superior part of the trochanter minor (C). Line B is called the Lower Limb Length and line C is the lateral offset. A perfect circle was drawn around the head of the prosthesis. The exact middle point of this circle we call the center point of rotation. From this point a line is drawn to the superior aspect of the teardrop (D) this line is called the Center of Rotation Distance (CORD). From the inferior aspect of the acetabular component a line was drawn towards the superior part of the acetabular component (E). The angle between this line and line A is called the inclination angle.

Statistical analysis

The relation between the inclination angle of the acetabular component and the serum cobalt level is the primary outcome measurement in this study and the secondary outcome measurement is the relation between the anatomical reconstruction of the hip and the serum cobalt levels.

Reliability of the radiological measurements and the procedure was evaluated by calculating interclass correlation coefficient (ICC). Cobalt levels were not normally distributed so these variables were transformed on a log 10 scale resulting

in distributions which were not markedly skewed. For ease of interpretation we back transformed to the original scale. A logistic regression analyses was used to assess the relation between patients with an anatomical reconstruction and a non-anatomical reconstruction with serum cobalt levels. The anteversion angle was analyzed by dividing patients in three groups (insufficient <10°, normal 10°-20° and excessive >20°). Logistic regression will be used to analyze if there is a difference between the serum cobalt in patients with a normal anteversion versus insufficient an excessive anteversion. Also a linear regression model was used for the analyses of the anteversion angle as described below.

A linear regression model was used to analyze the relation between serum cobalt with the post-operative inclination and anteversion angle, the deviation in lower limb length, lateral offset and CORD (corrected for age, gender and cup size). The results of the linear regressions are presented with the regression coefficient (beta) and 95% Confidence Interval (CI). The results of the logistic regression are shown with the 95% CI. For all tests, a two-tailed significance level of 0.05 was used. SPSS software (IBM Corp., version 20, Armok, NY, USA) was used for the analyses.

RESULTS

Intra rater reliability

The reliability for measuring post-operative cup inclination angle (ICC = 0.74, p= <0.001) was good. An excellent reliability for the pre- and post-operative measurements of the lower-limb length (pre-operative ICC = 0.95, p= <0.001 and post-operative ICC=0.94, p= <0.001), lateral offset (pre-operative ICC = 0.95, p= <0.001, post-operative ICC =0.94, p= <0.001) and for the center of rotation in distance (pre-operative ICC=0.94, p= <0.001, post-operative ICC=0.96, p= <0.001) was found.

An excellent reliability for the procedure measurements of the inclination angle (ICC = 0.95, p= <0.001), lower-limb length (ICC = 0.82, p= <0.001), lateral offset (ICC = 0.84, p= <0.001) and for the center of rotation in distance (ICC=0.91, p= <0.001) was found. The reliability for the procedure of the inner teardrop line (ICC = 0.78, p= <0.001) was good.

Measurements

The mean cup inclination angle was 44.4 degrees (SD 6.7) with a range of 23.9-63.8 degrees. The mean cup anteversion angle was 17.1 degrees (SD 10.2) with a range of 1.0-56.0 degrees. The mean limb length discrepancy comparing pre- and postoperative values was -5.0mm and the mean difference of the lateral offset was 3.1mm (table 2).

Cobalt levels

A significant association (beta 1.014, p=0.036) was found between the post-operative

Table 2 Measurements pre-and post-operative

Measurements (mean, sd)	*Pre-operative*	*Post-operative*	*Mean (difference)*
	All patients	*All patients*	*All patients*
Inclination (degrees)		44.4° (6.7)	
Anteversion (degrees)		17.1° (10.2)	
Lower limb length (mm)	31.7 (7.1)	36.7 (6.8)	5.0
Lateral offset (mm)	46.8 (7.0)	43.9 (7.3)	-3.1
Center of rotation in distance (mm)	38.0 (4.1)	36.1 (4.0)	-1.9

inclination angle and the cobalt values. Thus, for ten degrees increase in inclination an increase of 14% cobalt level was found. No significant relation has been found for the post-operative anteversion angle (table 3). No significant differences were found between the mean cobalt values of 89 patients with a normal anteversion (5.4µg/l (sd 5.1) versus 73 patients with an insufficient anteversion (5.3 µg/l (sd 4.5) p=0.962 and normal versus 88 patients with excessive anteversion (6.3 µg/l (sd 8.4) p=0.363.

Women with the same inclination angle showed a beta of 1.34 (p=0.013), indicating 34% higher cobalt serum levels than men (figure 3).

Table 3. Outcome of the linear regression analysis.

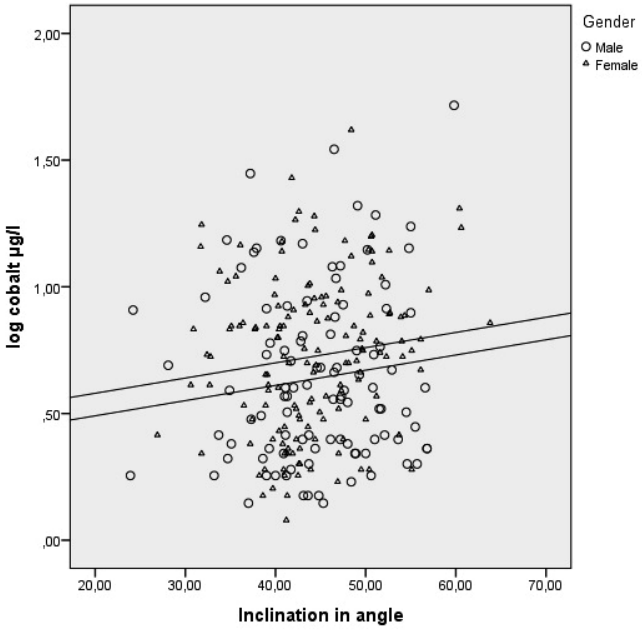
	B (95% CI)	**p-value**	**% increase per unit***
lineair regression cobalt			
Post-op inclination angle	1.014 (1.000-1.028)	0.036	1.4%
Post-op anteversion angle	1.000 (0.993-1.009)	0.806	0.0%
Difference in Lower Limb Length	1.012 (0.995-1.028)	0.158	1.2%
Difference in lateral offset	1.012 (0.998-1.026)	0.108	1.2%
Difference in CORD	1.007 (0.977-1.038)	0.626	0.7%

lineair regression is corrected for age, gender and cup size

No significant relation between the cobalt values and the deviation in lower limb length, lateral offset or CORD was found (table 3).

Anatomical reconstruction

No differences have been found in the patients with more than 5 millimeter positive or negative displacement compared to patients with an anatomical reconstruction as considered normal. (Table 4)



Description of figure 3: *Differences between men and woman in inclination angle and cobalt values. Upper line is the line for woman and the bottom line are the men.*

DISCUSSION

Although this study presents a large series of patients with MoM THA with good intra rater reliability of the radiographic measurements, some limitations exist.

Table 4. Outcome of the anatomical reconstruction

	Number of patients	Mean Cobalt (SD)	p-value
Lower Limb Length			
Normal	101	6.6(8.2)	
≥5 millimeter lengthening	15	5.6(5.6	0.67
≥5 millimeter shortening	134	5.1(4.5)	0.08
Lateral offset			
Normal	119	5.9(7.2)	
≥5 millimeter lengthening	98	6.0(5.9)	0.90
≥5 millimeter shortening	33	4.0(3.5)	0.14
CORD			
Normal	207	5.7(6.1)	
≥5 millimeter lengthening	40	5.5(7.3)	0.82
≥5 millimeter shortening	3	5.7(2.1)	0.99

First, no preoperative Cobalt serum levels were available. Therefore, serum cobalt levels between 0.04-0.64µg/l were considered normal as described earlier [16]. Secondly, the radiographs were not calibrated with an external calibration object,

but with the acetabular component in situ. However the founded ICC was good to excellent as well for the measurement as for the procedure.

The post-operative inclination angle of the acetabular component is associated with cobalt serum values. For every ten degrees increase of cup inclination the cobalt serum increases 14%. Women with the same acetabular cup inclination angle compared to men have 34% higher cobalt levels, which also was observed by others [13,14]. Placement of the cup in the safe zone is important, even more in women.

These higher values in women may be explained by differences in lean body mass between men and woman, cellular or extra-cellular storage or renal excretion. Others account the differences in hip anatomy and head/neck ratio between gender as a reason [19,20]. Remarkably, anatomical reconstruction does not influence the cobalt levels, but this does not explain the differences between the sexes. In our cohort the anteversion angle does not influence the cobalt levels.

De Haan et. al.[9] found higher cobalt levels only in patients with a cup inclination angle above 55 degrees. In this study a ten degrees increase in inclination caused an increase of 14% in serum cobalt level. Hart et. al. reported a positive relation between edge-loading and elevated serum cobalt levels. They also stated that edge loading exists in patients with an inclination angle below 55 degrees [10]. Contrary, other studies did not find a relation between inclination and cobalt serum levels [21,22]. Although cup inclination was associated with elevated cobalt serum levels, other changes in the postoperative anatomical orientation of the hip joint that could affect wear like differences in lower limb length, lateral offset and center point of rotation were not associated with serum cobalt levels.

A possible explanation is found in the retrieval studies of which some describe an asymmetric wear profile at the femoral taper which is possibly created by a togging mechanism [23]. Bishop et. al. wrote that this togging wear is probably created by turning moments resulting from the joint force vector acting medially to the center of the taper connection, in conjunction with joint friction moments [24]. This results in fretting with subsequent corrosion which is facilitating a galvanic reaction and thus can induce an increase of the corrosion when a combination of different metal is used [25,26]. This mechanism seems not to be influenced by the anatomical reconstruction, since serum cobalt values were equal in both groups.

From a mechanically point of view, only large outliers of a non-anatomical reconstruction probably influence postoperative pain and rehabilitation.

In conclusion: In metal on metal total hip arthroplasty a higher inclination of the acetabular component leads to higher serum cobalt levels, but a non-anatomical reconstruction and cup anteversion had no influence on serum cobalt levels. Woman

showed higher cobalt levels than men; independent from cup inclination, head size (all 38 mm) or other biomechanical parameters.

[1] Goldsmith AA, Dowson D, Isaac GH, Lancaster JG (2000) A comparative joint simulator study of the wear of metal-on-metal and alternative material combinations in hip replacements. Proc Inst Mech Eng H 1:39-47.

[2] Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH (2005) Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 1:11-9. doi:S0883540304003924 [pii];10.1016/j.arth.2004.07.008 [doi]

[3] Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW (2012) Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 9822:1199-204. doi:S0140-6736(12)60353-5 [pii];10.1016/S0140-6736(12)60353-5 [doi]

[4] Campbell P, Ebramzadeh E, Nelson S, Takamura K, De SK, Amstutz HC (2010) Histological features of pseudotumor-like tissues from metal-on-metal hips. Clin Orthop Relat Res 9:2321-7. doi:10.1007/s11999-010-1372-y [doi]

[5] Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, et al. (2012) Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. J Bone Joint Surg Am 4:317-25. doi:10.2106/JBJS.J.01508 [doi]

[6] Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, et al. (2008) Pseudotumours associated with metal-on-metal hip resurfacings. J Bone Joint Surg Br 7:847-51. doi:10.1302/0301-620X.90B7.20213 [doi];90-B/7/847 [pii]

[7] Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC (2012) High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. J Bone Joint Surg Br 6:755-61. doi:94-B/6/755 [pii];10.1302/0301-620X.94B6.28373 [doi]

[8] Prentice JR, Clark MJ, Hoggard N, Morton AC, Tooth C, Paley MN, et al. (2013) Metal-on-Metal Hip Prostheses and Systemic Health: A Cross-Sectional Association Study 8 Years after Implantation. PLoS One 6:e66186. doi:10.1371/journal.pone.0066186 [doi];PONE-D-13-00138 [pii]

[9] De HR, Pattyn C, Gill HS, Murray DW, Campbell PA, De SK (2008) Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. J Bone Joint Surg Br 10:1291-7. doi:90-B/10/1291 [pii];10.1302/0301-620X.90B10.20533 [doi]

[10] Hart AJ, Buddhdev P, Winship P, Faria N, Powell JJ, Skinner JA (2008) Cup inclination angle of greater than 50 degrees increases whole blood concentrations of cobalt and chromium ions after metal-on-metal hip resurfacing. Hip Int 3:212-9.

[11] Hart AJ, Skinner JA, Henckel J, Sampson B, Gordon F (2011) Insufficient acetabular version increases blood metal ion levels after metal-on-metal hip resurfacing. Clin Orthop Relat Res 9:2590-7. doi:10.1007/s11999-011-1930-y [doi]

[12] Langton DJ, Sprowson AP, Joyce TJ, Reed M, Carluke I, Partington P, et al. (2009) Blood metal ion concentrations after hip resurfacing arthroplasty: a comparative study of articular surface replacement and Birmingham Hip Resurfacing arthroplasties. J Bone Joint Surg Br 10:1287-95. doi:91-B/10/1287 [pii];10.1302/0301-620X.91B10.22308 [doi]

[13] Savarino L, Cadossi M, Chiarello E, Baldini N, Giannini S (2013) Do ion levels in metal-on-metal hip resurfacing differ from those in metal-on-metal THA at long-term followup? Clin Orthop Relat Res 9:2964-71. doi:10.1007/s11999-013-2981-z [doi]

[14] Vendittoli PA, Mottard S, Roy AG, Dupont C, Lavigne M (2007) Chromium and cobalt ion release following the Durom high carbon content, forged metal-on-metal surface replacement of the hip. J Bone Joint Surg Br 4:441-8. doi:89-B/4/441 [pii];10.1302/0301-620X.89B4.18054 [doi]

[15] Smeekes C, Ongkiehong B, van der Wal B, Wolterbeek R, Henseler JF, Nelissen R (2014) Large fixed-size metal-on-metal total hip arthroplasty: higher serum metal ion levels in patients with pain. Int Orthop doi:10.1007/s00264-014-2605-6 [doi]

[16] Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. (2011) Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br 10:1308-13. doi:93-B/10/1308 [pii];10.1302/0301-620X.93B10.26249 [doi]

[17] Patel SR, Toms AP, Rehman JM, Wimhurst J (2011) A reliability study of measurement tools available on standard picture archiving and communication system workstations for the evaluation of hip radiographs following arthroplasty. J Bone Joint Surg Am 18:1712-9. doi:10.2106/JBJS.J.00709 [doi]

[18] Woo RY, Morrey BF (1982) Dislocations after total hip arthroplasty. J Bone Joint Surg Am 9:1295-306.

[19] Grammatopoulos G, Pandit H, Murray DW, Gill HS (2010) The relationship between head-neck ratio and pseudotumour formation in metal-on-metal resurfacing arthroplasty of the hip. J Bone Joint Surg Br 11:1527-34. doi:92-B/11/1527 [pii];10.1302/0301-620X.92B11.24640 [doi]

[20] Traina F, De CM, Biondi F, Pilla F, Tassinari E, Toni A (2009) Sex differences in hip morphology: is stem modularity effective for total hip replacement? J Bone Joint Surg Am:121-8. doi:91/Supplement_6/121 [pii];10.2106/JBJS.I.00533 [doi]

[21] Emmanuel AR, Bergin KM, Kelly GE, McCoy GF, Wozniak AP, Quinlan JF (2013) The Effect of Acetabular Inclination on Metal Ion Levels Following Metal-on-Metal Hip Arthroplasty. J Arthroplasty doi:S0883-5403(13)00315-X [pii];10.1016/j.arth.2013.04.022 [doi]

[22] Maurer-Ertl W, Friesenbichler J, Sadoghi P, Pechmann M, Trennheuser M, Leithner A (2012) Metal ion levels in large-diameter total hip and resurfacing hip arthroplasty--preliminary results of a prospective five year study after two years of follow-up. BMC Musculoskelet Disord:56. doi:1471-2474-13-56 [pii];10.1186/1471-2474-13-56 [doi]

[23] Bishop N, Witt F, Pourzal R, Fischer A, Rutschi M, Michel M, et al. (2013) Wear patterns of taper connections in retrieved large diameter metal-on-metal bearings. J Orthop Res 7:1116-22. doi:10.1002/jor.22326 [doi]

[24] Bishop NE, Hothan A, Morlock MM (2013) High friction moments in large hard-on-hard hip replacement bearings in conditions of poor lubrication. J Orthop Res 5:807-13. doi:10.1002/jor.22255 [doi]

[25] Jacobs JJ, Gilbert JL, Urban RM (1998) Corrosion of metal orthopaedic implants. J Bone Joint Surg Am 2:268-82.

[26] Koerten HK, Onderwater JJ, Koerten EW, Bernoski FP, Nelissen RG (2001) Observations at the articular surface of hip prostheses: an analytical electron microscopy study on wear and corrosion. J Biomed Mater Res 4:591-6.

5 Pseudotumor in Metal on Metal hip arthroplasty. A comparison study of three grading systems with MRI

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ABSTRACT

Objective Pseudotumors, a well-known complication of metal-on-metal total hip arthroplasty (MoM THA), are well identified on metal artifact-reducing sequences magnetic resonance imaging (MARS-MRI). Several MRI grading systems are described in the orthopedic literature, but their validity is unknown in large clinical studies. Our study was undertaken to describe the classification of pseudotumors in a preselected cohort divided in high- and low- risk patients, using three pseudotumor grading systems applied on MARS-MRI, and to determine the interobserver reliability of the grading systems.

Patients and Methods A retrospective study was performed on 377 consecutive patients (240 MRI scans) treated with an M2a-38 and Taperloc stem combination (Biomet, Warsaw, IN, USA). Patients were divided in a high-risk and low-risk group based on previous published risk factors. Two observers determined the presence of pseudotumors using three different pseudotumor grading systems for classifying MARS-MRI results.

Results The prevalence of pseudotumors as determined with MARS-MRI was 59% in our high risk group, 0% in the low-risk group and 43% in the control group. Serum cobalt values were increased in the high-risk group. The kappa values of the Anderson, Hauptfleisch and Matthies grading system score were 0.43, 0.44 and 0.49 respectively.

Conclusions High-risk patients are at a high risk for pseudotumor development. No pseudotumor development was found in low-risk patients. Interobserver reliability scored best with the Matthies system, but all three grading systems showed only a moderate agreement.

INTRODUCTION

Concerns have been raised on the use of metal-on-metal total hip arthroplasty (MoM THA) because of frequent early revision rates[1], raised cobalt and chromium serum levels in the blood and their possible toxicological effects [2], and the occurrence of cystic and/or solid massed, or so-called pseudotumors, in the periprosthetic tissue [3]. Recent studies show that the incidence of pseudotumors is comparable with other THA systems such as cobalt on polyethylene and metal on polyethylene [4,5]. MoM THA-induced pseudotumors can cause compression of the neurovascular bundle [6,7]. This had also been described for conventional THA, though this pseudotumor compression was associated with a broken or worn-out inlay, which induces a MoM reaction [8,9]. A possible explanation could be that the MoM reaction stimulates the formation of pseudotumors with a larger mass than those observed in conventional THA, although recent research rejected this suggestion [4]. Associations between the presence of a pseudotumor and serum cobalt levels have been described [10]. High local cobalt values may induce pseudotumor formation and are known to cause osteolysis [11]. Risk factors for the formation of a pseudotumor are cobalt >5µg/l [10], female gender [12,13], pain [14], and a high inclination angle >55°[15]. Despite the observed associations and risk factors, the exact mechanism of THA-induced pseudotumors is still unclear. Pseudotumors are well defined on MRI and three grading systems have been described in the orthopedic literature by Anderson [16], Matthies [17] and Hauptfleisch [3]. Table 1 provides details of the scoring systems.

Van der Weegen et. al.[18] described kappa values for all three classification systems (49 hips) and Chang et. al.[14] describes a kappa for the Anderson classification (192 hips). Importantly, other radiological studies on pseudotumors do not report a kappa value and therefore the results has to be interpreted with caution [3,19-21]. The reproducibility of these grading systems is of clinical importance and might help to unravel the etiology of a pseudotumor.

The aims of this study were to describe the classification of pseudotumors in a preselected cohort by utilizing metal artifact-reducing sequences magnetic resonance imaging (MARS-MRI) in a high-risk and low-risk group for pseudotumor development, and to study interobserver reliability of three different pseudotumor grading systems in a large single cohort of MoM THA (240 hips).

PATIENTS AND METHODS

Our investigation reviewed 377 uncemented MoM THA performed in our institution between February 2008 and January 2011. In all cases, a cobalt and chromium bearing couple consisting of a monoblock acetabular cup with a 38-mm fixed size head design was implanted (M2a-38, Biomet Inc., Warsaw, IN, USA). The cup size ranged from 48 mm to 64 mm. All patients received a press-fit titanium femoral stem (Taperloc, Biomet Inc., Warsaw, IN, USA).

All patients were subjected to a pre-defined screening protocol, which was initiated after the first concerns of the MoM THA. The clinical results of this screening were reported recently [22]. In the current study, all patients with a MoM THA and available MARS-MRI were selected.

Screening protocol

Patients received a standardized outpatient consultation. This included physical examination, patient-reported questionnaires, blood analysis for serum cobalt, radiographs of the hip and pelvis and magnetic resonance imaging (MRI). Contrast-enhanced MRI of the hip region with MARS was performed in patients with osteolysis on the X-ray, elevated serum metal ion levels above 5μg/l, or pain. Patients without these criteria received routine annual follow-up which was the same as the first screening.

Pain was defined as the presence or absence of any pain in the hip area reported by the patient. Cobalt and chromium ion levels were determined in the serum with the use of an AAnalyst 800 Atomic Absorption Spectrophotometer (Perkin Elmer, Waltham, MA, USA). The blood samples were collected in a metal-free container. Serum cobalt levels ranging 0.04 to 0.64 μg/l are considered normal in the general population [23]. Cobalt serum levels higher than 5 μg/l were defined as elevated in MoM THA [2]. Inclination was measured on the 6-week post-operative X-ray. The observer who performed the measurements had shown good reliability for measuring post-operative cup inclination angle (ICC = 0.74, p= <0.001) in a previous study (Smeekes et al., accepted for publication)

Patients were divided into three groups based on the likelihood of developing a pseudotumor: one group was supposed to have a high risk for developing a pseudotumor based on the literature. Selection criteria for the high-risk group were: serum cobalt >5μg/l [10], female sex [12,13], hip pain [14] and a high cup inclination angle >45°, which is considered to be out of the safe zone in resurfacing prosthesis [16,24]. Inclusion criteria for the low-risk group were the opposing criteria (male sex, no hip pain, cup inclination <45° and serum cobalt <5μg/l). All other patients were used as the control group.

For description of the pseudotumors, the Anderson classification [16], the classification of Matthies [17], and the Hauptfleisch classification were used [3]. Also, a list of other findings on the MRI scan that are not reported in these scores is shown (Table 1). An experienced musculoskeletal radiologist and a musculoskeletal radiologist in training independently scored the MRI scans. The radiologists applied all grading systems at the same time. Kappa values were compared for each grad-

Table 1 Comparison of the three grading systems

Grading system of Anderson	
A Normal	Normal post-op appearances including seromas and small haematomas
B Infection	Fluid-filled cavity with high signal T2 wall; inflammatory changes in soft tissues; ± bone marrow oedema
C1 Mild MoM	Periprosthetic soft tissue mass with no hyperintense T2W fluid signal or fluid-filled peri-prosthetic cavity; either less than 5 cm maximum diameter
C2 Moderate MoM	Periprosthetic soft tissue mass/fluid-filled cavity greater than 5 cm diameter or C1 lesion with either of following: (1) muscle atrophy or edema in any muscle other than short externa rotators or (2) bone marrow edema: hyperintense on STIR
C3 Severe MoM	Any of the following: (1) fluid-filled cavity extending through deep fasci, (2) a tendon avulsion, (3) intermediate T1W soft tissue cortical or marrow signal, (4) fracture
Grading system of Hauptfleisch	
Type 1	Thin-walled cystic mass (cyst wall <3 mm)
Type 2	Thick-walled cystic mass (cyst wall > 3mm, but less than the diameter of the cystic component)
Type 3	A predominantly solid mass
Grading system of Matthies	
1 Thin-walled	Fluid like: hypointense on T1, hyperintense on T2 Shape Flat, with walls mainly in apposition
2a Thick-walled or irregular	Fluid like: hypointense on T1, hyperintense on T2 Shape Not flat, with >50% of the walls not in apposition
2b Thick-walled or irregular	Atypical fluid: hyperintense on T1, variable on T2 Shape Any shape
3 Solid throughout	Mixed signal Shape Any shape
Other deviations scored by the radiologists	
•	The dimensions of the pseudotumor
•	M. Gluteus minimus muscle atrophy
•	M. Gluteus medius muscle atrophy
•	Presence of a fluid filled bursa
•	Soft tissue erosion
•	Bone marrow oedema
•	Tendon tears

ing system. Discordant cases were discussed and consensus was obtained for the classification system with the best kappa value.

For the MRI scans, an MRI scanner with a field strength of 1.5 Tesla was used. The following MARS-MRI sequences were used: T1-weighted coronal plane with echo time (TE) 16 ms, repetition time (TR) 450-650 ms, slices (SL) 2.5 mm, field-of-view (FOV) 36x37.1 and bandwidth (BW) 435 HZ/pixel: T2-weighted coronal plane with TE 80 ms, TR 3,500-7,000 ms SL 2.5 mm, FOV 36x45 and BW 435 HZ/pixel; T2-weighted short tau inversion recovery (STIR) coronal plane with TE 40 ms, TR shortest ms, SL 3.5 mm, FOV 36x45 and BW 435.5 HZ/pixel.

The scientific committee of the Leiden University Medical Centre and the ethical committee in the Meander Medical Centre waived ethical approval.

Statistical analyses

Descriptive analyses were performed on baseline data and final outcomes. The results are expressed as means with standard deviations or medians with ranges where relevant. Reliability of the radiological measurements was evaluated by calculating interclass correlation coefficient using Cohen's Kappa. The differences among the cobalt values in the pseudotumor classification group were analyzed using post-hoc tests in a one-way ANOVA after logarithmic transformation of the cobalt values because of the skewed (positive) distribution of these values. Chi-squared test was used for the analyses of gender and pain between the pseudotumor classifications. Fisher's test was used to analyze the difference between the presence of a pseudotumor in the high- and low-risk groups. A *t* test was used for comparing the serum cobalt levels in the patients in the control group with and without a pseudotumor. For all tests, a two-tailed significance level of ≤0.05 was used. SPSS software (version 20; IBM, Armok, NY, USA) was used for the analyses.

RESULTS

A total of 240 patients with an M2a-38 and Taperloc stem combination (Biomet, Warsaw, IN, USA) were eligible for analyses. Demographics and reason for surgery are listed in table 2. Seventy-five patients had bilateral MoM prostheses: all 75 had prostheses of the M2a-38 type with a Taperloc stem and were included in the study. The contralateral hip prostheses were of different types and were not included in the study. Twenty-three patients had a bilateral M2a-38 prosthesis and Taperloc stem (=46 M2a-38) combination and 119 patients had a unilateral MoM prosthesis of the M2a-38 type and a Taperloc stem (=119 M2a-38).

Classification of the pseudotumors

In this single cohort of MoM THA hips, observer 1 identified 107 pseudotumors

Table 2 Demographics, indications for surgery and cobalt serum values of the high and low risk patients.

Demographics	*Total (n=240)*	*High risk group (n=34)*	*Low risk group (n=5)*	*Control group (n=201)*
Age in years (SD)	63.2 (7.4)	62.9 (5.6)	61.5 (3.0)	63.3 (7.8)
Follow up in months	29.6 (10.0)	31.4 (9.7)	29.8 (8.1)	29.3 (10.1)
BMI(kg/m^2)	27.4 (4.3)	28.5 (4.2)	25.7 (6.1)	27.1 (4.2)
Gender				
Male	79 (33%)	0 (0%)	5 (100%)	74 (36.8%)
Female	161 (67%)	34 (100%)	0 (0%)	127 (73.2%)
Side				
Left	99 (41%)	12 (35.3%)	4 (80%)	83 (41.3%)
Right	141 (59%)	22 (64.7%)	1 (20%)	118 (58.7%)
Bilateral MoM+	75	16	0	59
*Bilateral M2a-38**	23(46)	5(10)	0	18(36)
Unilateral M2a-38	119	8	5	106
Indication				
Osteoartritis	218 (90.8%)	32 (94.1)	4 (80%)	182 (90.5%)
Secondary osteoartritis	9 (3.8%)	1 (2.9%)	0(0%)	8 (4.0%)
Collum fracture	9 (3.8%)	1 (2.9%)	1 (20%)	7 (3.5%)
Osteonecrosis of the head	4 (1.7%)	0 (0%)	0 (0%)	4 (2.0%)
Cobalt serum level (mean)	9.5 (sd 15.0)	19.8 (sd 34.6)	1.6 (sd 0.9)	8.0 (sd 7.1)

+ Bilateral MoM means a M2a-38 metal on metal total hip arthroplasty one side and a metal on metal prosthesis (resurfacing or total hip) from another type on the other side.
*Bilateral M2a-38 means a M2a-38 metal on metal total hip arthroplasty on both sides

(44.6%) and observer 2 identified 96 pseudotumors (40%) regardless of the grading system used. Observer 1 identified: 46 type C1, 58 type C2, and 3 type C3 pseudotumors using the Anderson grading system. Using the Matthies grading system, observer 1 identified: 32 type 1, 62 type 2a, 1 type 2b and 12 type 3 pseudotumors. With the use of the Hauptfleisch grading, 62 type 1, 32 type 2 and 13 type 3 pseudotumors were classified. (Fig. 1 and Table 3) Observer 2 identified: 16 type C1, 65 type C2 and 15 type C3 pseudotumors using the Anderson grading system. Using the Matthies grading system observer 2 identified: 1 type 1, 85 type 2a, 1 type 2b and 9 type 3 pseudotumors. With the use of the Hauptfleisch grading: 63 type 1, 24 type 2 and 9 type 3 pseudotumors were classified by observer 2 (Fig. 2; Table 3) Interobserver reliability on whether a pseudotumor was present or not was 0.56 (p =<0.001). Interobserver reliability for pseudotumor severity with the Anderson, Matthies, and Hauptfleisch grading system was 0.43 (p=<0.001), 0.49 (p=<0.001) and 0.44 (p=<0.001) respectively. In our cohort, the Matthies score was the most reliable classification. (Table 4)

Figure 1

Flowchart of patients observer 1

(Anderson type b was not presented because of no scores)

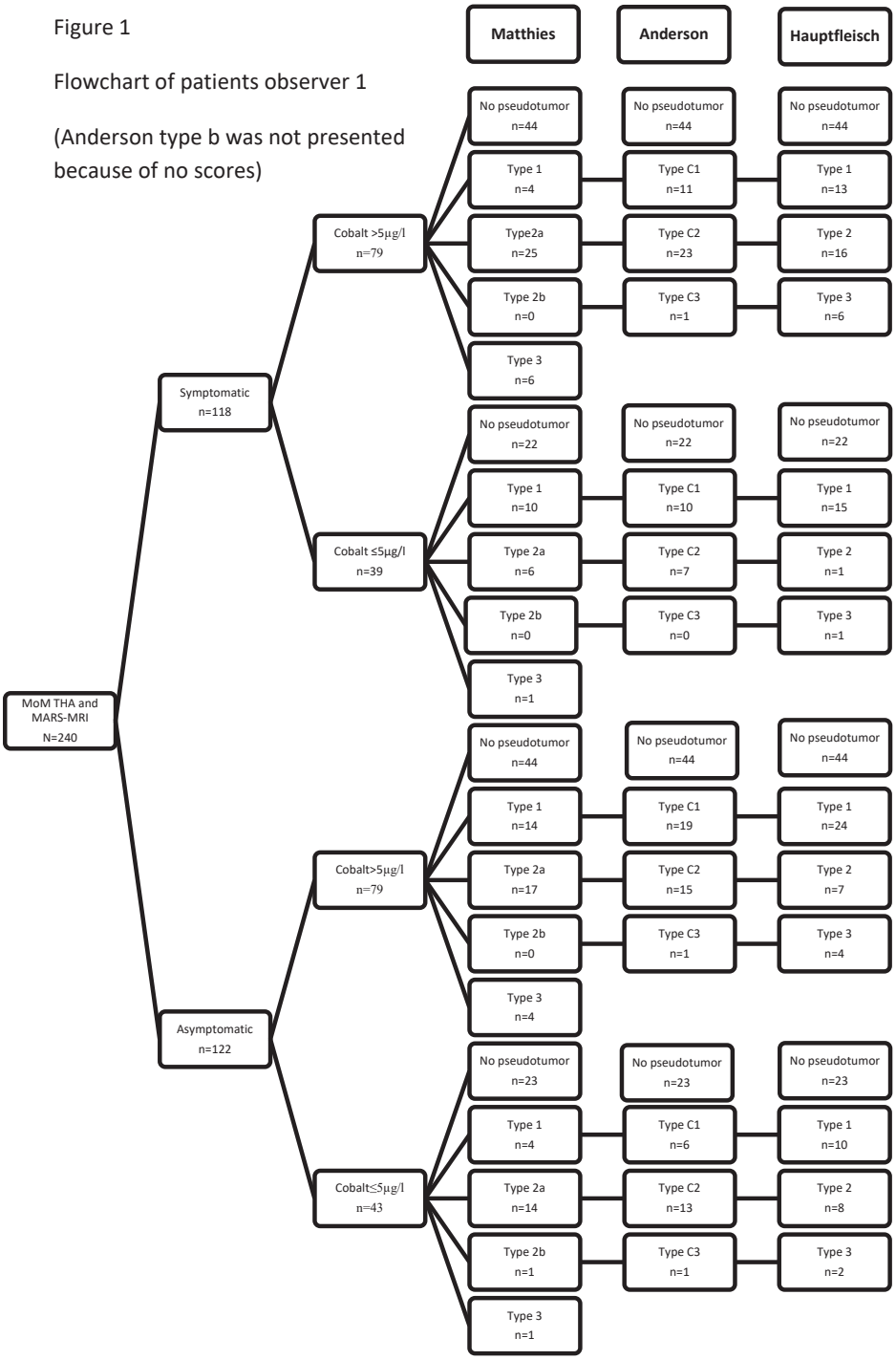


Table 3 findings on MRI by two observers

Findings on MRI		
	Observer 1	*Observer 2*
Pseudotumor		
Yes	107	96
No	133	144
Anderson		
C1	46	16
C2	58	65
C3	3	15
Hauptfleisch		
1	62	63
2	32	24
3	13	9
Matthies		
1	32	1
2a	62	85
2b	1	1
3	12	9
Dimensions of the pseudotumor		
Height in mm (mean,sd)	26.4 (39.5)	31.1 (45.0)
Width in mm (mean, sd)	17.1 (25.8)	22.2 (31.9)
Wallthickness in mm (mean, sd)	0.5 (0.75)	0.5 (0.69)
Other findings		
M. Gluteus minimus muscle atrophy	90	39
M. Gluteus medius muscle atrophy	72	16
presence of a fluid filled bursa	62	58
Soft tissue erosion	37	28
Bone Marrow Oedema	12	4
Tendon tears	8	2

A 17% complete agreement between observer 1 and observer 2 was reached for Anderson C1, 68% for Anderson C2, and 6% for Anderson C3. For the Matthies system, 3% complete agreement between observer 1 and observer 2 was reached for grade 1, 73% for grade 2a, 100% for grade 2b and 75% for grade 3 For the Hauptfleisch system, 48% complete agreement between observer 1 and observer 2 was reached for grade 1, 53% for grade 2, and 39% for grade 3.

The Matthies grading system was discordant for the results of 70 scans. Observer 1 scored 21 no pseudotumors whereas observer 2 scored the same scans as follows: 1 grade 1, 18 grade 2a and 2 grade 3 pseudotumors. Observer 1 scored 32 scans as a grade 1 pseudotumor and observer 2 scored 23 having no pseudotumor, whereas only 9 were scored as grade 1 pseudotumor. Observer 1 scored 10 grade 2a pseudotumors where observer 2 scored 8 no pseudotumors and 2 grade 3 pseudotumors. Lastly observer 1 scored 7 scans as a grade 3 pseudotumor were observer 2 scored 1 no pseudotumor and 6 grade 2a pseudotumors.

Figure 2

Flowchart of patients observer 2

(Anderson type b was not presented because of no scores)

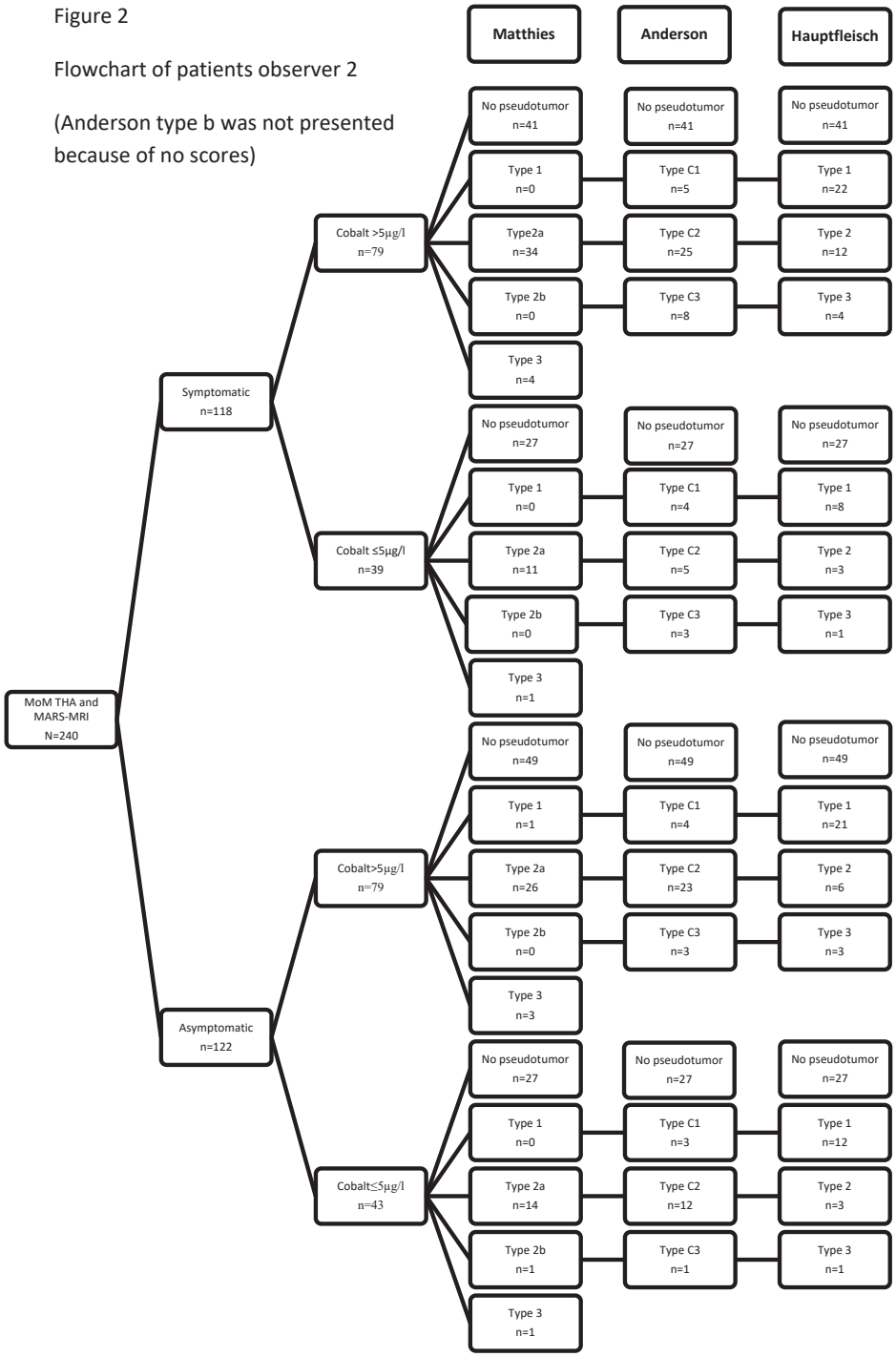


Table 4 ICC of the findings on MRI

Inter Class Correlation	Kappa	p-value
presence of a pseudotumor	0.56	<0.001
Classification		
Anderson	0.43	<0.001
Hauptfleisch	0.44	<0.001
Matthies	0.49	<0.001
Other findings		
M. Gluteus minimus muscle atrophy	0.26	<0.001
M. Gluteus medius muscle atrophy	0.33	<0.001
presence of a fluid filled bursa	0.6	<0.001
Soft tissue erosion	0.59	<0.001
Bone Marrow Oedema	0.29	<0.001
Tendon tears	0.19	<0.001
Foci of susceptibility	0.45	<0.001

A bursa filled with fluid (without connection with the joint) was found for 25.8% cases by observer 1 and for 24.2% of the cases by observer 2. Atrophy of the musc. gluteus medius and minimus was scored by observer 1 in 90 cases, whereas observer 2 scored 39 cases as positive. Atrophy of the medius was found in 72 of the cases by observer 1 and in 16 cases by observer 2.

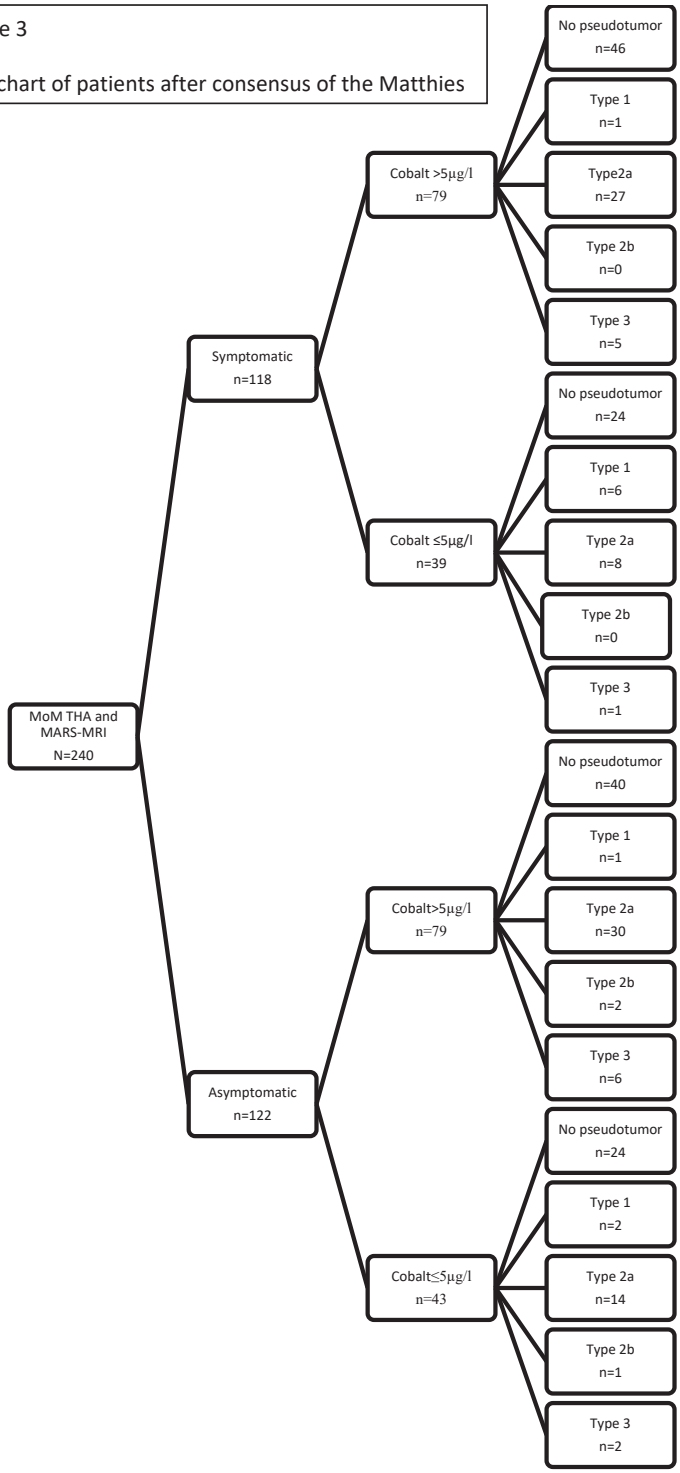
After the consensus, 106 pseudotumors were diagnosed with the use of the Matthies grading system. Type 2a pseudotumor was the most frequent classification. (Fig. 3) Patients with a type 2a pseudotumor had a mean serum cobalt of 13.1 μg/l (SD 23.7). Thirty-eight of these patients had pain and 61 were female. After the logarithmic transformation of the cobalt values, a significant difference could be observed between the group of patients without a pseudotumor and the group of patients with a type 1 or 2a pseudotumor ($p<0.05$), and also between a type 1 pseudotumor versus a type 2a pseudotumor ($p<0.05$) or type 3 pseudotumor ($p<0.05$) respectively. No difference between the pseudotumor classification and pain or gender could be detected (Table 5). Of the 106 pseudotumors, 52 pseudotumors were asymptomatic (49%). There is no difference between the presence of a pseudotumor in the symptomatic patients (54 out of 118) compared with the asymptomatic patients (52 out of 122; $p=0.62$; Table 6). Regarding categories of pseudotumor wall thickness (no wall, <3mm or ≥3mm), there were no difference between the symptomatic and asymptomatic patients (Table 5).

High- and low-risk patient screening

After classification of pseudotumors according to the Matthies grading, patients were divided in a high-risk group for pseudotumor development, a low-risk group, and a control group. A significantly higher risk was found for pseudotumor

Figure 3

Flowchart of patients after consensus of the Matthies



development in the high-risk group (59%, 20 out of 34) versus the low-risk group (0%, 0 out of 5; p<0.001). In the control group, 86 pseudotumors were diagnosed in 201 THA's (43%). The patients in the control group with a pseudotumor had a mean serum cobalt of 8.3µg/l (SD 6.6µg/l) and patients in the control group without a pseudotumor had a mean serum cobalt level of 7.8µg/l (SD 7.5µg/l ; p=0.61).

A difference was found between cobalt serum values and high- and low-risk patients. No differences were found in the control group between patients with a pseudotumor and those without a pseudotumor with regard to serum cobalt levels. No significant differences in the type of pseudotumor, pain and gender were found between the groups. Also, no differences in the control group were found between symptomatic and asymptomatic patients.

Table 5 classification of pseudotumors after consensus of the observers with the differences between the classification groups.

Matthies Classification	*No pseudotumor*	*Type 1*	*Type 2a*	*Type 2b*	*Type 3*
	n=134	n=10	n=79	n=3	n=14
Mean serum cobalt (sd)	7.8 (7.3)	4.0 (5.1)	13.1 (23.7)	8.4 (6.1)	10.2 (15.0)
Gender male/female	84 / 50	6 / 4	18 / 61	1 / 2	4/ 10
Pain	64	7	38	2	7

(There are significant differences between the group of patients without a pseudotumor versus the group of patients with a type 1 (p<0.05) and 2a (p<0.05) pseudotumor respectively, and of type 1 versus type 2a (p<0.05) and versus type 3 (p<0.05) respectively

Table 6 Pseudotumors in symptomatic and asymptomatic patients. Based on consensus assessments.

Pseudotumor	***Yes***	***No***	**Total**
Symptomatic	54 (45.8%)	64 (54.2%)	118 (100%)
Asymptomatic	52 (42.6%)	70 (57.4%)	122 (100%)

DISCUSSION

As far as we know, this is one of the largest series of MoM THA in which patients were screened for having a pseudotumor by utilizing MARS-MRI [25]. A total of 106 pseudotumors were diagnosed after consensus in 240 MoM THA (44%) of which 49% had no symptoms. In the low-risk patient group (male sex, no hip pain, cup inclination <45°, and serum cobalt <5 µg/l), no pseudotumors were diagnosed, whereas a high percentage of pseudotumors (59%, 20 out of 34) was found in the high-risk patient group (serum cobalt >5µg/l[10], female sex, hip pain and a high cup inclination angle >45°). However, the control group also showed a high

percentage of pseudotumors (43%, 86 out of 201). The high-risk group showed a significant higher risk of developing a pseudotumor.

A higher cobalt level is also correlated with different levels of pseudotumors. One may hypothesize that a (local) higher cobalt level influences the formation of a pseudotumor; however, several studies show that cobalt values are a poor predictor [17,26,27]. In the literature, it is reported that the existence of a pseudotumor varies by type of prosthesis. In large-head MoM prosthesis patients, 40%-60% of the patients develop a pseudotumor [10,28,29]. Our cohort results agree to these findings. Other studies showed that the prevalence of pseudotumors in conventional THA ceramics on polyethylene and metal on polyethylene is comparable with MoM THA [4,5], but they are less symptomatic and revisions because of pseudotumors are rare in non-MoM THA. More patients with MoM THA report pain compared with patients with conventional THA [30], which may be caused by the local toxicity of the cobalt, hypersensitivity reactions on the metal release, subsequent osteolysis and soft tissue damage [22,31]. Chang et. al. reports that soft-tissue damage is associated with pain and not the presence or size of a pseudotumor [14]. The behavior of pseudotumors on the long term is unclear.

A high complication rate (14%) in MoM revision surgery has been reported, with a 7% re-revision rate after 2 years (range: 26-52 months) [32] and a dislocation rate of up to 28% [33-35]. Three of the studies used a posterior approach and one study used a posterior approach in 80% of the cases and in 20% an anterolateral approach. The exact reason for the higher luxation rate after these revisions is not clear, but all authors suggest that the extensive destruction of soft tissue caused by the MoM prosthesis might play an imported role. Atrophy of the gluteal musculature and subsequent instability may contribute to the high dislocation rate. In case of symptomatic patients MARS-MRI can be used as a preoperative tool to classify the damage of the soft tissue before revision and add to decision-making to choose a dual mobility cup to lower the dislocation rate [36].

To the best of our knowledge, only one study has reported the interobserver reliability among the three grading systems [18]. In this study, the highest kappa (0.58) was found for the Anderson grading system. In our study, the highest kappa (0.49) was found for the Matthies classification, 0.44 for the Anderson classification, and 0.43 for the Hauptfleisch classification. Although this study included a larger cohort of patients compared to van der Weegen et. al., a lower kappa value was measured. We do not have an explanation for this, but in both studies, there was only moderate agreement, which questions the reproducibility and thus clinical use. Another difference is that we only used the M2a-38 system and in the other study, three different systems had been used. A shortcoming of the study is that the MARS-MRI scored all grading systems at the same time, which can create a

'cross-contamination' of results. The low kappa of the Anderson score can be partly explained by the inclusion of more parameters of periprosthetic tissue compared to the Matthies and Hauptfleisch scores, which only score the characteristics of the pseudotumor.

Compression by a pseudotumor on the neurovascular bundle, soft tissue damage, and osteolysis will aid in clinical decision-making whether to revise or not.

In conclusion, a higher occurrence of pseudotumor development in high-risk patients was found. No pseudotumor development was found in low-risk patients. However, patients in the control group also showed a high occurrence of pseudotumors. This means that every patient, except those defined as 'low risk', is at a substantial risk for developing a pseudotumor. No differences were found in the control group between patients with a pseudotumor and those without a pseudotumor regard to serum cobalt levels. The Matthies score was the most reliable classification, but all three grading systems showed a limited interobserver reliability. MARS-MRI is one of the tools that aids in clinical decision-making regarding revision MoM THA, but whether or not a pseudotumor grading system should be used, or if so, which one, is still under debate.

[1] Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW (2012) Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 9822:1199-204. doi:S0140-6736(12)60353-5 [pii];10.1016/S0140-6736(12)60353-5 [doi]

[2] Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. (2011) Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br 10:1308-13. doi:93-B/10/1308 [pii];10.1302/0301-620X.93B10.26249 [doi]

[3] Hauptfleisch J, Pandit H, Grammatopoulos G, Gill HS, Murray DW, Ostlere S (2012) A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. Skeletal Radiol 2:149-55. doi:10.1007/s00256-011-1329-6 [doi]

[4] Bisseling P, de Wit BW, Hol AM, van Gorp MJ, van KA, van Susante JL (2015) Similar incidence of periprosthetic fluid collections after ceramic-on-polyethylene total hip arthroplasties and metal-on-metal resurfacing arthroplasties: results of a screening metal artefact reduction sequence-MRI study. Bone Joint J 9:1175-82. doi:97-B/9/1175 [pii];10.1302/0301-620X.97B9.35247 [doi]

[5] Nikolaou VS, Petit A, Khoury V, Blain-Pare E, Zukor DJ, Huk OL, et al. (2015) Magnetic resonance imaging of painful metal-on-metal total hip replacement. Eur J Orthop Surg Traumatol 2:313-9. doi:10.1007/s00590-014-1491-3 [doi]

[6] Abdel-Hamid H, Miles J, Carrington RW, Hart A, Loh A, Skinner JA (2015) Combined Vascular and Orthopaedic Approach for a Pseudotumor Causing Deep Vein Thrombosis after Metal-on-Metal Hip Resurfacing Arthroplasty. Case Rep Orthop:926263. doi:10.1155/2015/926263 [doi]

[7] Clayton RA, Beggs I, Salter DM, Grant MH, Patton JT, Porter DE (2008) Inflammatory pseudotumor associated with femoral nerve palsy following metal-on-metal resurfacing of the hip. A case report. J Bone Joint Surg Am 9:1988-93. doi:90/9/1988 [pii];10.2106/JBJS.G.00879 [doi]

[8] Fischer SR, Christ DJ, Roehr BA (1999) Sciatic neuropathy secondary to total hip arthroplasty wear debris. J Arthroplasty 6:771-4. doi:S0883-5403(99)90237-1 [pii]

[9] Fokter SK, Repse-Fokter A, Takac I (2009) Case report: femoral neuropathy secondary to total hip arthroplasty wear debris. Clin Orthop Relat Res 11:3032-5. doi:10.1007/s11999-009-0894-7 [doi]

[10] Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC (2012) High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. J Bone Joint Surg Br 6:755-61. doi:94-B/6/755 [pii];10.1302/0301-620X.94B6.28373 [doi]

[11] Keegan GM, Learmonth ID, Case CP (2008) A systematic comparison of the actual, potential, and theoretical health effects of cobalt and chromium exposures from industry and surgical implants. Crit Rev Toxicol 8:645-74. doi:901626464 [pii];10.1080/10408440701845534 [doi]

[12] Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV (2010) Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. J Bone Joint Surg Br 1:38-46. doi:92-B/1/38 [pii];10.1302/0301-620X.92B1.22770 [doi]

[13] Moroni A, Savarino L, Hoque M, Cadossi M, Baldini N (2011) Do ion levels in hip resurfacing differ from metal-on-metal THA at midterm? Clin Orthop Relat Res 1:180-7. doi:10.1007/s11999-010-1424-3 [doi]

[14] Chang EY, McAnally JL, Van Horne JR, Statum S, Wolfson T, Gamst A, et al. (2012) Metal-on-metal total hip arthroplasty: do symptoms correlate with MR imaging findings? Radiology 3:848-57. doi:radiol.12120852 [pii];10.1148/radiol.12120852 [doi]

[15] Hart AJ, Muirhead-Allwood S, Porter M, Matthies A, Ilo K, Maggiore P, et al. (2013) Which factors determine the wear rate of large-diameter metal-on-metal hip replacements? Multivariate analysis of two hundred and seventy-six components. J Bone Joint Surg Am 8:678-85. doi:1674734 [pii];10.2106/JBJS.J.01447 [doi]

[16] Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF (2011) Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. Skeletal Radiol 3:303-7. doi:10.1007/s00256-010-1000-7 [doi]

[17] Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ (2012) Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. Clin Orthop Relat Res 7:1895-906. doi:10.1007/s11999-011-2201-7 [doi]

[18] van der Weegen W, Brakel K, Horn RJ, Wullems JA, Das HP, Pilot P, et al. (2014) Comparison of different pseudotumor grading systems in a single cohort of metal-on-metal hip arthroplasty patients. Skeletal Radiol 2:149-55. doi:10.1007/s00256-013-1755-8 [doi]

[19] Bisseling P, de Wit BW, Hol AM, van Gorp MJ, van KA, van Susante JL (2015) Similar incidence of periprosthetic fluid collections after ceramic-on-polyethylene total hip arthroplasties and metal-on-metal resurfacing arthroplasties: results of a screening metal artefact reduction sequence-MRI study. Bone Joint J 9:1175-82. doi:97-B/9/1175 [pii];10.1302/0301-620X.97B9.35247 [doi]

[20] Nawabi DH, Gold S, Lyman S, Fields K, Padgett DE, Potter HG (2014) MRI predicts ALVAL and tissue damage in metal-on-metal hip arthroplasty. Clin Orthop Relat Res 2:471-81. doi:10.1007/s11999-013-2788-y [doi]

[21] Reito A, Elo P, Puolakka T, Pajamaki J, Nieminen J, Eskelinen A (2014) Repeated magnetic resonance imaging in 154 hips with large-diameter metal-on-metal hip replacement. Acta Orthop 6:570-6. doi:10.3109/17453674.2014.961868 [doi]

[22] Smeekes C, Ongkiehong B, van der Wal B, Wolterbeek R, Henseler JF, Nelissen R (2014) Large fixed-size metal-on-metal total hip arthroplasty: higher serum metal ion levels in patients with pain. Int Orthop doi:10.1007/s00264-014-2605-6 [doi]

[23] Goulle JP, Mahieu L, Castermant J, Neveu N, Bonneau L, Laine G, et al. (2005) Metal and metalloid multi-elementary ICP-MS validation in whole blood, plasma, urine and hair. Reference values. Forensic Sci Int 1:39-44. doi:S0379-0738(05)00208-2 [pii];10.1016/j.forsciint.2005.04.020 [doi]

[24] Langton DJ, Joyce TJ, Jameson SS, Lord J, Van OM, Holland JP, et al. (2011) Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. J Bone Joint Surg Br 2:164-71. doi:93-B/2/164 [pii];10.1302/0301-620X.93B2.25099 [doi]

[25] Reito A, Elo P, Nieminen J, Puolakka T, Eskelinen A (2016) Gluteal muscle fatty atrophy is not associated with elevated blood metal ions or pseudotumors in patients with a unilateral metal-on-metal hip replacement. Acta Orthop 1:29-35. doi:10.3109/17453674.2015.1094713 [doi]

[26] Bayley N, Khan H, Grosso P, Hupel T, Stevens D, Snider M, et al. (2015) What are the predictors and prevalence of pseudotumor and elevated metal ions after large-diameter metal-on-metal THA? Clin Orthop Relat Res 2:477-84. doi:10.1007/s11999-014-3824-2 [doi]

[27] Bosker BH, Ettema HB, van RM, Boomsma MF, Kollen BJ, Maas M, et al. (2015) Pseudotumor formation and serum ions after large head metal-on-metal stemmed total hip replacement. Risk factors, time course and revisions in 706 hips. Arch Orthop Trauma Surg 3:417-25. doi:10.1007/s00402-015-2165-2 [doi]

[28] Hart AJ, Satchithananda K, Liddle AD, Sabah SA, McRobbie D, Henckel J, et al. (2012) Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using three-dimensional computed tomography and magnetic resonance imaging. J Bone Joint Surg Am 4:317-25. doi:10.2106/JBJS.J.01508 [doi]

[29] Williams DH, Greidanus NV, Masri BA, Duncan CP, Garbuz DS (2011) Prevalence of pseudotumor in asymptomatic patients after metal-on-metal hip arthroplasty. J Bone Joint Surg Am 23:2164-71. doi:10.2106/JBJS.J.01884 [doi]

[30] Nikolajsen L, Brandsborg B, Lucht U, Jensen TS, Kehlet H (2006) Chronic pain following total hip arthroplasty: a nationwide questionnaire study. Acta Anaesthesiol Scand 4:495-500. doi:AAS976 [pii];10.1111/j.1399-6576.2006.00976.x [doi]

[31] Gill HS, Grammatopoulos G, Adshead S, Tsialogiannis E, Tsiridis E (2012) Molecular and immune toxicity of CoCr nanoparticles in MoM hip arthroplasty. Trends Mol Med 3:145-55. doi:S1471-4914(11)00211-5 [pii];10.1016/j.molmed.2011.12.002 [doi]

[32] Liow MH, Dimitriou D, Tsai TY, Kwon YM (2016) Preoperative Risk Factors Associated With Poor Outcomes of Revision Surgery for "Pseudotumors" in Patients With Metal-on-Metal Hip Arthroplasty. J Arthroplasty 12:2835-42. doi:S0883-5403(16)30213-3 [pii];10.1016/j.arth.2016.05.034 [doi]

[33] De Smet KA, Van Der Straeten C, Van OM, Doubi R, Backers K, Grammatopoulos G (2011) Revisions of metal-on-metal hip resurfacing: lessons learned and improved outcome. Orthop Clin North Am 2:259-69, ix. doi:S0030-5898(11)00004-6 [pii];10.1016/j.ocl.2011.01.003 [doi]

[34] Grammatopoulos G, Pandit H, Kwon YM, Gundle R, McLardy-Smith P, Beard DJ, et al. (2009) Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. J Bone Joint Surg Br 8:1019-24. doi:91-B/8/1019 [pii];10.1302/0301-620X.91B8.22562 [doi]

[35] Munro JT, Masri BA, Duncan CP, Garbuz DS (2014) High complication rate after revision of large-head metal-on-metal total hip arthroplasty. Clin Orthop Relat Res 2:523-8. doi:10.1007/s11999-013-2979-6 [doi]

[36] Mohaddes M, Cnudde P, Rolfson O, Wall A, Karrholm J (2017) Use of dual-mobility cup in revision hip arthroplasty reduces the risk for further dislocation: analysis of seven hundred and ninety one first-time revisions performed due to dislocation, reported to the Swedish Hip Arthroplasty Register. Int Orthop doi:10.1007/s00264-016-3381-2 [doi];10.1007/s00264-016-3381-2 [pii]

6 Current Pathologic Scoring Systems for Metal-on-Metal THA Revisions are not Reproducible.

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ABSTRACT

Background The aseptic lymphocyte vasculitis-associated lesion (ALVAL) score and the modified Oxford ALVAL score are frequently used scoring methods to evaluate the morphologic features of periprosthetic tissues around metal-on-metal (MoM) hip implants. Except for the initial studies of these two morphology scoring methods, to our knowledge, no other studies have reported on intraclass correlation coefficient (ICC) values for interobserver reliability of these scoring methods.

Questions/purposes Are ALVAL and Oxford ALVAL scores reproducible?

Methods The periprosthetic tissue of 37 revisions of 36 patients with failed MoM THA's were independently scored by three experienced pathologists using ALVAL and Oxford ALVAL scoring methods. All patients were included who underwent revision surgery in our hospital until January 2013, with a large- head MoM prosthesis and also met the criteria: blood serum cobalt levels, available MRI scan, and intraarticular cobalt levels. The population included 26 patients with pseudotumors diagnosed by two radiologists using the method described by Matthies et al. The ALVAL describes morphologic features of the synovial lining, tissue organization, and inflammatory cell infiltrate in periprosthetic tissues. The Oxford-ALVAL score uses a semiquantitative measure of the immune response which should be easier to score.

Results The ALVAL score showed an ICC of 0.38 (95% CI, 0.18-0.58) (fair) for the sum score and this improved up to 0.50 (95% CI, 0.31-0.68) (moderate) using the modified Oxford ALVAL score. The individual parameters of the ALVAL score showed an ICC for the scoring of inflammatory infiltrate of 0.37 (95% CI, 0.17-0.57), an ICC of 0.32 (95% CI, 0.12-0.53) for the scoring of tissue organization, and an ICC of 0.14 (95% CI, 0.00 to 0.34) for synovial lining.

Conclusions Scoring morphologic features of MoM tissue is not reproducible using the ALVAL score or the Oxford ALVAL score. This may reflect heterogeneous morphologic features in tumor tissue and between different tumor tissue samples that cannot be reliably quantified by pathologists using the parameters of these two scoring methods. An alternative, simplified scoring system should be developed to improve the interrater agreement.

Level of Evidence Level III, diagnostic study

INTRODUCTION

Despite hopes that metal-on-metal (MoM) bearings would provide long-lasting pain relief and restoration of function in THA's, revision rates for many designs have been alarmingly high. Release of metal ions and particles from the MoM bearing leads to elevated high local and systemic exposure to cobalt and chromium ion levels. At the local level, pseudotumor is a frequent finding, described as development of a cystic solid mass in the periarticular region, which has a direct communication with the joint [1]. A possible explanation for the occurrence of pseudotumors and failure of the MoM THA is the toxicity of the local metal debris rich in cobalt particles that can induce DNA damage and cell death, which occurs either by disruption of the membrane or because of the DNA damage. An inflammatory mass develops in response to the cytokines released [2]. Although pseudotumors also are seen in patients after conventional THA with ceramic on polyethylene [3] and are described in metal on polyethylene in case reports [4,5], risk for development of these pseudotumors is increased in patients with elevated serum metal ion levels [6].

Aseptic lymphocyte vasculitis-associated lesion (ALVAL), first reported by Davies et al. [7], is a histologic description made from tissue sampling at the time of surgery identifying an abundance of lymphocytes in the local pericapsular tissue. ALVAL typically is associated with local metal ion release. A meta-analysis showed a pooled estimate of the incidence of pseudotumor or ALVAL in MoM hip articulations to be 0.6% [8], and another study showed up to 6.5% ALVAL [9]. The most-used description method of periprosthetic tissues around MoM hip implants is the ALVAL score of Campbell et al. [10]. This subsequently was modified by Grammatopoulos et al. [11], (herein referred to as the Oxford ALVAL) to be able to distinguish if the inflammatory changes and tissue necrosis seen in periprosthetic tissues around failed MoM hip resurfacing implants are attributable to cytotoxicity or hypersensitivity tissue necrosis, and the extent of the inflammatory cell infiltrate was included. Both scoring systems are widely used [12-19], however to our knowledge, other than the initial studies [10,11], no other studies have reported on interrater reliability. Thus, it is unclear if these scoring instruments are reproducible.

We therefore asked whether the ALVAL and Oxford ALVAL scores were reproducible.

PATIENTS AND METHODS

Between February 2008 and January 2011, a series of 377 uncemented primary MoM THA's with a M2a-38™ and Taperloc® stem combination (Biomet, Warsaw, IN, USA) were performed at the Meander Medical Centre. During that period, we used this implant when there was an indication for a THA. Of the patients who were treated with this approach, nine patients (3%) had died, three (1%) were lost to followup, and four (1%) underwent revision surgery before the screening protocol (two infections, one periprosthetic fracture, and one because of pain and subluxations). Three hundred thirty-five patients (361 hips; 95%) were available for followup at a minimum of 11 months (mean, 30 months; range, 11-58 months) [20]. After the first concerns of MoM THA and an alert issued by the Dutch Orthopaedic Association, all patients were subjected to a screening protocol. For the current study, patients who underwent revision surgery because of failure of their MoM hip prostheses were included. A total of 71 revisions were performed in 70 patients. Twenty revisions were not MoM related. Fifty-one revisions were related to MoM problems. Of these, 36 patients with 37 revisions (one bilateral) were selected for the current study because tissue samples, intraarticular cobalt values, and MR images were available. One patient had bilateral MoM THA and underwent revision on both sides; 10 patients had bilateral MoM THA's and underwent revision on one side; and all other patients underwent revision on their unilateral MoM THA. The mean age of the patients at primary surgery was 62 years (SD, 8.2 years); 29 patients were women. The main reason for primary surgery was osteoarthritis (Table 1). The mean serum cobalt level was 20 μg/L (SD, 33 μg/L) and the mean intraarticular fluid cobalt was 2240 μg/L (SD, 2689 μg/L) (Table 1). Pain was reported by 28 patients (76%).

Twenty-six pseudotumors were diagnosed on MRI. Most of the pseudotumors were described as 2A according to the classification described by Matthies et al.[21] (n = 24). Two Type 3 pseudotumors were diagnosed (Table 1). Reasons for revision were pseudotumor formation in combination with pain and elevated serum levels of cobalt or pain and elevated serum cobalt levels without pseudotumor formation and failure of the hip for other reasons (acetabular loosening [n = 2] and component impingent [n = 1]; these patients also had elevated cobalt levels). During revision surgery two to three samples were taken by the surgeon of the spots which were macroscopically affected by MoM disease. Each sample was formalin-fixed, paraffin-embedded, and sectioned. Slides were stained with standard hematoxylin and eosin. Sample slides (three to four for each patient) were independently examined by three pathologists (AHGC, RWR, SVD) who were experienced in diagnosing skeletal and soft tissue related diseases, and thus well trained in recognizing dif-

Table 1. Clinical data

Demographics	Mean (sd)				
Mean age at primary surgery (years)	62,2 (8,2)				
Gender	Male	Female			
	8 (21.6%)	29 (78.4%)			
BMI	27.5 (4.2)				
Time till revision (months)	35.7 (8.8)				
Reasons for surgery	Osteoartritis				
	33 (89.2%)				
	Secondary osteoartritis				
	3 (8.1%)				
	Necrosis of the femoral head				
	1 (2.7%)				
Serum cobalt (μg/l)	19.6 μg/l (sd 33.4 μg/l)				
Intra articulair cobalt (μg/l)	2240.2 μg/l (2689.0 μg/l				
Pseudotumor classification	*0*	*1*	*2a*	*2b*	*3*
	0	0	24	0	2

ferent types of inflammation cells and patterns of inflammation. These pathologists independently evaluated the tissue samples using the ALVAL score[10] and the adapted Oxford ALVAL scoring method [11]. The total scores of each pathologist are shown in a supplementary appendix that shows the distribution of low, moderate, or high ALVAL scores was comparable among the pathologists. The slides were scored with the ALVAL score as described by Campbell et al. [10] and the modifications of the Oxford ALVAL by Grammatopoulos et al. [11] (Table 2). All three pathologists were blinded to the clinical outcome. The intraclass correlation coefficient (ICC) was obtained from the individual parameter scores.

The scientific committee of the Leiden University Medical Centre and the ethical committee in the Meander Medical Centre waived approval for the human protocol for this investigation, because the removed tissue was sent for routine histopathologic analysis. Because revision surgery had to be performed at such a short followup and because scientific concerns were present regarding the tissue reactions potentially caused by the MoM articulation, performing a histopathologic analysis was considered part of good clinical practice.

During the outpatient clinic visit, patients answered a standard clinical questionnaire (pain: yes or no) and underwent a physical examination. Blood samples were collected in a metal-free container. Serum cobalt was determined with the use of an Aanalyst^{TM} 800 Atomic Absorption Spectrophotometer (Perkin Elmer, Waltham, MA, USA). Cobalt serum levels between 0.04 and 0.64 μg/L were

Table 2. Scoring of the histologic findings.

Synovial lining (ALVAL)	Points
Intact synovial lining	0
Focal loss of synovial surface, fibrin attachment may occur	1
Moderate to marked loss of synovial surface, fibrin attachment	2
Complete loss of synovium, abundant attached fibrin and/or necrosis of lining tissue	3

Inflammatory infiltrate (ALVAL)	Points
Minimal inflammatory cell infiltrates	0
Predominantly macrophages, occasional lymphocytes may occur	1
Mix of macrophages and lymphocytes, either diffuse and/or small (< 50% of hpf) perivascular aggregates	2
Mix of macrophages and lymphocytes , large (> 50% hpf) perivascular aggregates may occur	3
Predominantly lymphocytes, mostly in multiple, large (> 50% hpf) perivascular aggregates, follicles may be present	4

Tissue organization (ALVAL)	Points
Normal tissue arrangement	0
Mostly normal tissue arrangement, small areas of synovial hyperplasia, focal necrosis may occur	1
Marked loss of normal arrangement, appearance of distinct cellular and acellular zones, thick fibrous layers may occur	2
Perivascular lymphocytic aggregates mostly located distally, thick acellular areas may occur	3

Inflammatory cells (macrophages), (lymphocytes), (plasma cells), (eosinophil polymorphs) (Oxford ALVAL)	Points
Absent	0
Few	1+
Many	2+
Abundant	3+

Necrosis (Oxford ALVAL)	Points
Absent	0
Scattered small necrotic areas	1+
Frequent small or large necrotic areas with up to 25% tissue involvement	2+
Extensive necrosis with > 25% tissue necrosis	3+

Oxford ALVAL score (semiquantitative score)	Points
No evidence of a perivascular lymphocyte infiltrate	0
Little evidence of a perivascular lymphocytic infiltrate with lymphocyte cuffing of blood vessels being fewer than five cells in thickness	1
Several perivascular lymphoid aggregates with lymphocyte cuffing of vessels being five to 10 cells in thickness	2
Numerous large perivascular lymphoid aggregates with lymphocyte cuffing around vessels being more than 10 cells in thickness	3

The original ALVAL score exists using the first three categories (synovial lining, inflammatory infiltrate, and tissue organization). The Oxford scoring system assessed tissue necrosis and the extent of the inflammatory cell infiltrate in the periprosthetic tissues. The presence of specific inflammatory cells (macrophages, lymphocytes, plasma cells, eosinophil polymorphs) was noted, and the presence or absence of an ALVAL response was assessed semiquantitatively as previously described. In the current study all parameters are scored; The number of specific inflammatory cells is scored as 0 (absent),
1 (few), 2 (many), or 3 (abundant). Necrosis was scored as 0 (absent),
1 (scattered small necrotic areas), 2 (frequent small or large necrotic areas
with up to 25% tissue involvement), or 3 (extensive necrosis with > 25%
tissue involvement); ALVAL = aseptic lymphocyte vasculitis-associated lesion; hpf = high-power field.

considered normal in the general population [22]. In case of revision surgery, a sample of the intraarticular fluid was taken and the cobalt values of the fluid were determined using the AAnalyst™ 800 Atomic Absorption Spectrophotometer.

A contrast-enhanced MRI of the hip region with metal artifact reducing sequences (MARS) was performed on patients with osteolysis observed on the radiograph, elevated cobalt levels greater than 5 μg/L (cutoff value in patients with a MoM implant [23]), or with pain. Pain was defined as either the presence or absence of any pain in the hip area reported by the patient. Patients who met these criteria received routine annual followup. A 1.5-T MRI unit (Achieva; Philips Healthcare, Best, The Netherlands) was used to obtain the MARS sequences. As a contrast agent, Dotarem® (Guerbet, Paris, France) was used.

All MRI scans were evaluated by a senior musculoskeletal radiologist (MN) and a resident in radiology (BS) with expertise in musculoskeletal disease. The criteria of the Anderson et al. [24], Hauptfleisch et al. [1], and Matthies et al. [21] classifications were used. These criteria were periprosthetic soft tissue mass or fluid-filled peri-prosthetic cavity's and there diameter; the thickness and regularity of the wall; muscle atrophy; edema or bone marrow edema and tendon avulsion or fracture of the bone. The Anderson classification[24] is based on the authors' experience regarding how the MRI appeared to influence management of patients with a pseudotumor. The Matthies[21] and Hauptfleisch[1] classifications are based on radiologic findings to classify the pseudotumor. In the results, the classification of

Matthies et al. [21] was used to describe the findings because it provided the best ICC (0.49) in our cohort.

The original ALVAL score system described by Campbell et al.[10] uses three different histologic criteria: synovial lining, inflammatory infiltrate, and tissue organization, which add up to an overall score. The modified Oxford ALVAL scoring system of Grammatopoulos et al.[11] adds tissue necrosis and the extent of the inflammatory cell infiltrate in the periprosthetic tissues. The presence of specific inflammatory cells (macrophages, lymphocytes, plasma cells, eosinophil polymorphs) is noted and the ALVAL response is rated semiquantitatively (Table 2).

Statistical Analysis

Descriptive analyses were performed on final outcomes. The results are expressed as means with SD or medians with ranges where relevant.

The interobserver reliability was calculated as an ICC with a 95% CI based on a two-way-random-ANOVA with patient and pathologist as random factors for three pathologists. This ICC has an interpretation as a weighted kappa with quadratic weights.

The ICC value for agreement was interpreted as follows: poor < 0.20; fair, 0.21 to 0.40; moderate, 0.41 to 0.60; good, 0.61 to 0.80; and very good, 0.81 to 1.0 [25]. SPSS Statistics Version 20.0 (IBM Corporation, Armonk, NY, USA) was used for the analysis.

RESULTS

The ICC for the sum score using the ALVAL classification is 0.38 (95% CI, 0.18-0.58), which is categorized as fair. The individual parameters of this score show an ICC for the scoring of inflammatory infiltrate of 0.37 (95% CI, 0.17-0.57), an ICC of 0.32 (95% CI, 0.12-0.53) for the scoring of tissue organization, and an ICC of 0.12 (95% CI, 0.00 to 0.34) for synovial lining (Table 3). The ICC for the sum score using the Oxford ALVAL score is 0.50 (95% CI, 0.30-0.68), which is categorized as moderate. The scoring of inflammatory cells and necrosis showed ICC between 0.04 (95% CI, 0.00 to 0.24) and 0.50 (95% CI, 0.29-0.68). The highest ICC, 0.50 (95% CI, 0.29-0.68) was found for inflammatory cells (lymphocytes) (Table 3). Heterogeneous morphologic features in a discordant case with no dense lymphocytic infiltrate and areas with no intact synovial lining with fibrin attachment (Fig. 1) and in a discordant case with dense perivascular lymphocytic aggregates (Fig. 2) are shown.

Table 3. Intraclass correlation coefficients of the morphologic features of the scoring

Morphologic features	Intraclass correlation (95% CI)
Synovial lining	0.12 (0.00-0.34)
Inflammatory infiltrate	0.37 (0.17-0.57)
Tissue organization	0.32 (0.12-0.53)
Sum score	0.38 (0.18-0.58)
Inflammatory cells (macrophages)	0.44 (0.24-0.64)
Inflammatory cells (lymphocytes)	0.50 (0.29-0.68)
Inflammatory cells (plasma cells)	0.29 (0.09-0.50)
Inflammatory cells (eosinophil polymorphs)	0.04 (0.00-0.24)
Necrosis	0.37 (0.17-0.58)
Oxford ALVAL score	0.50 (0.30-0.68)

ALVAL = aseptic lymphocyte vasculitis-associated lesion.

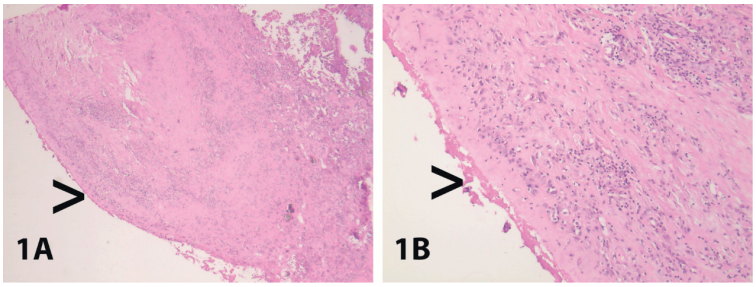

Fig. 1A-B Histologic analyses of hematoxylin and eosin-stainend sections at (A) x2.5 magnification and (B) x10 magnification show the morphologic spectrum in a discordant case with no dense lymphocytic infiltrate and areas with no intact synovial lining with fibrin attachment (black arrowhead).

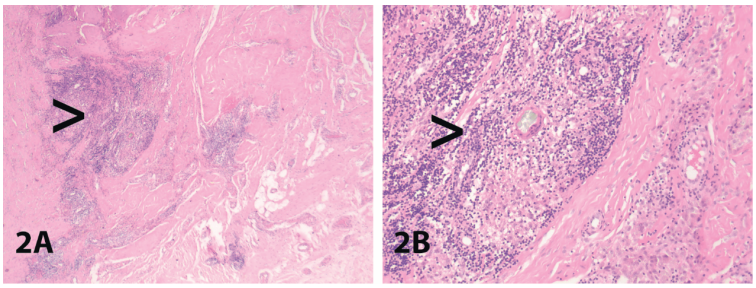

Fig. 2A-B Histologic analyses of hematoxylin and eosin-stainend sections at (A) x2.5 magnification and (B) x10 magnification show discordant cases with dense perivascular lymphocytic aggregates (black arrowhead).

DISCUSSION

MoM THA's have a high failure rate [26]. Elevated serum cobalt levels, pseudotumors, and tissue reaction have been described [1,23,27]. Pathologic findings in patients with failed MoM THA's have been described using the ALVAL and Oxford ALVAL scoring methods [10,11]. Only the initial studies [10,11] report ICC values for interobserver reliability. In the current study, we tested the reproducibility of these scoring systems by three independent pathologists. The scoring system of Campbell et al.[10] showed an ICC of 0.38 (95% CI, 0.18-0.58) for the sum score, which is rated as fair. The sum score improved up to 0.5 (95% CI, 0.30-0.68) using the modified Oxford ALVAL score.

This study had several limitations. Only one type of implant was used, which might not be characteristic of other MoM devices. The selection for revision surgery was made by using the described screening method. All patients who underwent revision surgery were symptomatic and most of the patients had high cobalt serum levels. Thus, our findings may not be applicable to patients with different presentations, such as asymptomatic patients with concerning MRI and laboratory findings. No prelearning meeting with all three pathologists was done to describe how to score the tissue slides using the scoring methods. Nevertheless all pathologists are experienced in diagnosing skeletal and soft tissue-related diseases, and thus well trained in recognizing different types of inflammation cells and patterns of inflammation. We believe that the poor ICC we found in our study regarding the ALVAL and Oxford ALVAL scores are attributable to the complex, and therefore not reproducible, scoring method rather than expert level of individual pathologists. We had a relatively small sample size, meaning that we might not have detected a truly high level of reliability. However, the studies reporting the original ALVAL [10] and Oxford ALVAL [11] scores were based on 32 and 65 samples, respectively.

Although the modified classification system improves the ICC value, it is still no more than moderate. A moderate score indicates inadequate interrater agreement and study results are not reliable to draw any definitive conclusions [25,28]. Our low ICC values for the individual parameters (inflammatory cells and necrosis) varying between 0.04 and 0.50 underline the low reproducibility of these morphologic findings. In contrast to our results, Campbell et al. [10] reported an interrater reliability of 0.71 and Grammatopoulos et al.[11] reported an interrater reliability of 0.74. The ICCs of the ALVAL and the Oxford ALVAL was scored by two observers in these original studies.

Despite that the ALVAL and Oxford ALVAL scoring methods are not well validated, these scoring systems were used in other studies without reporting an ICC value [12-19]. These study results should be interpreted with caution. Our results

clearly illustrate that the ALVAL and Oxford ALVAL scoring are not reproducible in our hands, and therefore we believe that clinicians should not use these scoring methods. Larger cohorts are required for the development of an alternative more simplified scoring method. Multiple pathologists should score a set of cases to investigate how well the new scoring method is reproducible. Digital imaging analysis showed good results in liver fibrosis [29] in assessing digital ulcers in patients with systemic sclerosis [30] and in analysis of cancer stem cell marker expression [31]. This type of tissue analysis might be a good alternative for the scoring of MoM periprosthetic tissue.

If this scoring method is reproducible, correlation with clinical meaningful data should be performed.

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[1] Hauptfleisch J, Pandit H, Grammatopoulos G, Gill HS, Murray DW, Ostlere S (2012) A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. Skeletal Radiol 2:149-55. doi:10.1007/s00256-011-1329-6 [doi]

[2] Gill HS, Grammatopoulos G, Adshead S, Tsialogiannis E, Tsiridis E (2012) Molecular and immune toxicity of CoCr nanoparticles in MoM hip arthroplasty. Trends Mol Med 3:145-55. doi:S1471-4914(11)00211-5 [pii];10.1016/j.molmed.2011.12.002 [doi]

[3] Bisseling P, de Wit BW, Hol AM, van Gorp MJ, van KA, van Susante JL (2015) Similar incidence of periprosthetic fluid collections after ceramic-on-polyethylene total hip arthroplasties and metal-on-metal resurfacing arthroplasties: results of a screening metal artefact reduction sequence-MRI study. Bone Joint J 9:1175-82. doi:97-B/9/1175 [pii];10.1302/0301-620X.97B9.35247 [doi]

[4] Mao X, Tay GH, Godbolt DB, Crawford RW (2012) Pseudotumor in a well-fixed metal-on-polyethylene uncemented hip arthroplasty. J Arthroplasty 3:493-7. doi:S0883-5403(11)00417-7 [pii];10.1016/j.arth.2011.07.015 [doi]

[5] Murgatroyd SE (2012) Pseudotumor presenting as a pelvic mass: a complication of eccentric wear of a metal on polyethylene hip arthroplasty. J Arthroplasty 5:820-4. doi:S0883-5403(11)00483-9 [pii];10.1016/j.arth.2011.09.008 [doi]

[6] Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC (2012) High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. J Bone Joint Surg Br 6:755-61. doi:94-B/6/755 [pii];10.1302/0301-620X.94B6.28373 [doi]

[7] Davies AP, Willert HG, Campbell PA, Learmonth ID, Case CP (2005) An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. J Bone Joint Surg Am 1:18-27. doi:87/1/18 [pii];10.2106/JBJS.C.00949 [doi]

[8] Wiley KF, Ding K, Stoner JA, Teague DC, Yousuf KM (2013) Incidence of pseudotumor and acute lymphocytic vasculitis associated lesion (ALVAL) reactions in metal-on-metal hip articulations: a meta-analysis. J Arthroplasty 7:1238-45. doi:S0883-5403(13)00269-6 [pii];10.1016/j.arth.2013.03.027 [doi]

[9] Korovessis P, Petsinis G, Repanti M, Repantis T (2006) Metallosis after contemporary metal-on-metal total hip arthroplasty. Five to nine-year follow-up. J Bone Joint Surg Am 6:1183-91. doi:88/6/1183 [pii];10.2106/JBJS.D.02916 [doi]

[10] Campbell P, Ebramzadeh E, Nelson S, Takamura K, De SK, Amstutz HC (2010) Histological features of pseudotumor-like tissues from metal-on-metal hips. Clin Orthop Relat Res 9:2321-7. doi:10.1007/s11999-010-1372-y [doi]

[11] Grammatopoulos G, Pandit H, Kamali A, Maggiani F, Glyn-Jones S, Gill HS, et al. (2013) The correlation of wear with histological features after failed hip resurfacing arthroplasty. J Bone Joint Surg Am 12:e811-10. doi:1694255 [pii];10.2106/JBJS.L.00775 [doi]

[12] Burge AJ, Gold SL, Lurie B, Nawabi DH, Fields KG, Koff MF, et al. (2015) MR Imaging of Adverse Local Tissue Reactions around Rejuvenate Modular Dual-Taper Stems. Radiology 1:142-50. doi:10.1148/radiol.2015141967 [doi]

[13] Ebramzadeh E, Campbell P, Tan TL, Nelson SD, Sangiorgio SN (2015) Can wear explain the histological variation around metal-on-metal total hips? Clin Orthop Relat Res 2:487-94. doi:10.1007/s11999-014-3874-5 [doi]

[14] Kolatat K, Perino G, Wilner G, Kaplowitz E, Ricciardi BF, Boettner F, et al. (2015) Adverse local tissue reaction (ALTR) associated with corrosion products in metal-on-metal and dual

modular neck total hip replacements is associated with upregulation of interferon gamma-mediated chemokine signaling. J Orthop Res 10:1487-97. doi:10.1002/jor.22916 [doi]

[15] Nawabi DH, Gold S, Lyman S, Fields K, Padgett DE, Potter HG (2014) MRI predicts ALVAL and tissue damage in metal-on-metal hip arthroplasty. Clin Orthop Relat Res 2:471-81. doi:10.1007/s11999-013-2788-y [doi]

[16] Nawabi DH, Nassif NA, Do HT, Stoner K, Elpers M, Su EP, et al. (2014) What causes unexplained pain in patients with metal-on metal hip devices? A retrieval, histologic, and imaging analysis. Clin Orthop Relat Res 2:543-54. doi:10.1007/s11999-013-3199-9 [doi]

[17] Phillips EA, Klein GR, Cates HE, Kurtz SM, Steinbeck M (2014) Histological characterization of periprosthetic tissue responses for metal-on-metal hip replacement. J Long Term Eff Med Implants 1:13-23. doi:76913a2b44f29f87,4c2325966f2ff31e [pii]

[18] Reito A, Parkkinen J, Puolakka T, Pajamaki J, Eskelinen A (2015) Diagnostic utility of joint fluid metal ion measurement for histopathological findings in metal-on-metal hip replacements. BMC Musculoskelet Disord:393. doi:10.1186/s12891-015-0851-4 [doi];10.1186/s12891-015-0851-4 [pii]

[19] Nawabi DH, Do HT, Ruel A, Lurie B, Elpers ME, Wright T, et al. (2016) Comprehensive Analysis of a Recalled Modular Total Hip System and Recommendations for Management. J Bone Joint Surg Am 1:40-7. doi:98/1/40 [pii];10.2106/JBJS.N.01121 [doi]

[20] Smeekes C, Ongkiehong B, van der Wal B, Wolterbeek R, Henseler JF, Nelissen R (2014) Large fixed-size metal-on-metal total hip arthroplasty: higher serum metal ion levels in patients with pain. Int Orthop doi:10.1007/s00264-014-2605-6 [doi]

[21] Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ (2012) Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. Clin Orthop Relat Res 7:1895-906. doi:10.1007/s11999-011-2201-7 [doi]

[22] Goulle JP, Mahieu L, Castermant J, Neveu N, Bonneau L, Laine G, et al. (2005) Metal and metalloid multi-elementary ICP-MS validation in whole blood, plasma, urine and hair. Reference values. Forensic Sci Int 1:39-44. doi:S0379-0738(05)00208-2 [pii];10.1016/j.forsciint.2005.04.020 [doi]

[23] Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. (2011) Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. J Bone Joint Surg Br 10:1308-13. doi:93-B/10/1308 [pii];10.1302/0301-620X.93B10.26249 [doi]

[24] Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF (2011) Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. Skeletal Radiol 3:303-7. doi:10.1007/s00256-010-1000-7 [doi]

[25] Brennan P, Silman A (1992) Statistical methods for assessing observer variability in clinical measures. BMJ 6840:1491-4.

[26] Smith AJ, Dieppe P, Vernon K, Porter M, Blom AW (2012) Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the National Joint Registry of England and Wales. Lancet 9822:1199-204. doi:S0140-6736(12)60353-5 [pii];10.1016/S0140-6736(12)60353-5 [doi]

[27] Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, et al. (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 1:28-36. doi:87/1/28 [pii];10.2106/JBJS.A.02039pp [doi]

[28] McHugh ML (2012) Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 3:276-82.

[29] Pavlides M, Birks J, Fryer E, Delaney D, Sarania N, Banerjee R, et al. (2017) Interobserver Variability in Histologic Evaluation of Liver Fibrosis Using Categorical and Quantitative Scores. Am J Clin Pathol 4:364-9. doi:3072330 [pii];10.1093/ajcp/aqx011 [doi]

[30] Ahrens HC, Siegert E, Tomsitz D, Mattat K, March C, Worm M, et al. (2016) Digital ulcers score: a scoring system to assess digital ulcers in patients suffering from systemic sclerosis. Clin Exp Rheumatol 5:142-7. doi:10045 [pii]

[31] Miller TJ, McCoy MJ, Hemmings C, Bulsara MK, Iacopetta B, Platell CF (2017) Objective analysis of cancer stem cell marker expression using immunohistochemistry. Pathology 1:24-9. doi:S0031-3025(16)40167-4 [pii];10.1016/j.pathol.2016.09.063 [doi]

APPENDIX

Pathologist 1 Pt-id	syn 0-3	inflamm 0-4	org 0-3	ALVAL sum score	macroph 0-3	lymp 0-3	plcells 0-3	eos 0-3	necr 0-3	Oxford ALVAL 0-3	Pathologist 2 Pt-id	syn 0-3	inflamm 0-4	org 0-3	ALVAL sum score	macrop 0-3	lymp 0-3	plcells 0-3	eos 0-3	necr 0-3	Oxford ALVAL 0-3	Pathologist 3 Pt-id	syn 0-3	inflamm 0-4	org 0-3	ALVAL sum score	macroph 0-3	lymp 0-3	plcells 0-3	eos 0-3	necr 0-3	Oxford ALVAL 0-3
1	3	3	3	9	3	2	1	1	3	1	1	3	4	2	9	2	3	1	0	1	3	1	3	3	2	8	2	2	1	0	0	3
2	3	3	3	9	3	2	1	0	2	3	2	3	3	3	9	2	2	0	0	1	2	2	3	2	2	7	2	2	1	0	0	2
3	2	2	1	5	2	2	1	0	2	1	3	3	2	2	7	2	2	2	1	1	2	3	3	2	2	7	2	2	1	0	0	2
4	3	3	3	9	2	2	1	0	2	2	4	3	3	3	9	3	3	1	0	2	3	4	3	2	2	7	2	2	1	0	1	2
5	3	1	2	6	2	1	0	0	1	1	5	1	1	1	3	3	1	0	0	0	0	5	1	0	1	2	1	1	1	0	0	0
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11	3	2	2	7	3	2	2	0	2	2	11	2	3	1	6	1	3	1	0	2	2	11	3	4	3	10	2	3	3	0	2	3
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15	x	x	x	x	x	x	x	x	x	x	15	3	1	2	6	3	2	1	0	1	2	15	3	1	2	6	1	1	1	0	1	2
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33	3	1	1	5	3	1	1	1	1	1	33	3	1	2	6	3	1	0	0	1	0	33	2	2	2	6	2	2	1	0	1	1
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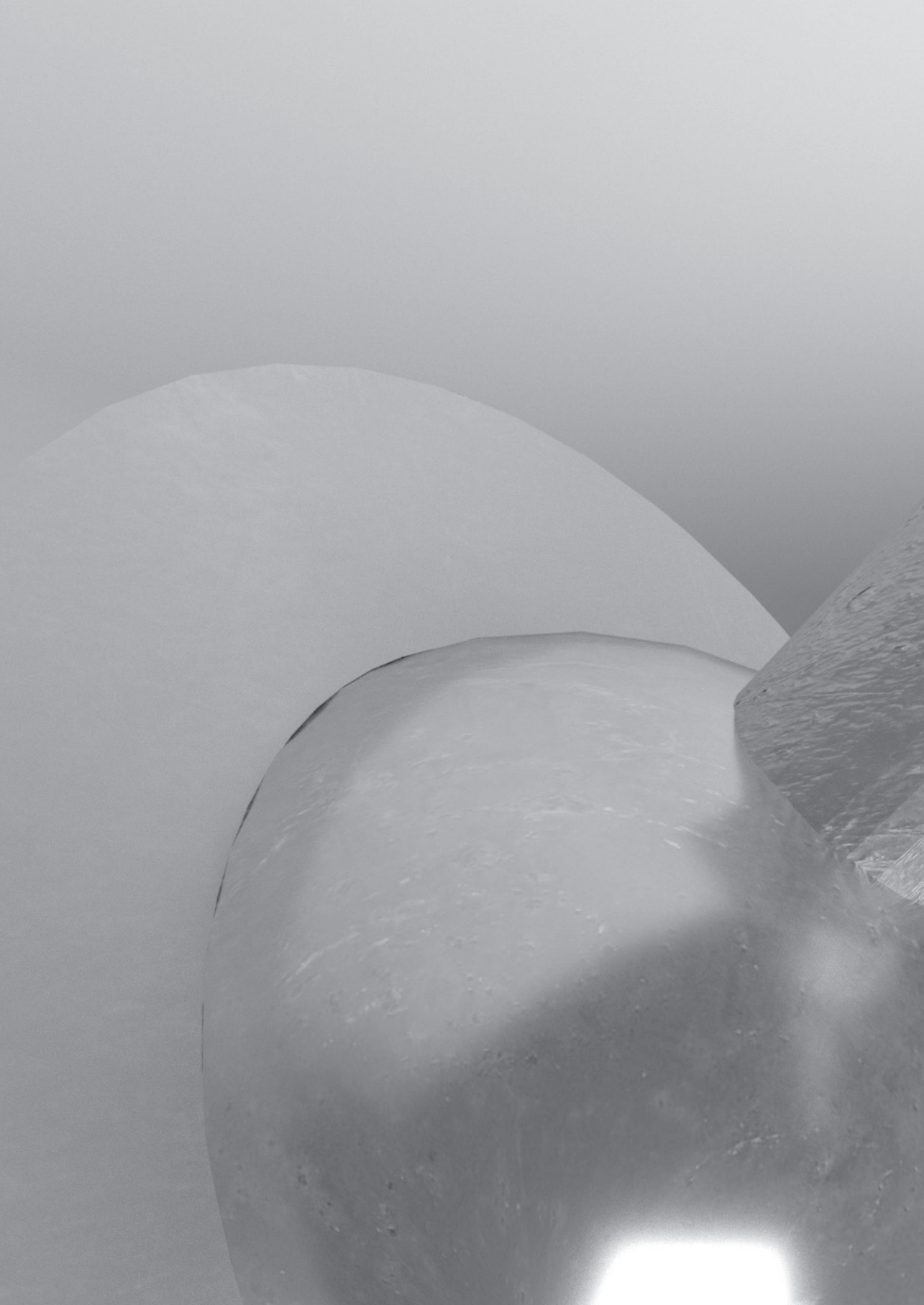


7 Summary and General discussion

There is a continuous ongoing drive to improve the survival of total hip arthroplasty (THA). However, innovation does not always lead to improvement. Materials that have been used in the early days can even have longer survival rates and might cause less complications than new innovations. Every implant seems to have their own specific causes of failure. For example breaking of the components in ceramic on ceramic THA [1].

In this thesis the survival and the different reasons of failure of cementless THA of a conventional ceramic on polyethylene (CoP) bearing and a THA with a metal on metal (MoM) bearing were investigated. In this chapter the results of this work will be discussed. Finally, we will describe the possibilities of a phased introduction of new types of implants in order to prevent complications on a world wide scale.

In **chapter 2** we have described the survival of the Cementless Spotorno system. This system uses a cementless femoral and acetabular component with a CoP bearing. At the time of implementation this was a THA used for younger patients, because theoretically cementless THA should avoid the risk of cement-disease and lower the prevalence of periprosthetic osteolysis and component loosing [2]. Earlier work described a short-term follow-up of this system with a 92% survival after 10 years [3]. This is an acceptable survival after 10 years, but in this thesis the long-term follow-up is described and these results are worrying as we observed a 72% survival at 24-years. Important factors that influenced the survival were the wear of the implant and the activity of the patients with the prosthesis. Our study supports earlier findings describing the cementless THA being not superior to the cemented THA and thus not an alternative for younger patients [4]. This led to the revival of the MoM bearing THA with the theoretical advantages of a lower wear rate, lower dislocation rate and a larger range of motion, which should increase the survival [5-7].

Chapter 3 describes the outcome of the M2a-38 (Biomet,Warsaw, IN, USA) MoM THA. The revision rate was 19% after a mean follow-up of 30 months, which is dramatically high and not acceptable. On top of this, additional complications occur such as higher metal ions (chapter 3), pseudotumors (chapter 5) and tissue reaction (chapter 6). Higher metal ion levels were detected in the blood of patients encountering pain. This relation was also described previously [8]. MoM THA induced pseudotumors were identified in another short follow up study and this related to higher serum metal ion levels [9]. Our study describes a significant lower quality of life. More recent studies now also describe longer term effects of MoM THA. Prentice *et al.* describes differences in bone and cardiac function between patient groups with MoM THA and without MoM THA. They found a lower cardiac ejection and a lower bone turnover in patients with a MoM THA.

This suggest that chronic exposure to metal ions caused by the wear of the bearing may have systemic effects in patients [10]. More worrying are the results of a meta-analysis which reports an increased mortality in patients with an MoM THA after ten years compared to patients with a conventional THA [11]. Increased levels of cobalt and chromium can be identified in the bone marrow from patients that received an MoM THA. This wear impairs the osteogenic differentiation of mesenchymal stromal cells, resulting in a decrease of successful in growing in the bone which can lead to early failure of the prosthesis [12].

This raised the question if there is a possible influence of the surgical factor in these wear-caused complications (elevated metal ion levels, pain and pseudotumors). A higher wear profile could be caused by a non-anatomical reconstruction of the hip joint. In **chapter 4** of this thesis the role of anatomical reconstruction of the MoM THA was investigated and a relation was found between the inclination angle of the acetabular component and the serum cobalt level. This finding is supported by other studies [13,14]. We observed that an increase of 10 degrees inclination results in a 14% increase of cobalt values. Women with the same cup inclination angle showed 34% higher cobalt levels than men. From these findings we can conclude that it is important to prevent steep placement of the acetabular component, however a joint implant without any friction is unfortunately not possible and therefore wear cannot be fully eliminated.

Higher levels of increased metal ions in the blood lead to more complications such as pseudotumors [9]. The pseudotumor is a common finding in the MoM THA and is described as a cystic solid mass in the periarticular region, which has a direct communication with the joint [15]. In **chapter 5** the incidence of pseudotumors is described in our cohort of patients that received MoM THA. Magnetic resonance imaging (MRI) analyses were performed to determine the frequency of these solid masses. This study included the analysis of the reliability of the different grading systems. It is important that grading systems show a good interobserver reliability to be able to compare the results of different studies. The prevalence of pseudotumors as determined with metal artifact-reducing sequences (MARS)-MRI was 44% in our cohort. Patients with a high risk profile as described in literature (serum cobalt >5μg/l [9], female sex [16,17], hip pain [18] and a high cup inclination angle >45°) [19,20] were compared to low risk patients. The high risk group showed in 58.8% of the patients a pseudotumor whereas no pseudotumors were described in the low risk patients.

Three different grading systems were used to describe the type of pseudotumor on MR imaging. The following three systems were analyzed: (1) described by Matties *et al.* [21], (2) described by Hauptfleisch *et al.*[15] and (3) described by Anderson *et al.*[22]. The best grading system is a system in which every researcher scores

exactly the same. These systems do not exist and therefore interrater reliability scores are used to decide if a scoring system is reliable. The level for agreement can be interpreted as follows: poor ≤ 0.20; fair, 0.21 to 0.40; moderate, 0.41 to 0.60; good, 0.61 to 0.80; and very good, 0.81 to 1.0 [23].

In our study all MR imaging were classified by a radiologist and a radiologist in training using all three different grading systems. The reliability of all three grading systems was moderate. The Kappa of the Anderson, Hauptfleisch and Matthies grading system score were 0.43, 0.44 and 0.49 respectively. This means that a substantial part of the pseudotumors are classified in another category or were not identified as pseudotumor. This leads to the conclusion that our results of the analyses should be interpreted with caution and a better grading system should be developed.

Besides pseudotumors, also tissue damage can be seen as a complication of MoM THA [24].The reaction to such tissue damage is described as: aseptic lymphocytic vasculitis-associated lesions (ALVAL). Scoring systems are available to characterize such complications Campbel *et al.* describes a scoring system better known as the ALVAL score [25]. Grammatopoulos *et al.* modified the ALVAL scoring method (Oxford ALVAL) by adding the inflammatory cell infiltrate such to be able to distinguish if the inflammatory changes and tissue necrosis seen in periprosthetic tissues around failed metal-on-metal hip resurfacing implants are due to cytotoxicity or hypersensitivity tissue necrosis [26]. These scoring systems are used in different studies as a description method for the morphological features. In several studies researchers try to find correlations between the histological features around the implant and radiological, clinical outcome and relations with the wear of the retrievals [25-33].

In none of the studies other than the studies from the developers of the scoring systems interrater reliability scores are mentioned. The reliability of scoring systems is important, because reliability refers to the repeatability of the test scores for clinical studies.

In **chapter 6** we investigated whether the ALVAL and Oxford ALVAL scores were reproducible. Three experienced pathologists independently scored the periprosthetic tissue of patients with failed MoM THA's. The results showed a moderate to fair agreement in the scoring of morphologic features of MoM tissue using the ALVAL score or the Oxford ALVAL. This study led to the conclusion that current pathologic scoring systems for MoM THA revisions are not reproducible. The fair to moderate agreement reflects the heterogeneous morphologic features in the pseudotumor tissue and between different tumor tissue samples that cannot reliably be quantified by pathologists using the parameters of these two scoring methods.

In this thesis the conventional CoP THA shows a much better survival rate than the MoM THA. A survival rate of 73 % for this implant (spotorno) after 24 years is at the lower range of comparable implants, but a revision rate of 19% after 30 months of the MoM implant is unacceptable and supports the withdrawal of the MoM implants from the Dutch market. New innovations and theoretical advantages are not always a precursor for better survival and performance. A fast introduction to the worldwide market without close monitoring and good long-term results can lead to severe and unexpected complications. Green *et al.* describes parallels in the progress in medical technology and the mechanisms of evolutionary biology. The parallel is that the release of some new devices eventually proves to be inferior or ineffective [34]. Is there a possibility to avoid these inferior and ineffective devices?

THE INTRODUCTION OF ORTHOPEDIC IMPLANTS

Each year many new medical devices are introduced in orthopedics. All medical devices have gone through different stadia before being approved for marketing by the U.S. Food and Drug Administration (FDA). They can be released after in vitro testing and limited supportive clinical data [35]. However, most medical devices are approved without demonstrating safety or effectiveness in vivo. The introduction of medical devices strongly differs to the introduction approach used in the pharmaceutical industry. Pharmaceuticals require multiple controlled clinical trials before approval. The procedure takes a mean of nine years and cost approximately 800 million dollar [35]. The introduction of a new drug has 4 difference stages before using the new drug in patients and a fifth stage after the introduction (0-5). These stages start with micro dose pharmacology tests to obtain information without the use of potentially harmful doses and after the introduction of the new drug the last stadia (5) is the post marketing surveillance to investigated the real world effectiveness of a drug [36].

In contrast to this drug development approach, the development of surgical techniques and medical devices seems unregulated, unstructured, and variable. Though McCulloch describes that different stages are recognizable in the development of surgical techniques [37]. The stages differ from the drug development, since operations are never tested on healthy volunteers, and the dose of surgery cannot be adjusted [37].

This parallel led to the development of the IDEAL model which is a descriptive model delineating stages of innovation, development, exploration, assessment, and long-term study [38]. The different stages have different control moments. First results with retrospectively applying the IDEAL criteria seem to work [39,40].

IDEAL has already been developed to introduce a new surgical technique and IDEAL-D has recently been introduced for evaluating and regulating the use of medical devices [41].

The phases can be described as follows: stage 0 is the preclinical stage. In this stage there must be ex-vitro evidence that safety and reliability have been conducted. In stage 1, a new procedure is prompted by the need for a new solution to a clinical problem. In this stage the surgeon must proof that the concept works and only a few surgeons are involved. The results from this stage should be described in detailed case reports. Stage 2 is the development and learning stage, which involves the planned use of a procedure in an initial small group of patients to support experience with its first use and often to refine or modify the precise technique or implant. Stage 3 is the assessment stage. In this stage the aim is to assess the effectiveness of the procedure compared to the other procedures. Stage 4 is the last stage; the procedure can be used worldwide and the long term results are monitored to investigate late complications.

Are these steps of a monitored phased introduction possible with orthopedic implants? Others have suggested phased introduction before [42-44]. Pijls et. al writes that a phased evidenced-based introduction will very likely encounter three categories of implant failure: (1) expected and early detected failure modes, (2) expected and late detected failure modes and (3) unexpected failure modes [43].

In pharmaceutical research it takes a mean of nine years to get to the last stage of worldwide introduction. How long do we have to wait to introduce a new THA system? Do we have to wait until the long term results are known? This will slow the innovation speed down. So we try to find surrogate markers to predict if there will be a long term failure.

In a recent systematic review Malak et. al tried to find validated surrogate markers of long-term outcome in patients undergoing primary total hip arthroplasty [45]. In this review the authors concluded that radiostereometric analyses (RSA) and ein bild röntgen analysis are validated surrogate markers for long-term primary THA outcome. Therefore they propose to use RSA in the pre-market testing of new prostheses. Unfortunately RSA could not predict the high failure rate in metal on metal THA [46].

In my opinion it has the highest priority of starting a phased introduction of orthopedic implants. It should exist of the IDEAL-(D) phases combined with the RSA and EBRA techniques. This to gather more pre- and postmarket information of new implants which leads to a safe worldwide introduction and optimal patient care.

[1] Allain J, Roudot-Thoraval F, Delecrin J, Anract P, Migaud H, Goutallier D (2003) Revision total hip arthroplasty performed after fracture of a ceramic femoral head. A multicenter survivorship study. J Bone Joint Surg Am 5:825-30.

[2] Ritter MA, Thong AE (2004) The role of cemented sockets in 2004: is there one? J Arthroplasty 4 Suppl 1:92-4. doi:S088354030400124X [pii]

[3] de Witte PB, Brand R, Vermeer HG, van der Heide HJ, Barnaart AF (2011) Mid-term results of total hip arthroplasty with the CementLess Spotorno (CLS) system. J Bone Joint Surg Am 13:1249-55. doi:10.2106/JBJS.I.01792 [doi]

[4] Toossi N, Adeli B, Timperley AJ, Haddad FS, Maltenfort M, Parvizi J (2013) Acetabular components in total hip arthroplasty: is there evidence that cementless fixation is better? J Bone Joint Surg Am 2:168-74. doi:1537036 [pii];10.2106/JBJS.K.01652 [doi]

[5] Anissian HL, Stark A, Gustafson A, Good V, Clarke IC (1999) Metal-on-metal bearing in hip prosthesis generates 100-fold less wear debris than metal-on-polyethylene. Acta Orthop Scand 6:578-82.

[6] Baker RP, Pollard TC, Eastaugh-Waring SJ, Bannister GC (2011) A medium-term comparison of hybrid hip replacement and Birmingham hip resurfacing in active young patients. J Bone Joint Surg Br 2:158-63. doi:93-B/2/158 [pii];10.1302/0301-620X.93B2.25625 [doi]

[7] Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH (2005) Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 1:11-9. doi:S0883540304003924 [pii];10.1016/j.arth.2004.07.008 [doi]

[8] Hart AJ, Sabah S, Henckel J, Lewis A, Cobb J, Sampson B, et al. (2009) The painful metal-on-metal hip resurfacing. J Bone Joint Surg Br 6:738-44. doi:91-B/6/738 [pii];10.1302/0301-620X.91B6.21682 [doi]

[9] Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC (2012) High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. J Bone Joint Surg Br 6:755-61. doi:94-B/6/755 [pii];10.1302/0301-620X.94B6.28373 [doi]

[10] Prentice JR, Clark MJ, Hoggard N, Morton AC, Tooth C, Paley MN, et al. (2013) Metal-on-Metal Hip Prostheses and Systemic Health: A Cross-Sectional Association Study 8 Years after Implantation. PLoS One 6:e66186. doi:10.1371/journal.pone.0066186 [doi];PONE-D-13-00138 [pii]

[11] Pijls BG, Meessen JM, Schoones JW, Fiocco M, van der Heide HJ, Sedrakyan A, et al. (2016) Increased Mortality in Metal-on-Metal versus Non-Metal-on-Metal Primary Total Hip Arthroplasty at 10 Years and Longer Follow-Up: A Systematic Review and Meta-Analysis. PLoS One 6:e0156051. doi:10.1371/journal.pone.0156051 [doi];PONE-D-16-02099 [pii]

[12] Rakow A, Schoon J, Dienelt A, John T, Textor M, Duda G, et al. (2016) Influence of particulate and dissociated metal-on-metal hip endoprosthesis wear on mesenchymal stromal cells in vivo and in vitro. Biomaterials:31-40. doi:S0142-9612(16)30134-X [pii];10.1016/j.biomaterials.2016.04.023 [doi]

[13] De HR, Pattyn C, Gill HS, Murray DW, Campbell PA, De SK (2008) Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. J Bone Joint Surg Br 10:1291-7. doi:90-B/10/1291 [pii];10.1302/0301-620X.90B10.20533 [doi]

[14] Hart AJ, Buddhdev P, Winship P, Faria N, Powell JJ, Skinner JA (2008) Cup inclination angle of greater than 50 degrees increases whole blood concentrations of cobalt and chromium ions after metal-on-metal hip resurfacing. Hip Int 3:212-9.

[15] Hauptfleisch J, Pandit H, Grammatopoulos G, Gill HS, Murray DW, Ostlere S (2012) A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. Skeletal Radiol 2:149-55. doi:10.1007/s00256-011-1329-6 [doi]

[16] Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV (2010) Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. J Bone Joint Surg Br 1:38-46. doi:92-B/1/38 [pii];10.1302/0301-620X.92B1.22770 [doi]

[17] Moroni A, Savarino L, Hoque M, Cadossi M, Baldini N (2011) Do ion levels in hip resurfacing differ from metal-on-metal THA at midterm? Clin Orthop Relat Res 1:180-7. doi:10.1007/s11999-010-1424-3 [doi]

[18] Chang EY, McAnally JL, Van Horne JR, Statum S, Wolfson T, Gamst A, et al. (2012) Metal-on-metal total hip arthroplasty: do symptoms correlate with MR imaging findings? Radiology 3:848-57. doi:radiol.12120852 [pii];10.1148/radiol.12120852 [doi]

[19] Hart AJ, Muirhead-Allwood S, Porter M, Matthies A, Ilo K, Maggiore P, et al. (2013) Which factors determine the wear rate of large-diameter metal-on-metal hip replacements? Multivariate analysis of two hundred and seventy-six components. J Bone Joint Surg Am 8:678-85. doi:1674734 [pii];10.2106/JBJS.J.01447 [doi]

[20] Langton DJ, Joyce TJ, Jameson SS, Lord J, Van OM, Holland JP, et al. (2011) Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. J Bone Joint Surg Br 2:164-71. doi:93-B/2/164 [pii];10.1302/0301-620X.93B2.25099 [doi]

[21] Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ (2012) Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. Clin Orthop Relat Res 7:1895-906. doi:10.1007/s11999-011-2201-7 [doi]

[22] Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF (2011) Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. Skeletal Radiol 3:303-7. doi:10.1007/s00256-010-1000-7 [doi]

[23] Brennan P, Silman A (1992) Statistical methods for assessing observer variability in clinical measures. BMJ 6840:1491-4.

[24] Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, et al. (2005) Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. J Bone Joint Surg Am 1:28-36. doi:87/1/28 [pii];10.2106/JBJS.A.02039pp [doi]

[25] Campbell P, Ebramzadeh E, Nelson S, Takamura K, De SK, Amstutz HC (2010) Histological features of pseudotumor-like tissues from metal-on-metal hips. Clin Orthop Relat Res 9:2321-7. doi:10.1007/s11999-010-1372-y [doi]

[26] Grammatopoulos G, Pandit H, Kamali A, Maggiani F, Glyn-Jones S, Gill HS, et al. (2013) The correlation of wear with histological features after failed hip resurfacing arthroplasty. J Bone Joint Surg Am 12:e811-10. doi:1694255 [pii];10.2106/JBJS.L.00775 [doi]

[27] Ebramzadeh E, Campbell P, Tan TL, Nelson SD, Sangiorgio SN (2015) Can wear explain the histological variation around metal-on-metal total hips? Clin Orthop Relat Res 2:487-94. doi:10.1007/s11999-014-3874-5 [doi]

[28] Kolatat K, Perino G, Wilner G, Kaplowitz E, Ricciardi BF, Boettner F, et al. (2015) Adverse local tissue reaction (ALTR) associated with corrosion products in metal-on-metal and dual

modular neck total hip replacements is associated with upregulation of interferon gamma-mediated chemokine signaling. J Orthop Res 10:1487-97. doi:10.1002/jor.22916 [doi]

[29] Nawabi DH, Gold S, Lyman S, Fields K, Padgett DE, Potter HG (2014) MRI predicts ALVAL and tissue damage in metal-on-metal hip arthroplasty. Clin Orthop Relat Res 2:471-81. doi:10.1007/s11999-013-2788-y [doi]

[30] Nawabi DH, Nassif NA, Do HT, Stoner K, Elpers M, Su EP, et al. (2014) What causes unexplained pain in patients with metal-on metal hip devices? A retrieval, histologic, and imaging analysis. Clin Orthop Relat Res 2:543-54. doi:10.1007/s11999-013-3199-9 [doi]

[31] Pelt CE, Erickson J, Clarke I, Donaldson T, Layfield L, Peters CL (2013) Histologic, serologic, and tribologic findings in failed metal-on-metal total hip arthroplasty: AAOS exhibit selection. J Bone Joint Surg Am 21:e163. doi:1761896 [pii];10.2106/JBJS.L.01446 [doi]

[32] Phillips EA, Klein GR, Cates HE, Kurtz SM, Steinbeck M (2014) Histological characterization of periprosthetic tissue responses for metal-on-metal hip replacement. J Long Term Eff Med Implants 1:13-23. doi:76913a2b44f29f87,4c2325966f2ff31e [pii]

[33] Reito A, Parkkinen J, Puolakka T, Pajamaki J, Eskelinen A (2015) Diagnostic utility of joint fluid metal ion measurement for histopathological findings in metal-on-metal hip replacements. BMC Musculoskelet Disord:393. doi:10.1186/s12891-015-0851-4 [doi];10.1186/s12891-015-0851-4 [pii]

[34] Green S.A. (2001) The evolution of medical technology: lessons from the Burgess Shale. Clin Orthop Relat Res:260-6.

[35] Zywiel MG, Johnson AJ, Mont MA (2012) Graduated introduction of orthopaedic implants: encouraging innovation and minimizing harm. J Bone Joint Surg Am 21:e158. doi:1386249 [pii];10.2106/JBJS.K.01675 [doi]

[36] Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, Altman DG, et al. (2009) Evaluation and stages of surgical innovations. Lancet 9695:1089-96. doi:S0140-6736(09)61083-7 [pii];10.1016/S0140-6736(09)61083-7 [doi]

[37] McCulloch P (2009) Developing appropriate methodology for the study of surgical techniques. J R Soc Med 2:51-5. doi:102/2/51 [pii];10.1258/jrsm.2008.080308 [doi]

[38] McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. (2009) No surgical innovation without evaluation: the IDEAL recommendations. Lancet 9695:1105-12. doi:S0140-6736(09)61116-8 [pii];10.1016/S0140-6736(09)61116-8 [doi]

[39] Ecke TH, Barski D, Weingart G, Lange C, Hallmann S, Ruttloff J, et al. (2017) Presentation of a method at the Exploration Stage according to IDEAL: Percutaneous nephrolithotomy (PCNL) under local infiltrative anesthesia is a feasible and effective method - retrospective analysis of 439 patients. Int J Med Sci 4:302-9. doi:10.7150/ijms.17963 [doi];ijmsv14p0302 [pii]

[40] Nikkels C, Vervoort AJMW, Mol BW, Hehenkamp WJK, Huirne JAF, Brolmann HAM (2017) IDEAL framework in surgical innovation applied on laparoscopic niche repair. Eur J Obstet Gynecol Reprod Biol:247-53. doi:S0301-2115(17)30304-4 [pii];10.1016/j.ejogrb.2017.06.027 [doi]

[41] Sedrakyan A, Campbell B, Merino JG, Kuntz R, Hirst A, McCulloch P (2016) IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. BMJ:i2372.

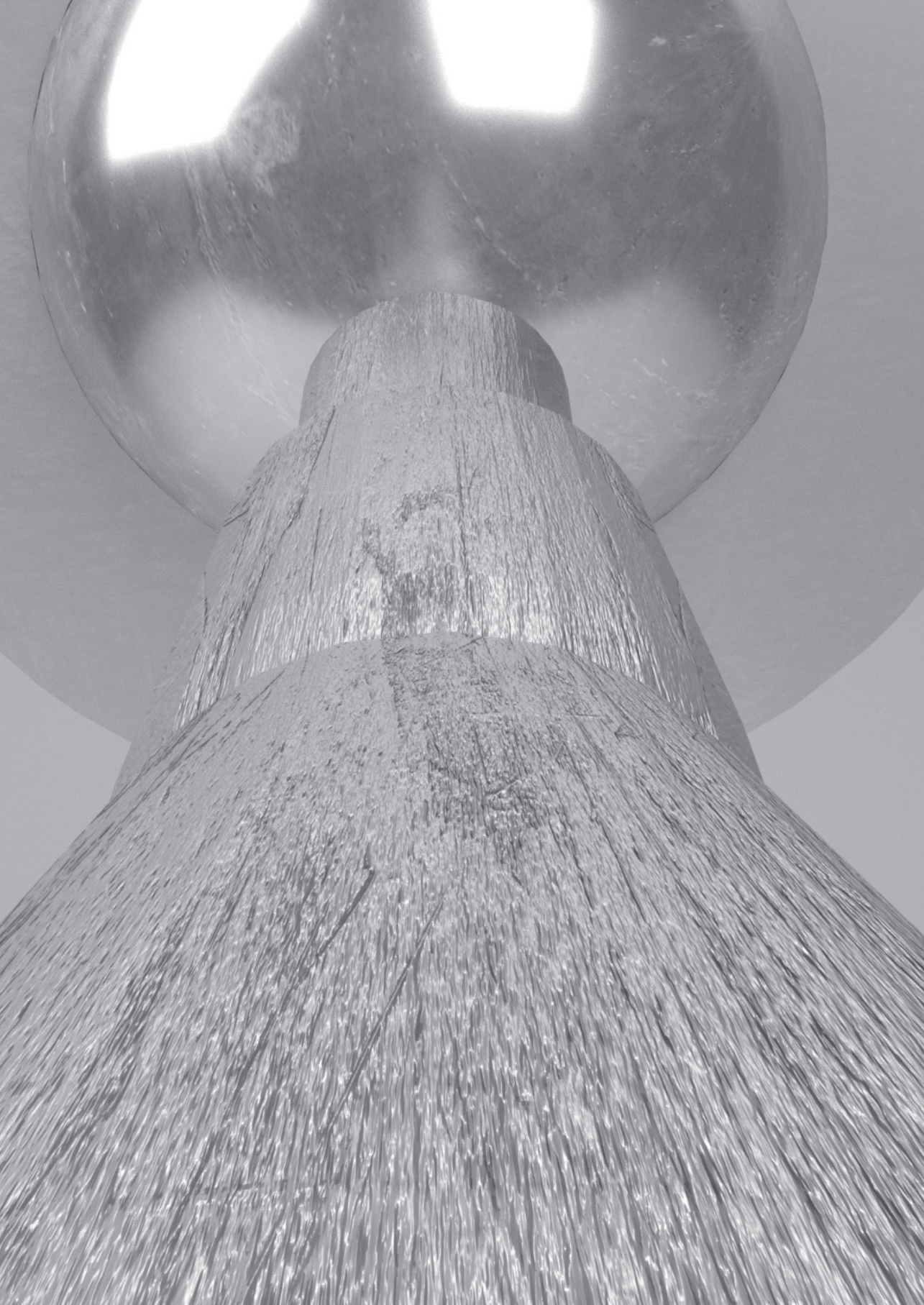
[42] Malchau H (2000) Introducing new technology: a stepwise algorithm. Spine (Phila Pa 1976) 3:285.

[43] Pijls BG, Nelissen RG (2016) The era of phased introduction of new implants. Bone Joint Res 6:215-7. doi:5/6/215 [pii];10.1302/2046-3758.56.2000653 [doi]

[44] Schemitsch EH, Bhandari M, Boden SD, Bourne RB, Bozic KJ, Jacobs JJ, et al. (2010) The evidence-based approach in bringing new orthopaedic devices to market. J Bone Joint Surg Am 4:1030-7. doi:92/4/1030 [pii];10.2106/JBJS.H.01532 [doi]

[45] Malak TT, Broomfield JA, Palmer AJ, Hopewell S, Carr A, Brown C, et al. (2016) Surrogate markers of long-term outcome in primary total hip arthroplasty: A systematic review. Bone Joint Res 6:206-14. doi:5/6/206 [pii];10.1302/2046-3758.56.2000568 [doi]

[46] Hjorth MH, Soballe K, Jakobsen SS, Lorenzen ND, Mechlenburg I, Stilling M (2014) No association between serum metal ions and implant fixation in large-head metal-on-metal total hip arthroplasty. Acta Orthop 4:355-62. doi:10.3109/17453674.2014.922731 [doi]



8 Samenvatting (summary in Dutch)

INLEIDING

Eén van de eerste pioniers op het gebied van heupimplantaten was professor Themistocles Glück uit Duitsland. In 1891 gebruikte hij ivoren implantaten om heupkoppen te vervangen. Deze faalden door infecties of doordat de patiënt overleed. Later werden technieken uitgeprobeerd waarbij alleen het gewrichtsvlak werd vervangen door glas of roestvrij staal [1,2].Deze implantaten waren echter niet in staat om de krachten uitgeoefend tijdens bewegingen te dragen en faalden daardoor kort na implantatie. Het falen van deze implantaten stimuleerde onderzoek naar betere materialen voor implantatie. In 1953 gebruikten George McKee en Watson Farrar de eerste Metaal op Metaal (MoM) totale heup prothese (THP). Rond dezelfde tijd ontwikkelde Sir John Charnley een ander type THP welke bestaat uit een polyethylene kom en een metalen kop die sterk lijkt op het ontwerp wat tegenwoordig veelal wordt gebruikt [3]. Bij beide typen prothesen wordt botcement gebruikt om de kom en de steel aan het bot te bevestigen. In de jaren 70 resulteerde de grootte hoeveelheid loslatingen van de componenten van de MoM-prothese en de superieure resultaten van de THP met de polyethylene kom tot het verlaten van het gebruik van de MoM THP. McKee-Farrar en Charnley worden beschouwd als de grondleggers van de moderne THP zoals wij die vandaag de dag kennen.

In 2015 werden meer dan 28.000 THP's geplaatst in Nederland [4]. Wereldwijd wordt het aantal uitgevoerde THP operaties geschat op ongeveer een miljoen per jaar [5]. Eén van de belangrijkste resultaten van een heupprothese is verlichting van pijn voor de patiënt dat leidt tot een betere mobiliteit. Het voorgaande in combinatie met uitstekende implantaatoverleving van minstens 95% overleving na 10 jaar voor de best presterende ontwerpen zorgt voor zeer goede resultaten. Tegenwoordig wordt het plaatsen van een THP beschouwd als de meest efficiënte en kosteneffectieve chirurgische ingreep van de 20ste eeuw [6]. Helaas zijn deze hoge overlevingscijfers niet aanwezig in de jongere patiënten populatie (<55 jaar populatie) [7], daarom zijn nieuwe technieken ontwikkeld om de overleving van bestaande heupimplantaten te verbeteren.

Een grote verandering in het THP ontwerp was de introductie van een cementloze THP naast de klassieke Charnley-achtige ontwerpen die met botcement waren geïmplanteerd. Opvallend genoeg verschenen er in de jaren '80 artikelen over de zogenaamde "cementziekte". De cementziekte zou botverlies rondom de THP veroorzaken, wat hoogstwaarschijnlijk verband houdt met het ontwerp van de steel en de kwaliteit van het polyethyleen en niet met het cement als zodanig [9,10]. Op dit moment is de cementloze kom het meest gebruikte type in Nederland (64%) [4], hoewel het niet bewezen is dat deze een betere overleving heeft dan de gecementeerde kom bij jonge patiënten [11].

Gezien de goede overleving van de THP, wordt de procedure in de laatste twee decennia steeds vaker gebruikt bij jongere patiënten [4]. Deze groep van patiënten is mobieler en actiever, wat de eisen aan het implantaat verhoogd. De zoektocht naar implantaten met een duurzamer concept en een hoger overlevingspercentage ging door waarop de introductie van de keramische kop op een keramische kom THP volgde. Er zijn complicaties beschreven zoals het breken van de kop en de kom en een zeer hinderlijk squeeking geluid [12,13]. Maar belangrijker nog het theoretische voordeel van lage slijtage-eigenschappen van dit type implantaat met een daarbij passend hoger overlevingspercentage werd niet altijd gezien [14]. Deze lagere overlevingspercentages in de jongere patiëntenpopulatie vergeleken met de oudere patiënten en de tekortkomingen van de keramiek op keramiek THP hebben geleid tot de opleving van de MoM THP. De theoretische voordelen waren een verminderde slijtage, minder luxaties en een groter bewegingsbereik [15-17]. Eerst werd de resurfacing design-prothese opnieuw geïntroduceerd. De goede resultaten bij de korte en middellange termijn follow-up van de nieuwe resurfacing-ontwerpen zoals de Birmingham hip resurfacing arthroplasty [18-20], leidde tot het ontwikkelen van een MoM THP ontwerp met grote kop vanwege de eerder genoemde theoretische voordelen [15-17].

Kort na de introductie van de MoM THP werden er echter complicaties gezien bij patiënten met deze MoM prothesen. Complicaties zoals onverklaarbare pijn, hoge metaalion waarden in het bloed, ontwikkeling van cystes en vaste massa's in het heupgebied, reactie van het weefsel rond de heupprothese en de belangrijkste complicatie een kortere overleving van de implantaten. Nationale Registers toonden een overlevingspercentage van 72% -89% na tien jaar [21-27]. Deze complicaties hebben geleid tot het onderzoek beschreven in dit proefschrift.

DOEL VAN HET ONDERZOEK

Dit proefschrift evalueert twee totale heupimplantaat ontwerpen die worden gebruikt in de jongere patiëntenpopulatie; (1) een cementloze conventionele keramiek op polyethyleen (KoP) THP en (2) een metaal op metaal THP. Een analyse van de uitkomst- en faalmechanismen van beide ontwerpen werd uitgevoerd met de focus op:

- De klinische uitkomst en overleving van een conventioneel KoP THP-cohort met een 24-jaar follow-up en een analyse van factoren die verband houden met klinische en radiologische uitkomsten.
- De klinische evaluatie van een MoM THP-cohort na 30 maanden. Analyse van het falen van de MoM THP in relatie tot de anatomische reconstructie van de heup.

- De faalmechanismen van de MoM THP zoals gevisualiseerd op magnetic resonance imaging beelden.
- De reproduceerbaarheid van het histologische scoresysteem van peri-articulaire weefselreacties van falende MoM THP.

In dit hoofdstuk wordt er een samenvatting van de resultaten van dit onderzoek gegeven. Ten slotte zullen we de mogelijkheden van een gefaseerde introductie van implantaten beschrijven om complicaties in de toekomst te voorkomen.

In **hoofdstuk 2** onderzoeken we de lange termijn resultaten van de Cementless Spotorno (CLS) totale heupprothese. Daarnaast zijn de verschillende factoren die verband houden met de klinische en radiologische resultaten van dit type prothese geanalyseerd.

Een reeks van 120 CLS heupprothesen werd bestudeerd in een jonge patientengroep (gemiddelde leeftijd tijdens de operatie: 55,9 ± 5,9 jaar). Tijdens de follow-up werd de Merle d'Aubigné-Postel score (meting van patiënt ervaring en resultaat van de behandeling) gescoord en polyethyleen slijtage werd gemeten met behulp van metingen aan de röntgenfoto's. Overlevingsanalyses en verscheidene statistische testen werden gebruikt voor de evaluatie. Na een gemiddelde follow-up van 14,6 jaar (range, 0,1 tot 24,2, inclusief de revisies en patiënten die lost to follow-up waren), werden 24 revisies uitgevoerd, waarvan 16 voor aseptische cup loslating. Overlevingsanalyse door middel van Kaplan-Meier analyse laat na 24 jaar een overleving zien van 72,8% (95% -CI: 63,0% -82,6%) voor revisie ongeacht de reden als eindpunt en 80,1% (95% -CI: 70,9% -89,3%) voor revisies door aseptische cup loslating als eindpunt. De gemiddelde Merle d'Aubigné-Postel score was 16,1 punten (range, 7 tot 18). De gemiddelde polyethyleen-slijtage was 2,3mm (range, 0,6mm tot 6,8mm). Een grotere hoeveelheid polyethyleen-slijtage werd geassocieerd met betere klinische scores, maar ook met revisies voor cup loslating. Factoren die verband houden met meer polyethyleen-slijtage waren: jongere leeftijd bij operatie, 32 mm kop, langere follow-up en een steilere inclinatiehoek. Op de lange termijn is de CLS-steel betrouwbaar met een overleving van 95.1% (95% CI, 90.0%-100.0%). Echter het hoge revisie percentage voor aseptische cup loslatingen in het tweede decennium is zorgwekkend, voornamelijk door het bestaan van (cementloze) alternatieven die een betere overleving hebben.

In **hoofdstuk 3** is een cross-sectioneel onderzoek beschreven. Deze studie werd uitgevoerd met een MoM THP om de volgende factoren te beschrijven en analyseren: incidentie van pijn, pseudotumoren, revisies, relatie tussen verhoogde metaalion waarden in het bloed, functioneel resultaat van de MoM THP en de kwaliteit van leven na het krijgen van een MoM THP. 377 MoM THP bij 351 patienten met een 38mm kop werden geëvalueerd na een gemiddelde follow-up van

30 maanden (range 11-58). Pijn, serum metaalion waarden, patiënt-gerapporteerde vragenlijsten (Short Form-36 (SF-36), Hip en Osteoarthritis Outcome Score (HOOS) en de Oxford Hip Score (OHS)) en radiologische beeldvorming werden geanalyseerd. 16 patiënten hebben niet deelgenomen aan de screening. 118 (35%) patiënten rapporteerden pijn en deze patiënten hadden tevens significant hogere kobalt- en chroom waarden in vergelijking met patiënten zonder pijn. De mediane serum kobalt waarde was 4,4 μg/l (Interquartile Range (IQR) 6,6) en het mediane chroomgehalte was 3,6 μg/l (IQR 4.8). Patiënten met kobalt waarden van ≤5μg/l meldden een significant beter resultaat op de SF-36 en HOOS vragenlijst. 57 pseudotumoren werden gezien bij 227 THP. Bij 19% van de prothesen werd een revisie operatie uitgevoerd.

In **hoofdstuk 4** hebben we onderzocht of er een relatie is tussen de inclinatie- en anteversiehoek van de acetabulum component, de anatomische reconstructie van het heupgewricht en de serum kobalt waarden. Postoperatieve kobalt serum waarden werden gemeten bij 250 patiënten met een M2a-38 kop en Taperloc steel combinatie. Op gestandaardiseerde röntgenfoto's werden de inclinatie- en anteversiehoek, de verlenging of verkorting van het been, de verbreding of versmalling naar de binnen of buitenzijde van de heup en het middelpunt van de rotatie gemeten. Een verschil van meer dan 5mm ten opzichte van de preoperatieve situatie werd beschouwd als een niet-anatomische reconstructie. Uit de analyse komt naar voren dat voor elke 10 graden toename van de inclinatiehoek het kobaltniveau met 14% ($p = 0,036$) stijgt. Vrouwen met dezelfde inclinatiehoek hebben 34% hogere kobaltgehalte dan mannen ($p = 0,013$). Er is geen relatie gevonden tussen de anteversiehoek, anatomische reconstructie en serumkobalt waarde. We kunnen vaststellen dat een steilere inclinatiehoek leidt tot hogere serum kobalt waarden, maar een niet-anatomische reconstructie heeft geen invloed op de serum kobalt waarde.

De incidentie van pseudotumoren in symptomatische en asymptomatische patiënten met een MoM THP is hoog, maar de validiteit van de verschillende pseudotumor classificatiesystemen gescoord op de MRI beelden varieert. In **hoofdstuk 5** hebben we de prevalentie van symptomatische en asymptomatische pseudotumoren onderzocht door gebruik te maken van MRI beelden van patiënten die ingedeeld zijn in een hoog risicogroep (serum kobalt >5 μg/l, een inclinatiehoek >45°, pijn en vrouwelijke geslacht) en een laag risicogroep (serum kobalt ≤5 μg/l, geen pijn, een inclinatiehoek <45° en mannelijk geslacht) voor pseudotumorontwikkeling. Ook werd de betrouwbaarheid tussen verschillende observanten onderzocht bij drie verschillende pseudotumor classificatiesystemen. Twee beoordelaars gebruikten drie frequent gebruikte pseudotumor classificatiesystemen voor het classificeren van de MRI beelden (Anderson [28], Hauptfleisch [29] en Matthies [30]).

Een retrospectieve studie werd uitgevoerd op 377 patiënten van welke 240 MRI scans beschikbaar waren. De resultaten geven een prevalentie van pseudotumoren beoordeeld met MRI van 58,8% in de vooraf bepaalde hoog risicogroep, 0,0% in de laag risicogroep en 42,8% in de controle groep. Het kappa getal wat de mate van overeenstemming weergeeft van de Anderson [28], Hauptfleisch[29] en Matthies[30] classificatiesystemen scoren respectievelijk 0,43, 0,44 en 0,49. De conclusie is dat er een verhoogde incidentie is voor pseudotumorontwikkeling bij patiënten met een hoog risico. Er is geen ontwikkeling van pseudotumoren gevonden bij patiënten met een laag risico profiel. De betrouwbaarheid tussen de beoordelaars scoorde het beste met het Matthies-systeem, maar alle drie de systemen vertoonden slechts een matige overeenkomst.

In **hoofdstuk 6** werden de aseptische lymfocyt vasculitis-geassocieerde laesie (ALVAL) score en de aangepaste Oxford ALVAL score onderzocht. De ALVAL score beschrijft morfologische eigenschappen van de synoviale rangschikking, weefselorganisatie en ontstekingscel infiltratie in het weefsel. De Oxford-ALVAL score maakt gebruik van een semiquantitative score van de immuunrespons die gemakkelijker te scoren zou zijn. Deze scores zijn een vaak gebruikte scoringsmethode om de morfologische eigenschappen van het weefsel rond MoM THP te beschrijven. De reden voor dit onderzoek is dat, behalve voor de initiële studies van deze twee morfologische scoringsmethoden, geen andere studies de betrouwbaarheid (intraclass correlatiecoëfficiënten ofwel ICC-waarden) van deze scoringsmethoden hebben gerapporteerd. In onze de studie werden 37 periprosthetische weefsels van 36 patiënten met een gereviseerde MoM THP gescoord door drie ervaren pathologen die de ALVAL en Oxford ALVAL scoringsmethoden gebruiken. Alleen patiënten met beschikbare kobalt waarden in het bloed en intra-articulair waarbij een MRI scan was gemaakt werden geselecteerd. In de groep waren er 26 patiënten waarbij er een pseudotumor gediagnosticeerd werd. Uit de resultaten blijkt dat de ALVAL-score een ICC van 0,38 (95% CI, 0,18-0,58) (matig) voor de som score vertoonde en dit verbeterde tot 0,50 (95% CI, 0,31-0,68) (matig) bij de Oxford ALVAL score. De individuele parameters van de ALVAL score vertoonden een ICC voor het scoren van inflammatoire infiltratie van 0,37 (95% CI, 0,17-0,57) (slecht), een ICC van 0,32 (95% CI, 0,12-0,53) (slecht) voor het scoren van weefselorganisatie en een ICC van 0,14 (95% CI, -0,04 tot 0,34) (zeer slecht) voor synoviale rangschikking. De conclusie is dat het scoren van morfologische eigenschappen van het MoM-weefsel niet reproduceerbaar is met behulp van de ALVAL-score of de Oxford ALVAL-score. Dit is mogelijk te verklaren door de heterogene morfologische eigenschappen in het pseudotumortumorweefsel dat niet betrouwbaar door pathologen kan worden gekwantificeerd met behulp van de parameters van deze twee scoringsmethoden.

DE INTRODUCTIE VAN ORTHOPEDISCHE IMPLANTATEN

Elk jaar worden veel nieuwe implantaten geïntroduceerd in de orthopedie. Alle implantaten hebben verschillende stadia doorlopen voordat ze zijn goedgekeurd om op de markt te brengen. Dit wordt onder andere gedaan door de Amerikaanse Food and Drug Administration (FDA) [31]. De implantaten kunnen worden vrijgegeven na in-vitrotesten en beperkte ondersteunende klinische gegevens. De meeste medische hulpmiddelen en implantaten zijn echter goedgekeurd zonder veiligheid of effectiviteit in vivo aan te tonen. De introductie van medische implantaten verschilt sterk van de introductiebenadering die wordt gebruikt in de farmaceutische industrie. De farmaceutische industrie vereist meervoudige gecontroleerde klinische proeven voor goedkeuring. De procedure duurt gemiddeld negen jaar en kost ongeveer 800 miljoen dollar [31]. De introductie van een nieuw medicijn heeft 4 verschillende stadia voordat het nieuwe geneesmiddel bij patiënten mag worden gebruikt. Na de vierde fase is er nog een vijfde fase na de introductie van het medicijn. Deze stadia beginnen met microdosis farmacologie testen om informatie te verkrijgen zonder het gebruik van een potentieel schadelijke doses en na de introductie van het nieuwe medicijn (stadium 4) is het laatste stadium de postmarketingsurveillance om de werkelijke effectiviteit van een medicijn te onderzoeken [32].

In tegenstelling tot de ontwikkeling van geneesmiddelen, lijkt de ontwikkeling van chirurgische technieken en medische hulpmiddelen ongereguleerd, ongestructureerd en variabel. Hoewel McCulloch beschrijft dat verschillende stadia herkenbaar zijn in de ontwikkeling van chirurgische technieken (innovatie, ontwikkeling, verkenning, beoordeling en lange termijnstudie) [33]. De stadia verschillen van de ontwikkeling van een geneesmiddel, omdat operaties nooit op gezonde vrijwilligers worden getest en de dosis chirurgie niet kan worden aangepast [33].

Deze parallel leidde tot de ontwikkeling van het IDEAL-model dat een beschrijvend model is dat de stadia van innovatie, ontwikkeling, verkenning, beoordeling en lange termijnstudie afbakenen [34]. De verschillende fasen hebben verschillende controle momenten. Eerste resultaten met retrospectieve toepassing van de IDEAL-criteria lijken te werken [35,36].

IDEAL is al ontwikkeld om een nieuwe chirurgische techniek te introduceren en IDEAL-D is onlangs geïntroduceerd voor het evalueren en reguleren van het gebruik van medische apparaten en implantaten [37].

De fasen kunnen als volgt worden beschreven: stadium 0 is het preklinische stadium. In deze fase moet er ex-vitro bewijs zijn dat veiligheid en betrouwbaarheid zijn gewaarborgd. In fase 1 wordt een nieuwe procedure gestart door de behoefte aan een nieuwe oplossing voor een klinisch probleem. In dit stadium moet de

chirurg bewijzen dat het concept werkt en zijn er maar een paar chirurgen bij betrokken. De resultaten van deze fase moeten in gedetailleerde case reports worden beschreven. Fase 2 is de ontwikkelings- en leerfase, welke het geplande gebruik van een procedure eerst in een kleine groep patiënten omvat om ervaring met het eerste gebruik te ondersteunen en vaak om de precieze techniek of het implantaat te verfijnen en zo nodig aan te passen. Fase 3 is de beoordelingsfase. In deze fase is het doel om de effectiviteit van de procedure te beoordelen in vergelijking met de andere procedures. Fase 4 is de laatste fase; de procedure kan wereldwijd worden gebruikt en de resultaten op lange termijn worden gecontroleerd om late complicaties te ontdekken.

Zijn deze stappen van een gecontroleerde gefaseerde introductie mogelijk met orthopedische implantaten? Anderen hebben eerder gefaseerde introductie voorgesteld [38-40] Pijls et al. schrijft dat een gefaseerde, op bewijzen gebaseerde introductie zeer waarschijnlijk drie categorieën implantaatfouten zal tegenhouden: (1) verwachte en vroegtijdig gedetecteerde implantaatfouten, (2) verwachte en laat gedetecteerde implantaatfouten en (3) onverwachte implantaatfouten [39].

In farmaceutisch onderzoek duurt het gemiddeld negen jaar om tot de laatste fase van wereldwijde introductie te komen. Hoe lang moeten we wachten om een nieuw THP te introduceren? Moeten we wachten tot de resultaten op de lange termijn bekend zijn? Dit zal de innovatie snelheid vertragen. Dus proberen we surrogaatmarkers te vinden om te voorspellen of er een probleem op de lange termijn zal zijn.

In een recente systematische review van Malak et al. wordt geprobeerd om gevalideerde surrogaatmarkers te vinden voor lange termijn uitkomsten bij patiënten die een THP geïmplanteerd krijgen [41]. In deze review concluderen de auteurs dat radiostereometrische analyses (RSA) en ein bild röntgen-analyse gevalideerde surrogaatmarkers zijn voor de lange termijn uitkomst van een THP. Daarom stellen de auteurs voor om RSA te gebruiken bij het testen van nieuwe prothesen voor deze op de markt te brengen. Helaas kon RSA het hoge percentage mislukkingen in de metaal op metaal prothesen niet voorspellen [42].

Naar mijn mening heeft het de hoogste prioriteit om te starten met een verplichte gefaseerde introductie van orthopedische implantaten. Het zou moeten bestaan uit de IDEAL-D fasen in combinatie met de RSA- en EBRA-technieken. Dit om meer pre- en postmarketing informatie van nieuwe implantaten te verzamelen, wat hopelijk zal leiden tot een veilige wereldwijde introductie van deze implantaten en optimale patiëntenzorg.

[1] Smith-Petersen MN (1948) The classic: evolution of mould arthroplasty of the hip joint. J Bone Joint Surg

[2] Wiles P (1957) The surgery of the osteoarthritic hip. hip Br J Surg 417 doi:45:488-97

[3] Charnley J (1961) Arthroplasty of the hip. A new operation. Lancet 7187:1129-32.

[4] The Dutch Arthroplasty Register (LROI). Annual report 2017. (2017) http://www lroi-rapportage nl/

[5] Kurtz SM, Roder C, Lau E. (2010) International survey of primary and revision total hip replacement. Paper #365. Presented at the 56th Annual Meeting of the Orthopaedic Research Society.

[6] Learmonth ID, Young C, Rorabeck C (2007) The operation of the century: total hip replacement. Lancet 9597:1508-19. doi:S0140-6736(07)60457-7 [pii];10.1016/S0140-6736(07)60457-7 [doi]

[7] Bayliss LE, Culliford D, Monk AP, Glyn-Jones S, Prieto-Alhambra D, Judge A, et al. (2017) The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. Lancet 10077:1424-30. doi:S0140-6736(17)30059-4 [pii];10.1016/S0140-6736(17)30059-4 [doi]

[8] Makela KT, Matilainen M, Pulkkinen P, Fenstad AM, Havelin L, Engesaeter L, et al. (2014) Failure rate of cemented and uncemented total hip replacements: register study of combined Nordic database of four nations. BMJ:f7592.

[9] McCombe P, Williams SA (2004) A comparison of polyethylene wear rates between cemented and cementless cups. A prospective, randomised trial. J Bone Joint Surg Br 3:344-9.

[10] Wilkinson JM, Hamer AJ, Stockley I, Eastell R (2005) Polyethylene wear rate and osteolysis: critical threshold versus continuous dose-response relationship. J Orthop Res 3:520-5. doi:S0736-0266(04)00253-0 [pii];10.1016/j.orthres.2004.11.005 [doi]

[11] Toossi N, Adeli B, Timperley AJ, Haddad FS, Maltenfort M, Parvizi J (2013) Acetabular components in total hip arthroplasty: is there evidence that cementless fixation is better? J Bone Joint Surg Am 2:168-74. doi:1537036 [pii];10.2106/JBJS.K.01652 [doi]

[12] Allain J, Roudot-Thoraval F, Delecrin J, Anract P, Migaud H, Goutallier D (2003) Revision total hip arthroplasty performed after fracture of a ceramic femoral head. A multicenter survivorship study. J Bone Joint Surg Am 5:825-30.

[13] Baek SH, Kim WK, Kim JY, Kim SY (2015) Do alumina matrix composite bearings decrease hip noises and bearing fractures at a minimum of 5 years after THA? Clin Orthop Relat Res 12:3796-802. doi:10.1007/s11999-015-4428-1 [doi];10.1007/s11999-015-4428-1 [pii]

[14] Nieuwenhuijse MJ, Nelissen RG, Schoones JW, Sedrakyan A (2014) Appraisal of evidence base for introduction of new implants in hip and knee replacement: a systematic review of five widely used device technologies. BMJ:g5133.

[15] Anissian HL, Stark A, Gustafson A, Good V, Clarke IC (1999) Metal-on-metal bearing in hip prosthesis generates 100-fold less wear debris than metal-on-polyethylene. Acta Orthop Scand 6:578-82.

[16] Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH (2005) Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. J Arthroplasty 1:11-9. doi:S0883540304003924 [pii];10.1016/j.arth.2004.07.008 [doi]

[17] Goldsmith AA, Dowson D, Isaac GH, Lancaster JG (2000) A comparative joint simulator study of the wear of metal-on-metal and alternative material combinations in hip replacements. Proc Inst Mech Eng H 1:39-47.

[18] Back DL, Dalziel R, Young D, Shimmin A (2005) Early results of primary Birmingham hip resurfacings. An independent prospective study of the first 230 hips. J Bone Joint Surg Br 3:324-9.

[19] Baker RP, Pollard TC, Eastaugh-Waring SJ, Bannister GC (2011) A medium-term comparison of hybrid hip replacement and Birmingham hip resurfacing in active young patients. J Bone Joint Surg Br 2:158-63. doi:93-B/2/158 [pii];10.1302/0301-620X.93B2.25625 [doi]

[20] Daniel J, Pynsent PB, McMinn DJ (2004) Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis. J Bone Joint Surg Br 2:177-84.

[21] National Joint Registery for England, Wales and North Ireland. Annual report 2016. (2014) http://www njrcentre org uk/njrcentre/Reports,PublicationsandMinutes/tabid/85/Default aspx

[22] The Danish Hip Arhtroplasty Register. Annual report 2016. (2015) http://danskhofteallo-plastikregister dk/en/publications/annual-reports/

[23] Swedish Hip Arthroplasty Register. Annual Report 2014 (2015) https://shpr registercentrum se/shar-in-english/shar-in-english/p/ryouZwaoe

[24] Australian Orthopedic Association National Joint Replacement Registery. Annual Report 2016. (2015) https://aoanjrr sahmri com/annual-reports-2016

[25] Norwegian Arthroplasty Register. Annual report 2016. (2015) http://nrlweb ihelse net/eng/default htm

[26] New Zealand Joint Registry. Annual report 2015. (2017) http://nzoa org nz/nz-joint-registry

[27] Seppanen M, Karvonen M, Virolainen P, Remes V, Pulkkinen P, Eskelinen A, et al. (2016) Poor 10-year survivorship of hip resurfacing arthroplasty. Acta Orthop 6:554-9. doi:10.1080/17453674.2016.1246316 [doi]

[28] Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF (2011) Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. Skeletal Radiol 3:303-7. doi:10.1007/s00256-010-1000-7 [doi]

[29] Hauptfleisch J, Pandit H, Grammatopoulos G, Gill HS, Murray DW, Ostlere S (2012) A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. Skeletal Radiol 2:149-55. doi:10.1007/s00256-011-1329-6 [doi]

[30] Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ (2012) Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. Clin Orthop Relat Res 7:1895-906. doi:10.1007/s11999-011-2201-7 [doi]

[31] Zywiel MG, Johnson AJ, Mont MA (2012) Graduated introduction of orthopaedic implants: encouraging innovation and minimizing harm. J Bone Joint Surg Am 21:e158. doi:1386249 [pii];10.2106/JBJS.K.01675 [doi]

[32] Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, Altman DG, et al. (2009) Evaluation and stages of surgical innovations. Lancet 9695:1089-96. doi:S0140-6736(09)61083-7 [pii];10.1016/S0140-6736(09)61083-7 [doi]

[33] McCulloch P (2009) Developing appropriate methodology for the study of surgical techniques. J R Soc Med 2:51-5. doi:102/2/51 [pii];10.1258/jrsm.2008.080308 [doi]

[34] McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. (2009) No surgical innovation without evaluation: the IDEAL recommendations. Lancet 9695:1105-12. doi:S0140-6736(09)61116-8 [pii];10.1016/S0140-6736(09)61116-8 [doi]

[35] Ecke TH, Barski D, Weingart G, Lange C, Hallmann S, Ruttloff J, et al. (2017) Presentation of a method at the Exploration Stage according to IDEAL: Percutaneous nephrolithotomy

(PCNL) under local infiltrative anesthesia is a feasible and effective method - retrospective analysis of 439 patients. Int J Med Sci 4:302-9. doi:10.7150/ijms.17963 [doi];ijmsv14p0302 [pii]

[36] Nikkels C, Vervoort AJMW, Mol BW, Hehenkamp WJK, Huirne JAF, Brolmann HAM (2017) IDEAL framework in surgical innovation applied on laparoscopic niche repair. Eur J Obstet Gynecol Reprod Biol:247-53. doi:S0301-2115(17)30304-4 [pii];10.1016/j.ejogrb.2017.06.027 [doi]

[37] Sedrakyan A, Campbell B, Merino JG, Kuntz R, Hirst A, McCulloch P (2016) IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. BMJ:i2372.

[38] Malchau H (2000) Introducing new technology: a stepwise algorithm. Spine (Phila Pa 1976) 3:285.

[39] Pijls BG, Nelissen RG (2016) The era of phased introduction of new implants. Bone Joint Res 6:215-7. doi:5/6/215 [pii];10.1302/2046-3758.56.2000653 [doi]

[40] Schemitsch EH, Bhandari M, Boden SD, Bourne RB, Bozic KJ, Jacobs JJ, et al. (2010) The evidence-based approach in bringing new orthopaedic devices to market. J Bone Joint Surg Am 4:1030-7. doi:92/4/1030 [pii];10.2106/JBJS.H.01532 [doi]

[41] Malak TT, Broomfield JA, Palmer AJ, Hopewell S, Carr A, Brown C, et al. (2016) Surrogate markers of long-term outcome in primary total hip arthroplasty: A systematic review. Bone Joint Res 6:206-14. doi:5/6/206 [pii];10.1302/2046-3758.56.2000568 [doi]

[42] Hjorth MH, Soballe K, Jakobsen SS, Lorenzen ND, Mechlenburg I, Stilling M (2014) No association between serum metal ions and implant fixation in large-head metal-on-metal total hip arthroplasty. Acta Orthop 4:355-62. doi:10.3109/17453674.2014.922731 [doi]

Appendices

List of publications

Acknowledgements (dankwoord)

Curriculum vitae

LIST OF PUBLICATIONS

Long-term results of total hip arthroplasty with the CementLess Spotorno (CLS) system **Christiaan Smeekes,** Pieter B. de Witte, Bas F. Ongkiehong, Bart C.H. van der Wal, Alexander F.W. Barnaart
Hip International 2017; Sep 19;27(5):465-471

Large fixed-size metal-on-metal total hip arthroplasty: higher serum metal ion levels in patients with pain
Christiaan Smeekes, Bas F. Ongkiehong, Bart C.H. van der Wal, Ron Wolterbeek, Jan-Ferdinand Henseler, Rob G.H.H. Nelissen
International Orthopedics 2015 Apr;39(4):631-8

Inclination but not anatomical reconstruction is related with higher cobalt levels in MoM hip arthroplasty
Christiaan Smeekes, Bas F. Ongkiehong, Bart C.H. van der Wal, Ron Wolterbeek, Jan Ferdinand Henseler, Rob G.H.H. Nelissen
Acta Orthopaedica Belgica 2017 (accepted for publication)

Pseudotumor in Metal on Metal hip arthroplasty. A comparison study of three grading systems with MRI
Christiaan Smeekes, Bart J. M. Schouten, Maarten Nix, Bas F. Ongkiehong, Ron Wolterbeek, Bart C.H. van der Wal, Rob G.H.H. Nelissen
Skeletal Radiology 2018 Aug;47(8):1099-1109

Current Pathologic Scoring Systems for Metal-on-Metal THA Revisions are not Reproducible.
Christiaan Smeekes, Arjen H. G. Cleven, Bart C. H. van der Wal, Stefan V. Dubois, Remigio W. Rouse, Bastiaan F. Ongkiehong, Ron Wolterbeek, Rob G. H. H. Nelissen
Clinical Orthopaedics and Related Research 2017 Dec;475(12):3005-3011

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CURRICULUM VITAE

Christiaan Smeekes, de auteur van dit proefschrift, werd geboren op 2 januari 1984 te Naarden. Hij groeide op in Weesp. In 2002 behaalde hij zijn VWO diploma aan het sint Vitus college te Bussum. Het jaar hierop studeerde hij Biomedische Wetenschappen aan de Vrije Universiteit. Na een jaar Biomedische Wetenschappen gestudeerd te hebben startte hij met de opleiding geneeskunde aan de Vrije Universiteit. Hij liep zijn laatste stage op de afdeling Heelkunde in het Spaarne Ziekenhuis. Tijdens zijn wetenschappelijke stage deed hij een onderzoek naar alledaagse klachten in de huisartspraktijk. Na het voltooien van zijn studie is hij gestart als arts-assistent op de afdeling heelkunde in het Amstelland ziekenhuis. Na anderhalf jaar is hij gaan werken in het Meander Medisch centrum als arts-assistent op de afdeling orthopedie. In 2013 begon hij aan zijn promotie onderzoek getiteld "Uncemented Total Hip Arthroplasty Wear is the problem" onder begeleiding van Dr. B.C.H. van der Wal (Meander Medisch Centrum Amersfoort/ UMCU) en prof. dr. R.G.H.H. Nelissen (LUMC). Na een jaar te hebben gewerkt als arts-assistent heeft hij een jaar 3 dagen in de week onderzoek gedaan in Amersfoort en 2 dagen in de week in Leiden. Tijdens deze periode heeft hij besloten zich verder te willen specialiseren in de huisartsgeneeskunde. Na dit besluit heeft hij een half jaar gewerkt bij Symfora Meander in Amersfoort op de afdeling spoedeisende psychiatrie als arts-assistent, waarna hij de huisartsopleiding is gestart aan het Academisch Medisch Centrum Amsterdam. Hij heeft het eerste jaar van de huisartsopleiding voltooid bij huisartsenpraktijk de Jong & te Braak in Laren. Het tweede jaar heeft hij een stage ziekenhuispsychiatrie gedaan in het Medisch Centrum Alkmaar en een stage geriatrie in het Slotervaart ziekenhuis. Het laatste jaar van zijn opleiding heeft hij voltooid in gezondheidscentrum de Driehoek in Almere onder begeleiding van W.M. Mol en D.A. de Wit.

Op dit moment is hij werkzaam als waarnemend huisarts op verschillende plekken in de regio en wil in zich in de toekomst richten op een eigen huisartspraktijk.

Chris is getrouwd met Susanna en samen zijn ze zeer gelukkig met hun dochters Eva en Hanna. Ze wonen met veel plezier in Weesp.