Hip resurfacing, does it meet the expectations?

Clinical outcome, metal ion analysis and bone mineral density

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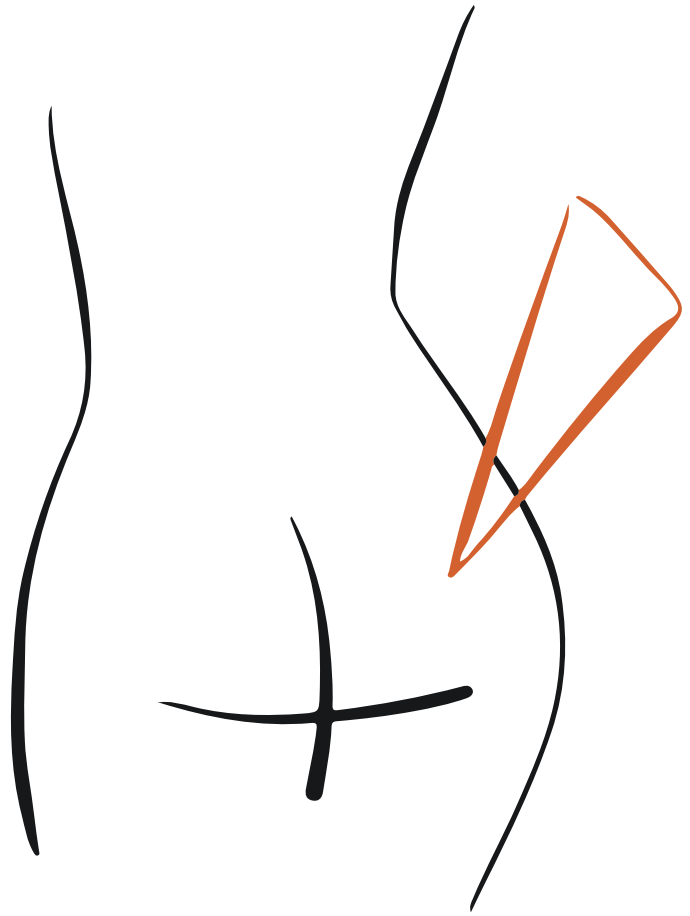


Introduction and aims of thesis

Introduction

In 2007 in the Netherlands there were about 238.000 people with osteoarthritis of the hip, two-thirds of this population is female and over 65 years of age, with 27.000 new cases registered each year.[1] Osteoarthritis of the hip can significantly influence daily functioning, and the *osteoarthritis patient* may become dependent on their environment and health care facilities. The recommended first choice of treatment for this condition is a combination of acetaminophen (if necessary combined with non-steroidal anti-inflammatory drugs (NSAID)) and physical therapy to reduce pain and improve physical function.[2,3] If this initial treatment does not improve symptoms, total hip arthroplasty (THA) may be indicated for the elderly patient with advanced osteoarthritis. Almost 21.000 hip arthroplasties are implanted each year in the Netherlands, and based on a expected 53% increase of incidence of osteoarthritis of the hip, in 2030 the number of THA is expected to be 32.000. The trend projection suggests even a 149% increase to 51.680 THA's.[4] In the treatment of secondary osteoarthritis in young patients, joint preserving surgery (like femoral and acetabular osteotomies) can be considered.[2,3] However, due to the great success of the THA, with promising results, a good quality of life and little to no loosening of the prosthesis, the age limits for hip replacement have been lowered. Unfortunately, the long-term outcome is worse for young patients than for the older age groups. Ten year survival ranges from 72%-86% in patients less than sixty years of age, versus 90-96% in older patients.[5] Since the young, active and high-demand patient is recognized to have relatively disappointing results after a conventional THA, there is still ongoing research for better solutions for this troublesome patient category. Innovations in hip arthroplasty focus on potential improvement in implant survival rates, which is expected to come from alternative bearing materials.

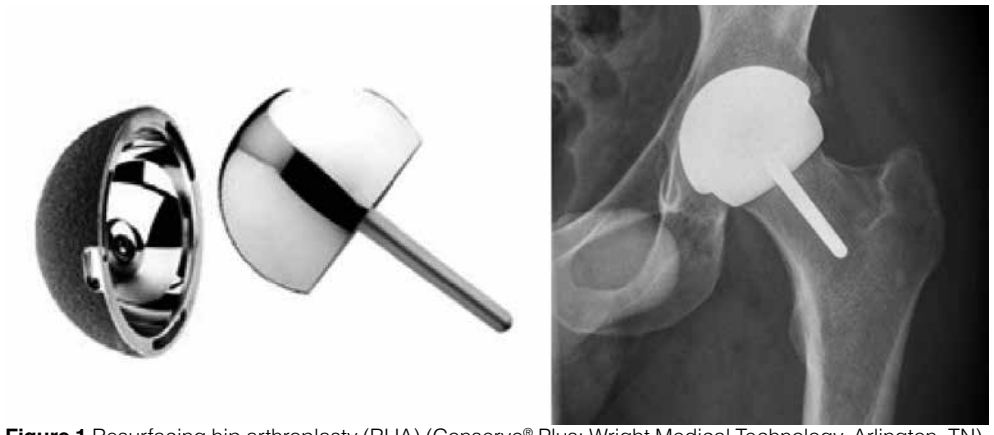


Figure 1 Resurfacing hip arthroplasty (RHA) (Conserve® Plus; Wright Medical Technology, Arlington, TN).

This thesis is about the results of resurfacing hip arthroplasty (RHA) (Figure 1), which unlike conventional hip replacement does not replace the femoral head. The osteoarthritic femoral head is reshaped and covered with a rounded metal cap. The socket is pressfitted with a

metal cup, which is similar to a conventional acetabular cup, although for the latter generally a polyethylene liner is used. The different design of an RHA results in a bigger hip-ball, no invasion of a stem in the femoral canal and a metal-on-metal (MoM) bearing instead of, for example, metal-on-polyethelene (MoP).

History

Due to its clinical success total hip arthroplasty (THA) has already been called 'the operation of the century'.[6] In the 1960s, total hip replacement completely changed the quality of life of patients with disabling osteoarthritis. A disease that had left millions of people 'crippled' suddenly had a cure. Since the beginning of the 20th century ways were explored to treat patients with osteoarthritis of the hip surgically by less invalidating methods than performing a girdlestone or hip arthrodesis. In 1923 Smith-Peterson introduced a mould interposition arthroplasty of glass, pyrex and bakalite. However, none of these implants could withstand the forces applied during motion and failed relatively soon during use. In 1938 subsequently he developed a vitalium cup covering the femoral head, also with poor results. At the same time Wiles implanted the first uncemented total hip arthroplasty with matched acetabular and femoral components of stainless steel, which can be considered the first MoM hip implant.[7] McKee and Watson-Farrar developed a cobalt-chromium-molybdenum (Co-Cr-Mo) MoM hip arthroplasty of the ball-and-socket type in 1956 (Figure 2A).[8,9] The first hip arthroplasties implanted already consisted of a metal-on-metal bearing and the concept itself is not new.

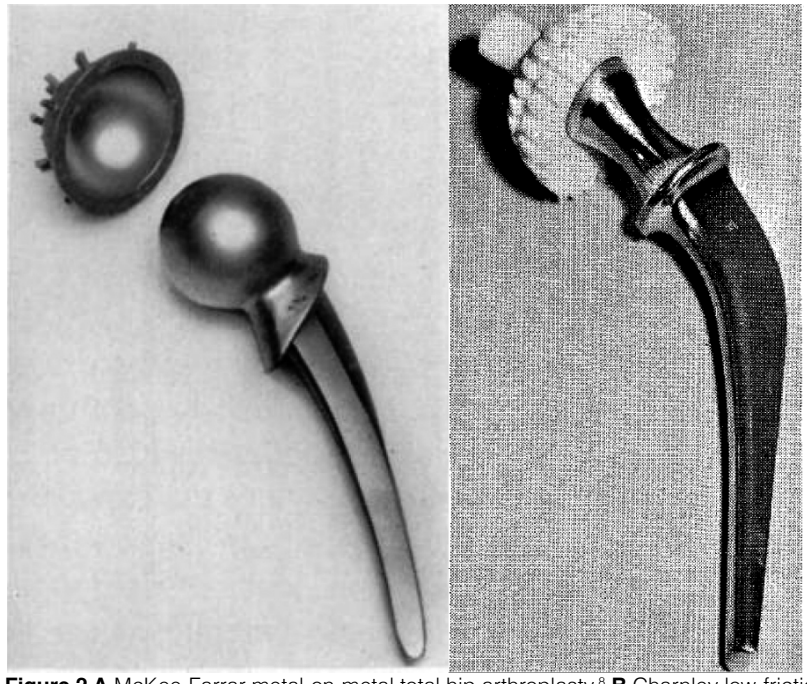


Figure 2 A McKee-Farrar metal-on-metal total hip arthroplasty.[8] **B** Charnley low-friction arthroplasty.[10]

In 1962 Charnley revolutionized the total hip arthroplasty design with the idea of a low friction arthroplasty, the use of acrylic cement to fix the components to living bone and the introduction of high-density polyethylene (UHMPWE) as a bearing material (Figure 2B).[10] Until the 1970s K.M. Sivash, P. Ring, J. Scales, M. Postel, M. Muller and A. Huggler experimented with the MoM design.[9] Analysis of this first generation of MoM THA (from 1960s and 1970s) with a chrome-cobalt-molybdenum alloy and a press-fit acetabular fixation, suggested that the failures were not due to the MoM bearing surface. Low in vivo wear rates were measured in both the McKee-Farrar and Metasul retrievals and the bearing surface showed to be durable as established by the retrieval study of implants more than 20 years after the index operation.[11] The rate of component loosening of the MoM total hip replacements and the superior clinical results of Charnley's prosthesis with a metal-on-polyethylene bearing during the 1970s discouraged the use of the MoM bearing. There are reports of comparable loosening rates for Charnley's low friction and McKee-Farrar's arthroplasty after 20 years,[13] but others found significant differences to the detriment of McKee-Farrar 14 years after implantation.[14]

Although in general the cemented total hip arthroplasty of Charnley proved to be a superior design in its time, an increasing number of aseptical loosening was found, especially in younger patients.[15,16] Initially, this premature loosening and osteolysis was addressed as *cement disease*[17] and therefore cementless press-fit designs were developed. Regardless of these new fixation techniques periprosthetic osteolysis continued to exist and it was found to originate from the use of polyethelene. Implants wear at the point where the head moves (under load) in the socket. As a result, the cyclic loading of a MoP THA leads to polyethylene wear particles, which in their turn result in a foreign body reaction with osteolysis. Osteolysis is regarded the main long-term problem in THA which, in time, will lead to aseptic loosening of the components. This phenomenon is particularly problematic in younger, more active patients who will put more load on their implant and will likely outlive their hip prosthesis. Hence, especially for this group of younger patients, an ongoing search for improvements, related to the wear properties of polyethelene, alternative bearing materials and enhanced fixation techniques took place. This led to the introduction of highly cross-linked polyethylene, the addition of vitamine E, improvements in cementing techniques and uncemented designs. Alternative bearing materials that were considered are ceramic-on-ceramic, ceramic-on-polyethelene, ceramicized metal-on-polyethelene and the concept of metal-on-metal was re-introduced.

Metal-on-metal hip resurfacing

The search for an other than metal-on-polyethylene bearing facilitated the initiation of a second and third generation of MoM RHA's in the 1980s and 1990s. This resulted in the development of a low wear, high-carbon chrome-cobalt-molybdenum alloy[18] with a combined annual linear wear rate of 1 to 6 microns according to implant retrieval studies.[19-21] In the third generation the alloy evolved into hard high-carbon cobalt-chromium, and this allowed a thinner acetabular component design, which accommodates corresponding larger femoral

heads.[9] Manufacturers used modern manufacturing techniques which resulted in very smooth surfaces, and therefore very little wear particle release. The design features, like roundness and radial clearance (the distance between the articulating surfaces) of RHA were further optimized.[22] The combination of a large femoral head and low radial clearance would promote fluid film lubrication between femoral head and cup and diminish wear. The femoral component of RHA has a large contact area and will have more sliding distance and greater speed than a component with a small radius. In MoP articulations increasing head size leads to increased wear. However, in MoM articulations the bigger femoral head and thus the bigger sliding distance, theoretically, helps to promote fluid film formation which keeps the irregularities of the articulating surfaces apart.[23]

In hip simulator studies, it was found that MoM hip bearings generate 100-fold less wear debris than MoP.[24] In addition to the attractive wear characteristics of MoM implants, the design of hip resurfacing was also appealing as no more bone than necessary has to be removed. In case of a femoral revision from RHA to THA, the normal surgical procedure of a THA can be followed and the concept of resurfacing thus introduced an extra revision option. After placement of a rigid intramedullar THA stem the loading forces will be transferred through the prosthesis instead of through the medial femoral cortex (calcar). In the long-term, this stress-shielding effect results in a decrease of proximal femoral bone stock.[25,26] RHA enables a more natural loading of the femur with reduced stress-shielding, which will preserve the patient's femoral bone stock.[27] In this young patient population, the preservation of bone is very important, in view of inevitable future revisions. Another theoretical advantage of RHA is the jump distance, the maximum distance between femoral head and acetabulum before the joint dislocates. In a THA, the head and socket are small, resulting in a small jump distance. Resurfacing has a larger jump distance, because of the more anatomically sized femoral head, which results in a significantly lower dislocation rate.[28-30] Because of the larger femoral head, improved joint mechanics with a greater range of motion, faster speed and gait were claimed.[29,31] It is, however, debatable whether the improved range of motion does not only apply to the combination of a large head and a slim neck,[32] while the small head-neck ratio of the RHA might even cause impingement.[33] The claimed advantages of RHA, low volumetric wear, preservation of femoral bone stock with easy revisions, better functional outcomes and a better stability[26,34-37] are only clinically beneficial if the survivorship is equal or better than the gold standard. The early clinical results of RHA showed to be favorable, with survivorship of 94% to 99% survivorship after two to five year follow-up in young patients.[38-41]

Current concept

The RHA was marketed as the latest advancement in hip replacement and was targeted at young active patients who needed a hip that would last a lifetime. The disadvantages, however, like the more technical demanding procedure, with a potential risk of femoral neck fractures, the occurrence of excessive metal ion release and the adverse reactions to metal debris (ARMD),[35,42-45] were less widely specified and in hind view maybe underestimated.

Based on all mentioned (theoretical) advantages RHA and MoM were appealing concepts to both surgeon and patient. Despite the absence of long-term results, there was a rapid global increase in the use of large diameter MoM hip implants. In 2007 the worldwide use of large diameter MoM implants peaked, and in the UK MoM hip prosthesis accounted for 20% of the market.[46] In this rapidly emerging market of RHA, we felt that there was a lack of literature where this new concept was balanced against the 'gold standard' of conventional THA. In a period with considerable promotion for the use of MoM implants we designed a randomized clinical trial between RHA and an established THA (with a small-diameter MoM bearing) to determine whether some of the proposed benefits of RHA could be clinically confirmed.

Aims of the thesis

With the rapidly increasing global use of and patient demand for RHA — despite only short-term results — we felt the need to introduce this implant in a controlled setting and perform an objective comparison with the gold standard, a conventional THA. The overall aim of this thesis is to evaluate the clinical outcome, metal ion blood levels and bone mineral density evolution after RHA and compare these results with THA. Therefore, this thesis seeks to answer a number of research questions that can be divided into the following seven objectives:

- To determine the single surgeon learning curve of RHA
- To compare RHA and 28-mm MoM THA with regard to short-term metal ion evolution, functional results and complications
- To assess whether a profound patient preference for RHA did influence clinical outcome and patient satisfaction
- To determine the interchangeability and provide a conversion formula between serum and whole blood metal ion measurements
- To assess the difference in trend evolution of metal ions after well and sub-optimal functioning RHA
- To determine the rate of silent pseudotumors in a cohort of hip resurfacing patients
- To compare bone mineral density evolution after RHA and a 28-mm MoM THA

Outline of the thesis

The surgical technique of RHA is technically demanding and optimal implant positioning is crucial for a good clinical outcome. In Chapter 2 the learning curve of a single surgeon judged by radiographic analysis of implant position is evaluated.

The expectations of patients and orthopaedic surgeons about the RHA were high. In Chapter 3 the two-year results of a prospective randomized clinical trial are described. This was

designed to investigate whether RHA gives better functional results, more stability and fewer complications than a small-diameter MoM THA. Furthermore, a detailed analysis of the evolution of the ion levels in both patient groups was performed.

Some patients have an extremely high preference for RHA. This impeded randomization for our randomized clinical trial, since a group of patients refused participation and demanded an RHA. This gave the opportunity to evaluate the effect of preference on the postoperative satisfaction and functional results between two groups of RHA patients, one from the randomization RHA arm in the RCT and the other not willing to be randomized in the RCT, followed in the RHA cohort. The influence of preference bias after RHA is presented in Chapter 4.

The MoM bearing of the RHA generates cobalt and chromium ions. There is no consensus whether whole blood or serum should be used as surrogate measure of metal ion exposure. In Chapter 5 we explain whether whole blood and serum measurements could be used interchangeably, provide a conversion formula between serum and whole blood and present guidelines for interpretation of metal ion analysis in clinical practice.

In national screening protocols for potential dysfunctioning implants a single metal ion measurement is recommended, however consensus about cut off values is not available. We hypothesize that the trend in metal ion levels in time is more informative for implant function than single measurements. In Chapter 6 we analyzed whether short-term trend differences of metal ion levels can differentiate between a well or a sub-optimal functioning implant.

Wear of MoM implants can lead to ARMD, which includes pseudotumors. Patients with pseudotumor formation can present themselves with complaints and high systemic metal ion levels. However, suspicion arises that silent pseudotumors occur as well. Silent pseudotumors are considered an ARMD, visible on ultrasound or MRI, in completely asymptomatic patients. In Chapter 7 the incidence of silent pseudotumors in a cohort of RHA patients is presented.

RHA claims to be bone preserving by preserving the femoral head and collum. However, periprosthetic stress shielding could lead to loss of bone stock on both the femoral and acetabular side. It might play a role in the evolution of neck narrowing and neck fractures. One of the proposed benefits of hip resurfacing is the ease of revision (and conversion to a THA). How is the evolution of bone mineral density in femoral and acetabular after RHA in comparison to an established THA? Is there bone preservation which provides future revision with good bone stock? The differences in bone mineral density after RHA and a 28-mm MoM THA are presented in Chapter 8 and Chapter 9.

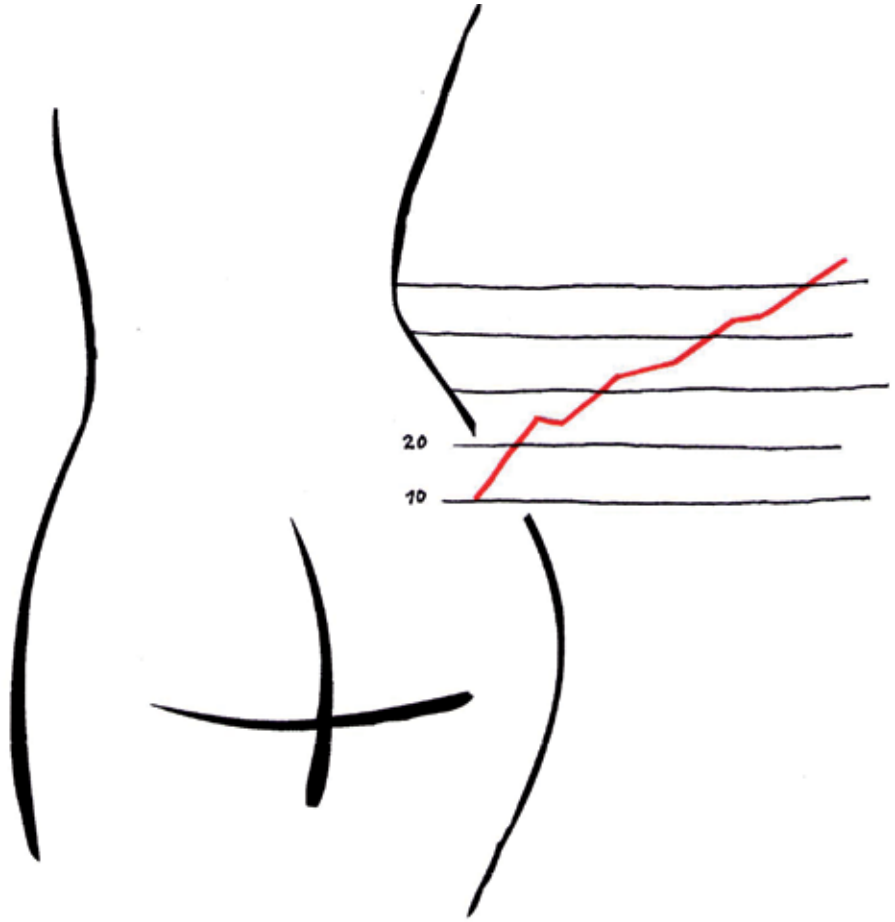
A summary of the preceding chapters and general discussion is presented in Chapter 10 and Chapter 11 (Dutch).

References

1. Rijksinstituut voor Volksgezondheid en Milieu. Artrose: Prevalentie en incidentie naar leeftijd en geslacht. *Nationaal Kompas Volksgezondheid.* 2007.
2. Nederlandse Orthopaedische Vereniging. Richtlijn diagnostiek en behandeling van heup- en knieartrose. *Kwaliteitsinstituut voor de Gezondheidszorg CBO*. 2007.
3. Nederlandse Orthopaedische Vereniging. Richtlijn totale heupprothese. *Kwaliteitsinstituut voor de Gezondheidszorg CBO*. 2010.
4. Otten R, van Roermund PM, Picavet HS. Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030 [Dutch article] *Ned Tijdschr Geneeskd.* 2010;154:A1534.
5. Corbett KL, Losina E, Nti AA, Prokopetz JJ, Katz JN. Population-based rates of revision of primary total hip arthroplasty: a systematic review. *PLoS One.* 2010;5(10):e13520.
6. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet.* 2007;370(9597):1508-1519.
7. Wiles P. The surgery of the osteoarthritic hip. *Br J Surg.* 1958;45(193):488-497.
8. McKee GK, Watson-Farrar J. Replacement of arthritic hips by the McKee-Farrar prosthesis. *J Bone Joint Surg Br.* 1966;48-B(2):245-259.
9. Triclot P. Metal-on-metal: history, state of the art (2010). *Int Orthop.* 2011;35(2):201-206.
10. Charnley J. Total hip replacement by low-friction arthroplasty. *Clin Orthop Relat Res.* 1970;72:7-21.
11. Zahiri CA, Schmalzried TP, Ebramzadeh E, Szuszczewicz ES, Salib D, Kim C, et al. Lessons learned from loosening of the McKee-Farrar metal-on-metal total hip replacement. *J Arthroplasty.* 1999;14(3):326-332.
12. Semlitsch M, Streicher RM, Weber H. The wear behavior of capsules and heads of CoCrMo casts in long-term implanted all-metal hip prostheses [German article]. *Orthopade.* 1989;18(5):377-381.
13. Jacobsson SA, Djerf K, Wahlstrom O. Twenty-year results of McKee-Farrar versus Charnley prosthesis. *Clin Orthop Relat Res.* 1996(329 Suppl):S60-68.
14. August A, Aldam C, Pynsent P. The McKee-Farrar hip arthroplasty. A long-term study. *J Bone Joint Surg Br.* 1986;68-B(4):520-527.
15. Chandler HP, Reineck FT, Wixson RL, McCarthy JC. Total hip replacement in patients younger than thirty years old. A five-year follow-up study. *J Bone Joint Surg Am.* 1981;63(9):1426-1434.
16. Dorr LD, Takei GK, Conaty JP. Total hip arthroplasties in patients less than forty-five years old. *J Bone Joint Surg Am.* 1983;65(4):474-479.
17. Jones LC, Hungerford DS. Cement disease. *Clin Orthop Relat Res.* 1987(225):192-206.
18. Weber BG, Rieker BC. The history of Metasul. [German article]. *Acta Chir Orthop Traumatol Cech.* 2002;69(5):277-284.
19. McKellop H, Park SH, Chiesa R, Doorn P, Lu B, Normand P, et al. In vivo wear of three types of metal on metal hip prostheses during two decades of use. *Clin Orthop Relat Res.* 1996(329 Suppl):S128-140.
20. Rieker CB, Schon R, Kottig P. Development and validation of a second-generation metal-on-metal bearing: laboratory studies and analysis of retrievals. *J Arthroplasty.* 2004;19(8 Suppl 3):5-11.
21. Sieber HP, Rieker CB, Kottig P. Analysis of 118 second-generation metal-on-metal retrieved hip implants. *J Bone Joint Surg Br.* 1999;81(1):46-50.
22. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, Nargol JP, De Smet KA. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. *J Bone Joint Surg Br.* 2011;93(2):164-171.

23. Dowson D, Hardaker C, Flett M, Isaac GH. A hip joint simulator study of the performance of metal-on-metal joints: Part II: design. *J Arthroplasty.* 2004;19(8 Suppl 3):124-130.
24. Anissian HL, Stark A, Gustafson A, Good V, Clarke IC. Metal-on-metal bearing in hip prosthesis generates 100-fold less wear debris than metal-on-polyethylene. *Acta Orthop Scand.* 1999;70(6):578-582.
25. Kim Y-H, Yoon S-H, Kim J-S. Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement: Alumina-on-alumina versus alumina-on-polyethylene articulation. *J Bone Joint Surg Br.* 2007;89-B(2):174-179.
26. Venesmaa PK, Kroger HP, Jurvelin JS, Miettinen HJ, Suomalainen OT, Alhava EM. Periprosthetic bone loss after cemented total hip arthroplasty: a prospective 5-year dual energy radiographic absorptiometry study of 15 patients. *Acta Orthop Scand.* 2003;74(1):31-36.
27. Kishida Y, Sugano N, Nishii T, Miki H, Yamaguchi K, Yoshikawa H. Preservation of the bone mineral density of the femur after surface replacement of the hip. *J Bone Joint Surg Br.* 2004;86-B(2):185-189.
28. Beaule PE, Schmalzried TP, Udomkiat P, Amstutz HC. Jumbo femoral head for the treatment of recurrent dislocation following total hip replacement. *J Bone Joint Surg Am.* 2002;84-A(2):256-263.
29. Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH. Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. *J Arthroplasty.* 2005;20(1):11-19.
30. Padgett DE, Lipman J, Robie B, Nestor BJ. Influence of total hip design on dislocation: a computer model and clinical analysis. *Clin Orthop Relat Res.* 2006;447:48-52.
31. Vail TP, Mina CA, Yergler JD, Pietrobon RMD. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. *Clin Orthop Relat Res.* 2006;453:123-131.
32. Bader R, Scholz R, Steinhauser E, Zimmermann S, Busch R, Mittelmeier W. The influence of head and neck geometry on stability of total hip replacement: a mechanical test study. *Acta Orthop Scand.* 2004;75(4):415-421.
33. Kluess D, Zietz C, Lindner T, Mittelmeier W, Schmitz KP, Bader R. Limited range of motion of hip resurfacing arthroplasty due to unfavorable ratio of prosthetic head size and femoral neck diameter. *Acta Orthop.* 2008;79(6):748-754.
34. Amstutz HC, Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA for patients younger than 50 years: Results of 2- to 9-year followup. *Clin Orthop Relat Res.* 2007;460:159-164.
35. Grigoris P, Roberts P, Panousis K, Bosch H. The evolution of hip resurfacing arthroplasty. *Orthop Clin North Am.* 2005;36(2):125-134, vii.
36. Vendittoli PA, Lavigne M, Roy AG, Lusignan D. A prospective randomized clinical trial comparing metal-on-metal total hip arthroplasty and metal-on-metal total hip resurfacing in patients less than 65 years old. *Hip Int.* 2006;4:73-81.
37. Witzleb WC, Knecht A, Beichler T, Kohler T, Gunther KP. Hip resurfacing arthroplasty [German article]. *Orthopade.* 2004;33(11):1236-1242.
38. Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid surface arthroplasty: two to six-year follow-up study. *J Bone Joint Surg Am.* 2004;86-A(1):28-39.
39. Daniel J, Pynsent PB, McMinn DJ. Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis. *J Bone Joint Surg Br.* 2004;86(2):177-184.
40. Hing CB, Back DL, Bailey M, Young DA, Dalziel RE, Shimmin AJ. The results of primary Birmingham hip resurfacings at a mean of five years. An independent prospective review of the first 230 hips. *J Bone Joint Surg Br.* 2007;89(11):1431-1438.
41. Treacy RB, McBryde CW, Pynsent PB. Birmingham hip resurfacing arthroplasty. A minimum follow-up of five years. *J Bone Joint Surg Br.* 2005;87(2):167-170.
42. Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. *J Bone Joint Surg Am.* 2003;85-A(11):2168-2173.

43. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. *J Arthroplasty.* 2004;19(8 Suppl 3):78-83.
44. MacDonald SJ. Metal-on-metal total hip arthroplasty: the concerns. *Clin Orthop Relat Res.* 2004(429):86-93.
45. Shimmin AJ, Bare J, Back D. Complications associated with hip arthroplasty. *Orthop Clin North Am.* 2005;36(2):187-193.
46. Cohen D. How safe are metal-on-metal hip implants? *BMJ.* 2012;344:e1410.



Learning from the learning curve in total hip resurfacing: a radiographic analysis

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Abstract

Background Operation of hip resurfacing prosthesis is a technically demanding procedure accompanied by a learning curve. To our knowledge no objective data on this learning curve are available in the literature.

Methods For the first forty resurfacing hip prostheses implanted by a single-surgeon radiographic 'learning curve' analysis was performed. Optimal implant positioning on pre-operative digital templating was compared with the eventual implant position postoperatively, measured by six establishes radiographic parameters and compared for four chronological cohorts of patients.

Results A learning curve was clearly present and an optimal result was established in the last cohort. Pitfalls were a relatively steep cup position initially and a stem position in the posterior one-third of the collum. Besides marginal medialization a fully anatomic reconstruction of the center of rotation was achieved.

Conclusion In total hip resurfacing one should recognize the presence of a learning curve. This learning curve appears to be acceptable and a reproducible optimal implant positioning can be achieved quickly.

Introduction

The results of total hip arthroplasty (THA) as treatment for osteoarthritis are excellent in the older age group, but long term survival of the implant remains a matter of concern in young patients.[1-3] Since young and active patients can also suffer from debilitating osteoarthritis, the concept of total hip resurfacing has been introduced and is rapidly increasing in popularity.[1,4-6]

Several advantages of total hip resurfacing have been described, which make the implant suitable for especially the younger age group. A greater inherent stability can be achieved with a resurfacing implant as compared to a regular THA.[4] More importantly, the femoral head is retained and thus the proximal femoral bone mass is preserved, which facilitates potential revision surgery at a later stage. In addition, revision of a modern generation metal-on-metal resurfacing arthroplasty to a regular THA is expected to be relatively straightforward and easier to perform for both the surgeon and the patient.[7,8] For example, Beaulé and associates reported a survivorship of 94% at ten years in a group of ninty converted resurfacings where the primary socket was retained.[9] This theoretical advantage of an easy revision surgery was also supported by a recent study on the early results of conversions to a regular THA.[10] They reported on a match-paired analysis of 21 failed hip resurfacings where the socket was retained and 58 primary cementless total hip replacements, done during the same period. At a mean follow-up of 46 months, functional outcome hip scores were comparable and no differences were found between the two groups in the perioperative and postoperative course. In terms of surgical effort, safety and early clinical outcomes, the revision procedure appeared to be comparable with a primary total hip arthroplasty operation.[7,10]

Besides these advantages, also the possible disadvantages of hip resurfacing have already been described in the literature. There appears to be a risk of femoral neck fracture, early implant loosening has been described and there are anatomic limitations to the indication for hip resurfacing.[11,12] Moreover, the operation is a technically demanding procedure accompanied with a substantial learning curve for surgeons.[11] Beaulé once claimed that surface arthroplasty should not be considered a standard arthroplasty and should not be done than only by surgeons with considerable experience in hip reconstruction.[1] Since surgical technique, optimal implant positioning and cementing technique are crucial for a good clinical outcome of the procedure,[12] we believe that further insight in the potential learning curve of total hip resurfacing should be established.

The aim of our study was to evaluate the learning curve on optimal implant positioning of a single surgeon series of total hip resurfacing. Since the number of surgeons performing hip resurfacing is rapidly increasing, lessons can be learned from such a learning curve and pitfalls may be avoided in future learning curves.

Materials and methods

From July 2005 total hip resurfacing is performed in Rijnstate Hospital Arnhem. The first 40 implants were considered to represent the learning curve of a single surgeon, experienced in hip surgery. All operations were performed by the same surgeon (JvS) without the use of computer navigation. A modern third-generation hip resurfacing implant was used (Conserve® Plus, Wright Medical Technology, Arlington, TN, USA) with both components made of a cast, heat-treated solution-annealed Co-Cr alloy. This metal on metal resurfacing arthroplasty has been introduced in the United States in 1996 and has a press fit cementless fixation of the acetabular component, whereas for the femoral component cement fixation is used.[2] In all cases a posterolateral approach was used.

Pre- and postoperative radiographic measurements were carried out on all implants. On the calibrated pre-operative AP pelvic X-rays anatomical radiographic parameters, such as the femoral offset, body moment arm (BMA) and abductor moment arm (AMA), as well as the neck shaft angle (NSA), were measured as previously described (Figure 1A).[13] Subsequently, the surgeon (JvS) performed pre-operative planning of the ideal implant positioning using the available digital templating software (Philips, Easyvision). Ideally the stem of the femoral component should be placed in the centre of the proximal femoral neck, maybe with a slight valgus positioning on anteroposterior radiographs as described by Beaulé et al.[13] On these pre-operatively planned ideal implant positioning, the cup abduction angle (CA), stem shaft angle (SSA) and equator angle between cup and femoral component (called cup head angle, CHA) were determined by an independent observer (SW) (Figure 1B).

After surgery, the postoperative calibrated follow-up radiographs were used for repeated measurements. Both the anatomical radiographic parameters (femoral offset, BMA and AMA) and the final implant positioning (CA, SSA and CHA) were blindly determined on anteroposterior pelvic radiographs (Figure 2A).

In addition, stem positioning of the femoral component was determined on the AP and lateral view (Figure 2B). To establish stem positioning the femoral neck was divided in three equal thirds on both views. Only with the entire length of the femoral stem situated in the middle third of the femoral neck, the stem position could be classified as in the optimal central region. Valgus positioning of the implant could then result in a stem positioning in the inferior region, whereas varus positioning ended in the superior region (Figure 2B).

For all radiographic parameters pre-operative values on the digital templating radiograph with optimal implant positioning were compared to the same parameters from the postoperative radiograph by an independent observer (SW). In order to establish a possible learning curve effect the entire study population was divided in four chronological cohorts of each ten patients. Radiographic parameters for each subgroup of patients were clustered and compared. Statistical analysis of the data was performed with One-Way ANOVA models in SPSS analysis software.

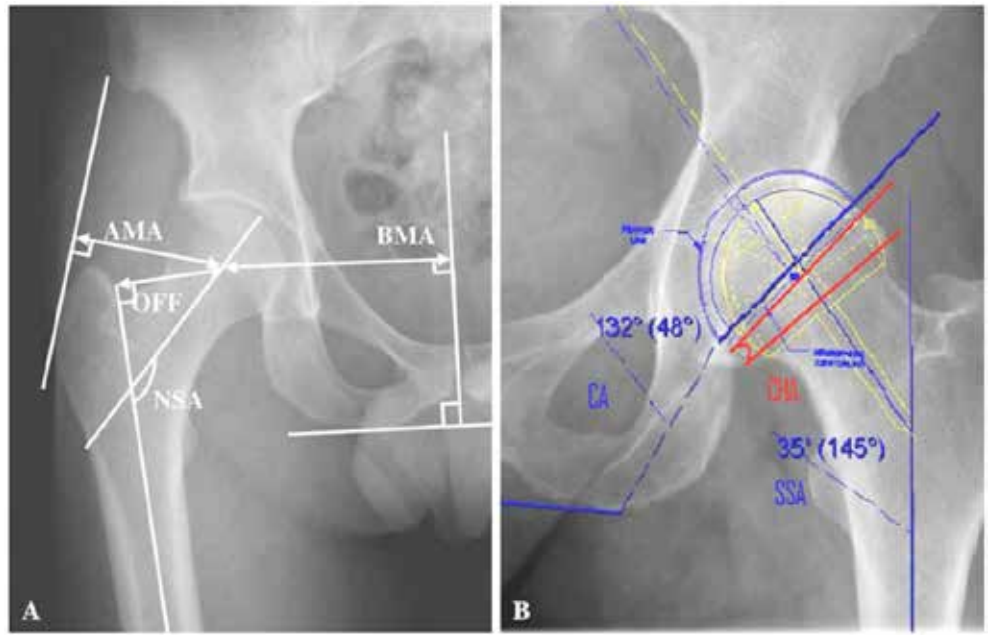


Figure 1 Radiographic measurements on pre-operative X-ray. **A** Anatomic references for femoral offset, body moment arm (BMA), abductor moment arm (AMA) and neck shaft angle (NSA). **B** Digital templating for cup angle (CA), stem shaft angle (SSA) and cup head angle (CHA).

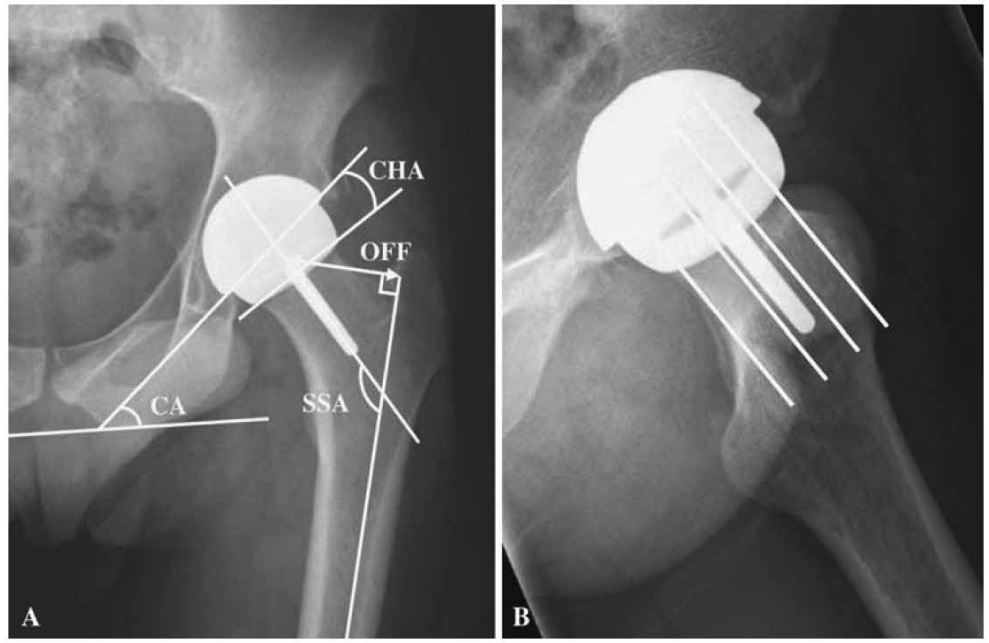


Figure 2 Example of radiographic measurements on the postoperative X-ray from the first cohort. **A** Anteroposterior radiograph with the CA, SSA, CHA and stem position in the frontal plane. **B** Lateral radiograph showing stem position in the middle-third of the collum.

Results

Forty implants were placed in 38 patients (21 males and 17 females). The mean age at surgery was 53 years (23-65). Left- and right-sided implants were equally divided with twenty on either side. The pre-operative diagnosis of the vast majority of patients (97,5%) was primary arthritis and one patient (2,5%) had a secondary osteoarthritis following an acetabular fracture. The average blood loss was 391 cc (250-800), with no statistically significant difference between the four separate cohorts. In contrast, the time of surgery did show a significant learning curve effect. The mean operation time in the first cohort of ten patients was 89 minutes, with a significant decrease (p=0.013) to 79 minutes in the last cohort (Figure 3).

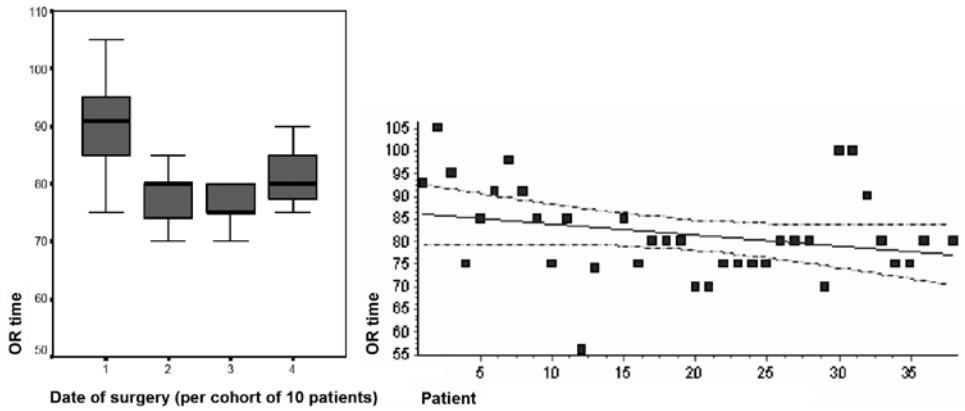


Figure 3 Learning curve for operation time. The mean operation time in the first cohort of ten patients was 89 min, with a significant decrease to 79 min in the last cohort.

The average cup abduction angle (CA) on postoperative radiographs for the first cohort of ten patients was relatively high (mean 52°, ranging from 41° to 76°) as compared to the situation on templated pre-operative radiographs (mean 44°, ranging from 46° to 54°), which indicates a rather steep cup placement initially. This was corrected in the second cohort of patients, where the average final CA (mean 49°, ranging from 40° to 59°) approached the pre-operative planning, although ranges remained substantially (50°, ranging from 45° to 52°). Subsequently, in cohort three and four, a trend to overcorrection towards a lesser steep cup placement can be observed (Figure 4A). No statistically significant differences between the four cohorts could be detected. The mean SSA for the entire group of forty patients was 134° (SD 7.4°) both for the final implant positioning and for the pre-operative planning. Apart from a slight tendency to a more valgus positioning of the stem in the last cohort, overall no significant differences between the actual implant positioning and the pre-operative planning could be detected (Figure 4B).

A trend towards more valgus positioning of the stem in relation to the anatomy of the proximal femoral neck also appeared from the calculated SSA versus the NSA (Figure 4C).

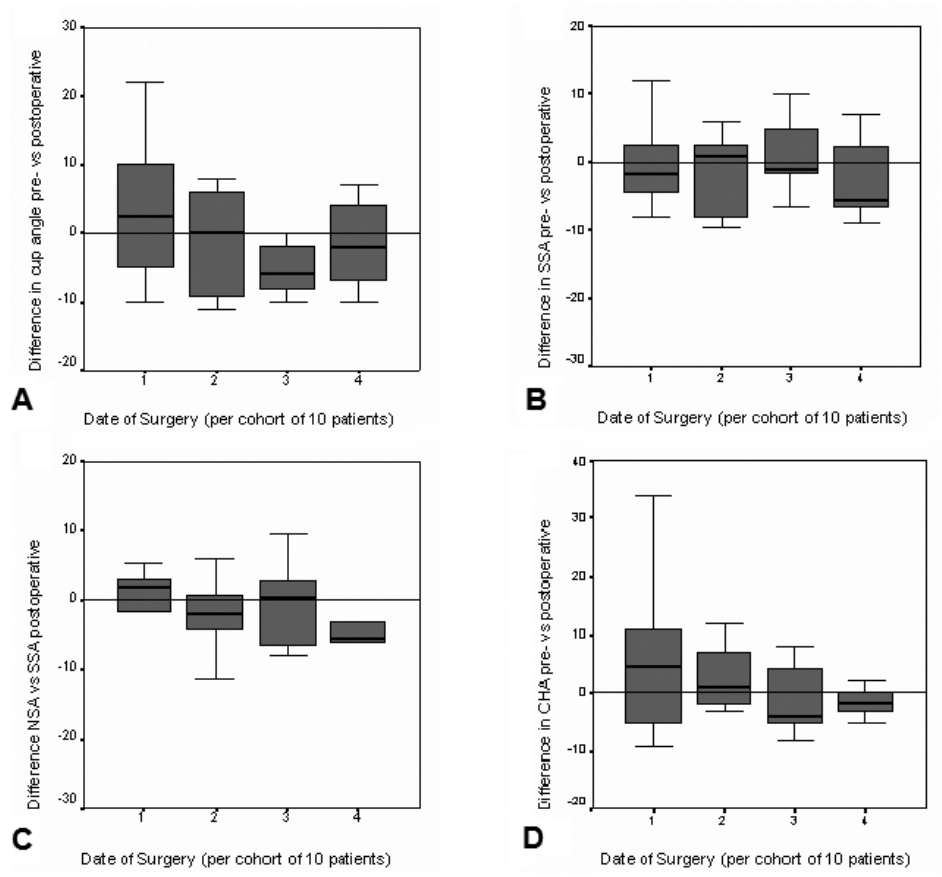


Figure 4 Learning curve trends of prosthesis implantation. Differences between pre-operative planning and ultimate implant position measures for **A** Cup-abduction-angle, **B** Stem-shaft-angle, **C** Neck-shaft-angle versus stem-shaft-angle, **D** Cup-head-angle. Positive values indicate a relatively high value on final implant position as compared to the pre-operative planning.

The average NSA for the entire group of patients was 132° (SD 6.3°), whereas the postoperative SSA increased in later cohorts. The CHA is defined as the angle between cup (i.e. cup-angle) and the femoral component. This angle is also important from a biomechanical point of view, since values close to zero degrees indicate optimal coverage of the femoral component by the cup, thus preventing peak stresses.[12] For the entire group a CHA of 7.6° (SD 4.3°) on average was calculated on final implant positioning and no significant differences could be detected with values from pre-operative planning. For each subsequent cohort, however, a dramatic decrease in standard deviation was visible indicating improved accuracy in implant positioning (Figure 4D). This trend with a decreased standard deviation was statistically significant on heterogeneous variance analysis (p=0.006).

Like described by Beaulé, ideally the stem of the femoral component should be placed in the centre of the proximal femoral neck, maybe with a slight valgus positioning on anteroposterior radiographs.[13] We defined optimal stem positioning with the entire length of the stem in the middle third of the femoral neck on both anteroposterior and lateral radiographs. In the frontal plane the stem was placed in the inferior third of femoral neck in 26% and in the central region in 74% of the entire group. On the lateral view especially in the first cohorts there was a tendency of posterior placement of the stem (Figure 5). Over time, a clear trend towards optimal stem positioning in the central third of the femoral neck in both radiographic planes could be detected throughout the four cohorts. Due to a relatively small number of patients no significant difference could be calculated for this trend (p=0.163).

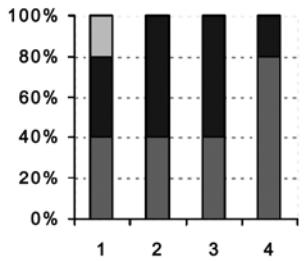


Figure 5 Percentage of stem position in central 1/3 position on AP and/or lateral X-rays for each of the four chronological cohorts of ten patients; AP+ Lat+ stands for stem position in the central third of collum in both AP and lateral radiographs.

Anatomic joint reconstruction was established comparing the pre- and postoperative body-moment-arm (BMA), abductor-moment-arm (AMA) and femoral off-set (Figure 1A). In spite of a rather large standard deviation overall for these three parameters the pre-operative values on templated radiographs were actually matched on postoperative radiographs with final implant positioning (Figure 6). Only on average a slightly negative value was encountered for the planned versus the established BMA, which was obligatorily compensated by a comparable positive value for the AMA. These two minor changes indicate some medialization of the centre of rotation (COR). No cranial or caudal migration of the COR was observed. The femoral offset on postoperative radiographs on average equalized the offset pre-operatively templated (Figure 6).

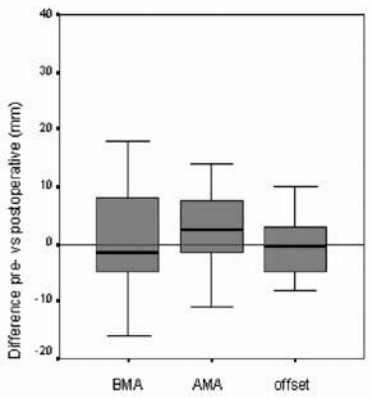


Figure 6 Globally reached anatomic joint reconstruction, with slight trend of medialization as can be concluded from a slight decrease in BMA after surgery and a slight increase in AMA.

Discussion

Hip resurfacing is an alternative to total hip replacement, but it is clearly a more demanding procedure. The skin incision is generally larger and both the operation time and the learning curve seem to be longer for hip resurfacing than for THA.[5] In this study we tried to elucidate aspects of the recognized learning curve and attempted to further define pitfalls in this learning curve.

Our data clearly indicate the presence of a learning curve in total hip resurfacing. Due to the relatively small number of patients in each subsequent cohort and the relatively large standard deviations, only for some radiographic parameters significant differences could be detected between cohorts initially. On the other hand, some clear trends were observed. First, the overall standard deviation in differences in radiographic parameters between pre-operatively templated and postoperative eventual implant positioning significantly decreased in time, thus indicating improved reproducibility in outcome.

We saw that SSA increased in later cohorts, so that the stem was placed in a progressively valgus position, what is in accordance with current recommendations from the literature.[12,13] Thus a slight valgus positioning of the stem in the femoral neck, like we attained in the later cohorts, seems favorable. Secondly, the 7° CHA appeared to reach highly reproducible values with very small standard deviations for the fourth cohort of ten patients. Furthermore, in the beginning there appeared to be tendency towards relatively steep cup placement, varus positioning of the stem on frontal radiographs and posterior placement on the lateral radiographs. These all were typical learning curve pitfalls, which appeared to be controlled in the fourth cohort of patients.

Obviously, this learning curve revealed no dramatically significant differences in time and thus the learning curve appears to be relatively mild and with a total number of approximately forty patients of an acceptable length. However, optimal implant positioning remains a rather subjective criterion. Until now the literature only provides us with a hypothetically optimal implant positioning and there is no clinical data to support this. For example, it is commonly recognized that a slight valgus position of the femoral implant should be established, since this may lead to stress reduction in the collum and decreased risk of femoral neck fractures.[12-14] This way it is also recommended to aim for a CHA close to zero, with the cup in a parallel position with the head. In our series, however, an average CHA of 7.2° was calculated on templated pre-operative radiographs. We recognize that from a biomechanical point of view the CHA should be as close to zero as possible, however, clearly this is not always feasible due to the limitations from the pre-existing pelvic cup anatomy and valgus orientation of the femoral neck.

Besides comparing the templated optimal versus the postoperative actually established implant positioning, we also wanted to evaluate whether anatomic joint reconstruction was realised. Girard et al. already evaluated the biomechanical and anatomical joint reconstruction following conventional THA versus surface replacement arthroplasty in a randomized

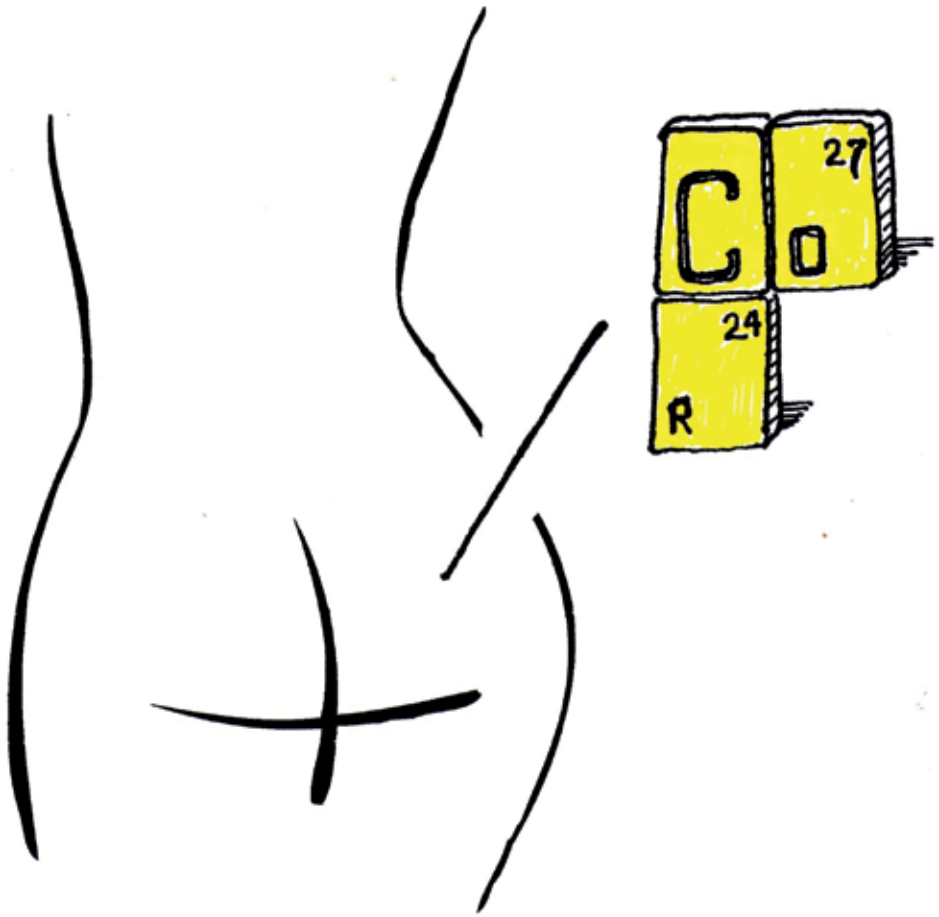
study with 120 patients.[15] They found that the radiological parameters of acetabular reconstruction were similar in both groups and that restoration of the normal proximal femoral anatomy was more precise with resurfacing. In our study population an anatomic joint reconstruction was also achieved, with only a slight medialization of the COR. This phenomenon has been recognized before, where medialization of the COR of approximately 6 mm has been described in both resurfacing hip and conventional THA.[16]

Weaknesses of our study are the limited number of patients and the fact that our data are describing the results of only one surgeon. It has been described in the literature that poor implant positioning after hip resurfacing can lead to early failures,[12] although there is still a lack of evidence based information on long term clinical outcome measures. Nevertheless, orthopaedic surgeons starting with hip resurfacing can expect a moderate learning curve, so in spite of these limitations we still believe important lessons can be learnt from these learning curve data. One should beware of a rather steep cup positioning initially. As for the femoral component, attention should be paid to avoid a varus and posterior positioning in relation to the femoral neck. Overall we are of the opinion that the learning curve of the first forty RHA appears acceptable. In general, one thinks that computer-assisted orthopaedic surgery technology may improve task performance by providing continuous feedback, which may be advantageous to learning.[17] The role of computer navigation has also been advocated in total hip resurfacing to support optimal implant positioning,[5,18] but in literature there is still no consensus on the truly effects. Since we were able to encounter an acceptable learning curve and reproducible optimal implant positioning without using any form of navigation, we wonder whether could be the benefit of computer navigation in hip resurfacing. So we are looking forward to the results of further research and learning curves of computer navigation supported implantations of resurfacing hip prostheses.

The aim of our study was to evaluate the learning curve on optimal implant positioning of a single surgeon series of total hip resurfacing. Since the number of surgeons performing hip resurfacing is rapidly increasing, lessons can be learned from such a learning curve and pitfalls may be avoided in future learning curves.

References

1. Beaulé PE, Dorey FJ, Le Duff MJ, Gruen T, Amstutz HC. Risk factors affecting outcome of metal-on-metal surface arthroplasty of the hip. *Clin Orthop Relat Res.* 2004;418:87-93.
2. Grigoris P, Roberts P, Panousis K, Bosch H. The evolution of hip resurfacing arthroplasty. *Orthop Clin North Am.* 2005;36(2):125-134, vii.
3. Kim WC, Grogan T, Amstutz HC, Dorey F. Survivorship comparison of THARIES and conventional hip arthroplasty in patients younger than 40 years old. *Clin Orthop Relat Res. 1987(214):269-277.*
4. Amstutz HC, Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA for patients younger than 50 years: Results of 2- to 9-year followup. *Clin Orthop Relat Res.* 2007;460:159-164.
5. Barrett AR, Davies BL, Gomes MP, Harris SJ, Henckel J, Jakopec M, et al. Preoperative planning and intraoperative guidance for accurate computer-assisted minimally invasive hip resurfacing surgery. *Proc Inst Mech Eng H.* 2006;220(7):759-773.
6. Vail TP, Mina CA, Yergler JD, Pietrobon RMD. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. *Clin Orthop Relat Res.* 2006;453:123-131.
7. Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid surface arthroplasty. Surgical technique. *J Bone Joint Surg Am.* 2006;88(1_suppl_2):234-249.
8. Schmalzried TP. The optimal metal-metal arthroplasty is still a total hip arthroplasty: In opposition. *J Arthroplasty.* 2006;21(4, Supplement 1):77-79.
9. Beaule PE, Le Duff MJ, Dorey FJ, Amstutz HC. Fate of cementless acetabular components retained during revision total hip arthroplasty. *J Bone Joint Surg Am.* 2003;85-A(12):2288-2293.
10. Ball ST, Le Duff MJ, Amstutz HC. Early results of conversion of a failed femoral component in hip resurfacing arthroplasty. *J Bone Joint Surg Am.* 2007;89(4):735-741.
11. Cuckler JM. The optimal metal-metal arthroplasty is still a total hip arthroplasty: In the affirmative. *J Arthroplasty.* 2006;21(4 suppl 1):74-76.
12. Long JP, Bartel DL. Surgical variables affect the mechanics of a hip resurfacing system. *Clin Orthop Relat Res.* 2006;453:115-122.
13. Beaule PE, Lee JL, Le Duff MJ, Amstutz HC, Ebramzadeh E. Orientation of the femoral component in surface arthroplasty of the hip. A biomechanical and clinical analysis. *J Bone Joint Surg Am.* 2004;86-A(9):2015-2021.
14. Anglin C, Masri BA, Tonetti J, Hodgson AJ, Greidanus NV. Hip resurfacing femoral neck fracture influenced by valgus placement. *Clin Orthop Relat Res.* 2007;465:71-79.
15. Girard J, Lavigne M, Vendittoli PA, Roy AG. Biomechanical reconstruction of the hip: a randomised study comparing total hip resurfacing and total hip arthroplasty. *J Bone Joint Surg Br.* 2006;88(6):721-726.
16. Silva M, Lee KH, Heisel C, Dela Rosa MA, Schmalzried TP. The biomechanical results of total hip resurfacing arthroplasty. *J Bone Joint Surg Am.* 2004;86-A(1):40-46.
17. Gofton W, Dubrowski A, Tabloie F, Backstein D. The effect of computer navigation on trainee learning of surgical skills. *J Bone Joint Surg Am.* 2007;89(12):2819-2827.
18. Cobb JP, Kannan V, Brust K, Thevendran G. Navigation reduces the learning curve in resurfacing total hip arthroplasty. *Clin Orthop Relat Res.* 2007;463:90-97.



Metal ion levels and functional results after either resurfacing hip arthroplasty or conventional metal-on-metal hip arthroplasty. Short-term outcome of a randomized controlled trial

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Abstract

Background Modern metal-on-metal hip resurfacing was introduced as a bone-preserving method of joint reconstruction for young and active patients; however, the large diameter of the bearing surfaces is of concern for potentially increased metal ion release.

Patients and methods 71 patients (< 65 yrs) were randomly assigned to receive either a resurfacing (RHA) (n=38) or a conventional metal-on-metal (THA) (n=33) hip arthroplasty. Functional outcomes were assessed pre-operatively, and at 6, 12 and 24 months. Cobalt and chromium blood levels were analyzed pre-operatively, and at 3, 6, 12 and 24 months.

Results All functional outcome scores improved for both groups. At 12 and 24 months the median UCLA Activity score was 8 in the RHA patients and 7 in THA patients ($p<0.05$). At 24 months OHS was median 16 in THA patients and 13 in RHA patients ($p<0.05$). However, in spite of randomization UCLA scores also appeared to be higher in RHA patients at baseline. Satisfaction was similar in both groups at 24 months. Cobalt concentrations were statistically significantly higher for RHA only at three and six months. Chromium levels remained significantly higher for RHA until 24 months. No pseudotumors were encountered in either group so far. One RHA was revised for early aseptic loosening and in two THA's a cup insert was exchanged for recurrent dislocation.

Conclusion RHA patients scored higher on UCLA, OHS and satisfaction at some intervals, however, as for the UCLA pre-operative levels were already in favor of RHA. The differences, although statistically significant were of minor clinical importance. Chromium blood levels were statistically significantly higher for RHA at all follow-up measurements, whereas for cobalt this was only observed up to six months. The true value of RHA against THA will be determined by longer follow-up and a possible shift of balance between their respective (dis) advantages.

Introduction

Hip resurfacing arthroplasty has been proposed as the best treatment option for advanced osteoarthritis of the hip in young and active patients, with a component survivorship of 94% to 99.8% at three to eight years follow-up.[1,2] In comparison to a conventional total hip arthroplasty, resurfacing claims several advantages including femoral bone stock preservation, better functional outcomes, and lower rates of dislocation.[2-4] There is, however, very limited evidence available to support these claims.

Only a limited number of studies have been published in which the clinical results of resurfacing and a conventional hip arthroplasty were compared. Most of these studies were matched cohort series, since true randomized controlled trials (RCT) are difficult to perform. There has been only one RCT where the clinical results of a resurfacing arthroplasty were compared with the clinical results a of a 28-mm metal-on-metal hip arthroplasty.[5] Both in that RCT and in some of the matched cohort series, a statistically significantly better functional score was found in selected outcome parameters for resurfacing at short-term follow-up; however, the clinical relevance is argued by the authors.[2,6-8] In addition, the higher level of activity encountered for resurfacing hip prostheses in some series applies to both pre- and postoperative values.[6-8] Another confounding factor, especially in the matched cohort series, may also have been the profound implant preference in the resurfacing group — which may have biased the eventual functional outcome relative to that of a conventional hip arthroplasty group.[7,9]

In contrast to the potential advantage of a resurfacing, there is increasing concern about the possible toxic effects of focal and systemic metal ion exposure from these implants. It is well recognized that hip arthroplasties with a metal-on-metal bearing lead to an increase in blood levels of metal ions, especially cobalt (Co) and chromium (Cr).[10-13] High wear from metal bearings may cause severe complications such as pseudotumor formation and soft tissue necrosis.[14-16] In general, one would expect higher release of Co and Cr from resurfacing, with a relatively large articulating metal-on-metal bearing, as compared to a regular metal-on-metal hip arthroplasty, but there have been no conclusions in the literature about this issue.[17]

In the only RCT that has been published (from Canada) clinical results of resurfacing were compared to those from a conventional 28-mm metal-on-metal hip arthroplasty.[5,18] Since the amount of metal ion release may play an important role in the eventual outcome and revision rate of an implant, we decided to perform a similar trial comparing resurfacing with a conventional 28-mm metal-on-metal hip arthroplasty.

In contrast to the earlier trial,[18] besides functional outcome we also assessed the blood levels of Co and Cr for both implants with time. In this RCT, we questioned whether the functional results of resurfacing would indeed be superior to a conventional metal-bearing hip arthroplasty and whether a large-diameter resurfacing bearing would induce more release of metal ions than a similar but relatively small 28-mm bearing. As there is currently a lot of debate in the literature about the potential (dis)advantages of resurfacing, we felt that it would

be appropriate to present the data of our exploratory RCT after short-term follow-up.

Patients and methods

Study design and randomization procedure

The present RCT was an exploratory study designed to compare the functional results and metal ion blood levels of patients who received a resurfacing total hip arthroplasty (RHA) against those from a conventional uncemented metal-on-metal total hip arthroplasty (THA) in the short term, medium term, and long term.

From June 2007 through January 2010, 82 patients were randomly assigned to receive one of the two hip implants (RHA or THA). A computer-generated variable block schedule was used for randomization. The randomization list was generated by an independent statistician and the resulting treatment allocations were stored in sealed opaque envelopes. Randomization occurred at the outpatient consultation by the orthopedic surgeon at the time of planning the hip arthroplasty. The patient and surgeon could not be blinded regarding the eventual type of implant; neither of them could, however, affect the outcome of randomization.

The criteria for inclusion were patients under 65 years who needed a primary hip replacement for arthritis. Patients were excluded if they had had (previous) infection of the hip or at other sites, hip fracture, avascular necrosis with collapse, osteoporotic bone mineral density, neoplasm, or renal failure. Inclusion and subsequent follow-up of patients is summarized in Figure 1. A per-protocol analysis was used in this study, because revised patients cannot be followed for metal ions. Five patients (three in the RHA group and two in the THA group) were lost to follow-up: directly after operation (n=1), after 12 months (n=3), or after 24 months (n=1). Four patients did not participate in all follow-ups because of revision at 12 months (n=1) or 24 months (n=2), and one patient did not attend the 24-month follow-up (Figure 1). Of the randomized patients, seventy had a minimal follow-up of 12 months: 38 patients in the RHA group, and 32 patients in the THA group. We obtained approval from the regional ethics committee of Radboud University Nijmegen Medical Center (LTC 419-071206). All patients agreed to sign an informed consent statement. The study was performed in compliance with the Helsinki declaration and has been registered in EudraCT (2006-005610-12).

Surgical technique

All operations were performed by one of three experienced hip surgeons using a posterolateral approach. In the RHA group, a resurfacing prosthesis was implanted with both components made of a cast, heat-treated solution-annealed Co-Cr alloy (Conserve® Plus; Wright Medical Technology, Arlington, TN). Mean resurfacing femoral head size was 48.7 mm (SD 3.5). The femoral component was cemented with low-viscosity cement after preparation of the femoral head with multiple subchondral anchor holes, and the HA coated cup was press-fitted into the acetabulum. The surgical technique has been described previously.[19] In the

THA group, an uncemented tapered stem and a threaded titanium cup with a polyethylene insert with a metal liner was placed (Zweymüller® Classic; Zimmer Orthopaedics, Warsaw, IN) together with a metal 28-mm head (Metasul®; Zimmer Orthopaedics). Both groups received identical antibiotic prophylaxis with Cephalosporine pre-operatively and 24 hours postoperatively, periarticular ossification prophylaxis using Diclofenac for three days, and thrombosis prophylaxis with fraxiparine during hospital admission and until six weeks later. Patients were rehabilitated with immediate unrestricted weight bearing according to what they could tolerate.[20]

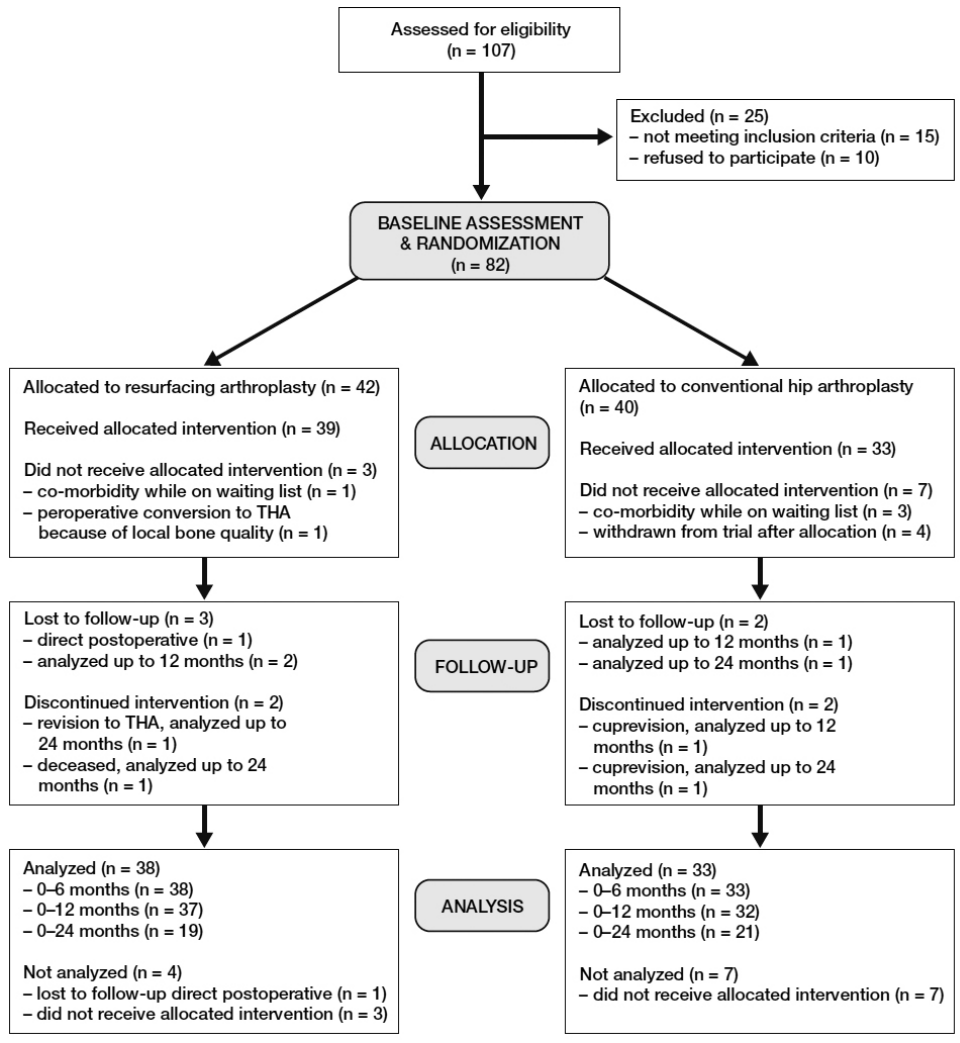


Figure 1 Consort statement – flow chart of participants throughout the study.

Clinical evaluation

Questionnaires that included the SF-12, Oxford hip score (OHS), and VAS implant satisfaction were filled in pre-operatively and at 6, 12, and 24 months. The Harris hip score (HHS) and the University of California at Los Angeles (UCLA) activity score were assessed by an independent member of the research staff (AH).

Blood levels of cobalt and chromium

Whole blood samples were collected pre-operatively and at 3, 6, 12, and 24 months postoperatively, and assessed for Co and Cr concentrations. Blood was collected in metal-free Vacutainers and the first 5 mL was discarded to eliminate metal contamination from the needle. Tubes were stored at 2–8°C and sent to the toxicology laboratory of Ghent University Hospital, Belgium for analysis. The metal ion levels in serum and whole blood were determined using an inductively-coupled plasma mass spectrometer (ICP-MS).

Since nine patients (five in the RHA group and four in the THA group) with a bilateral implant (Figure 3) had double exposure to wear and thus tended to have higher blood levels of metal ions, these data are presented separately from those of unilateral implants. Extracted data from the unilateral group were considered to represent the metal ion concentration curves in the RHA and THA groups most reliably. Following the recommendations of Daniel et al.,[21] we only report on metal ion levels in whole blood.

Statistics

Metal ion data distributions were asymmetric and are expressed as a group median and range. Friedman's ANOVA was used for analysis. To determine the between-time differences within the groups, we used the non-parametric Wilcoxon signed-ranks test. To protect against type-1 error, a Bonferroni correction was applied. To determine differences between the two groups and between functional results, we used the Mann-Whitney U test. Symmetrical data are represented by mean and standard deviation (SD).

In box plots, the outliers are represented by a dot (°) and extreme outliers (more than three times deviation of the interquartile range from the upper quartile) are characterized by an asterisk (*). Differences were considered statistically significant at p-values of <0.05. Lack of information about metal ion levels and functional results because of patients not participating in all follow-ups, the small number of patients, and multiple endpoints made this an exploratory trial. The results should therefore be read as provisional. Because of the exploratory nature of the study, formal adjustment for multiplicity between endpoints was not made. All the statistical analyses were performed using SPSS software version 17.0.

Results

The patient characteristics, without statistical significant differences between the two groups, are given in Table 1. Mean follow-up for both groups was twenty months. Of the seventy-one patients, we present a follow-up of seventy at one year, and of forty at two years. Mean operating time was longer for the RHA group, 77 min as opposed to 57 min (p<0.001). Median blood loss was the same for the two groups.

Table 1 Patients characteristics

	RHA (n=38)	THA (n=33)
Median age in years (range)	58 (24–65)	59 (37–65)
Mean body mass index (SD)	26 (3.1)	28 (5.1)
Sex ratio (men:women)	21:17	21:12
Uni- or bilateral MoM prosthesis	33:5	29:4
Diagnosis (OA/AVN/CHD) [a]	35/1/2	31/0/2
Charnley category (A/B)	24/14	23/10

[a] OA = osteoarthritis; AVN = avascular necrosis; CHD = congenital hip dysplasia.

Table 2 Clinical scores and satisfaction (VAS), values are median (range)

	Pre-operative		12 months		24 months	
	RHA (n=38)	THA (n=33)	RHA (n=38)	THA (n=32)	RHA (n=19)	THA (n=21)
Harris hip score	57 (28-77)	53 (25-82)	98 (60-100)	96 (49-100)	96 (63-100)	95 (47-100)
UCLA activity	5 [b] (2-10)	4 [b] (2-8)	8 [b] (4-10)	7 [b] (2-9)	8 [b] (5-10)	7 [b] (2-10)
SF-12	88 [b] (59-112)	79 [b] (55-113)	107 (71-116)	107 (51-117)	110 (69-117)	110 (51-133)
Oxford hip score	34 (20-46)	37 (21-44)	13 (12-31)	15 (12-40)	13 [b] (12-34)	16 [b] (12-37)
VAS satisfaction	89 [a] (49-100)	82 [a] (10-100)	92 [b] (52-100)	85 [b] (12-100)	92 (37-100)	89 (15-100)

[a] VAS satisfaction: 6-month value. [b] Significant difference between resurfacing (RHA) and conventional (THA) hip arthroplasty (p≤0.05).

Clinical evaluation

The clinical scores are summarized in Table 2 and Figure 2. In spite of the fact that we performed a randomized trial, the pre-operative values of UCLA activity score and SF-12 were lower in the THA group. The HHS, OHS, UCLA activity score, and SF-12 all improved after surgery in both groups (p<0.001). This improvement in clinical scores remained stable throughout the 24-month follow-up. At 6 and 24 months, we found a better OHS in the RHA group than in the THA group (p=0.04, r=–0.33). The median UCLA activity score was better

for the RHA group at all three time points with medium effect size (6 months: p=0.01, r=–0.30; at 12 months: p=0.002, r=–0.38; and at 24 months: p=0.04, r=–0.32). At 24 months, there was one negative outlier in the THA group with a UCLA activity score of 2. This patient has a contralateral hip arthritis, which may explain his low activity score since his satisfaction score for the operated side was 98/100. RHA patients were more satisfied after 12 months than THA patients (p=0.01, r=–0.30); this difference remained but was not statistically significant at 24 months.

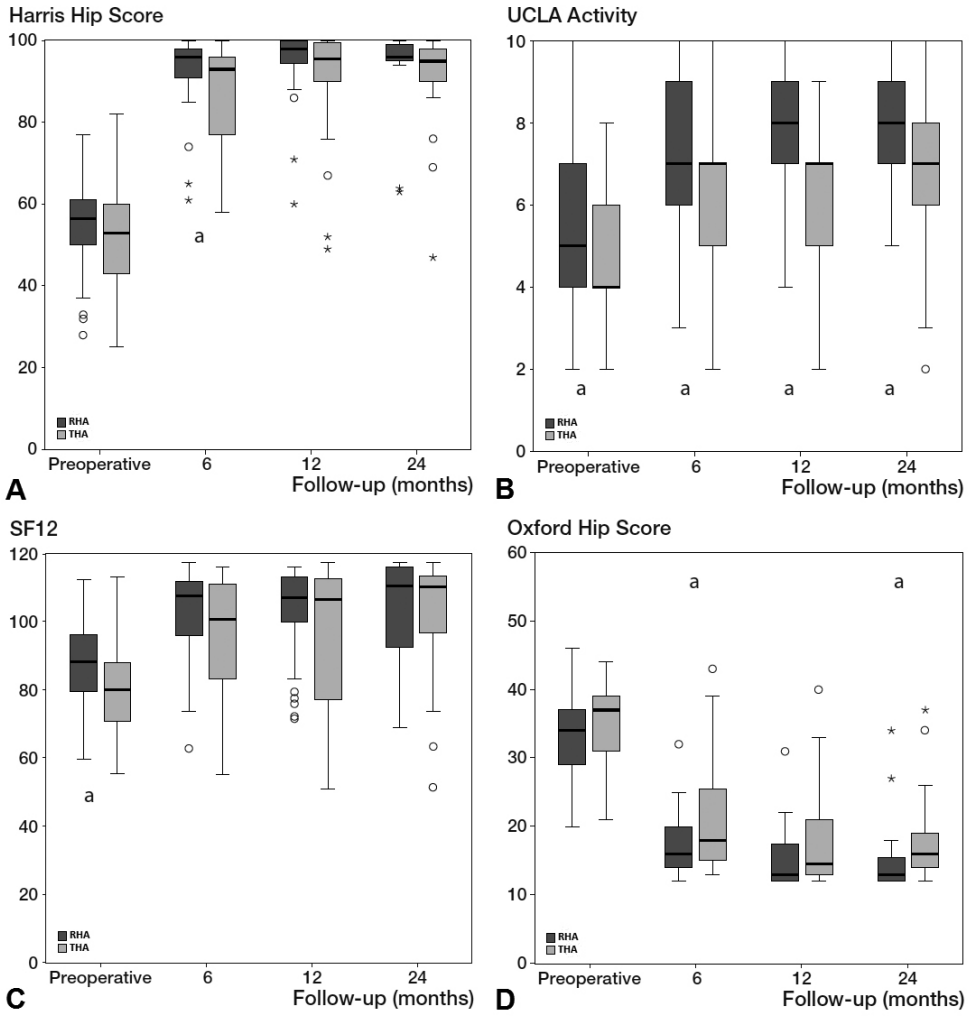


Figure 2 A Boxplot of Harris hip score. **B** Boxplot of UCLA activity score. [a] Significant differences between the RHA and THA groups. **C** Boxplot of SF-12. **D** Boxplot of Oxford hip score. [a] Significant differences between the RHA and THA groups.

Since we encountered statistically significantly better functional scores for RHA patients at some time points, including the pre-operative one, we also compared the actual improvement in score between groups. In this analysis, statistically significant differences in actual improvement in the various clinical scores could no longer be detected.

Blood levels of cobalt and chromium

The concentrations of Co and Cr in whole blood of patients in the RHA and THA groups for each time point are summarized in Table 3 and Figure 3. As expected, baseline pre-operative Co and Cr concentrations were below the reference level of 0.1 µg/L for patients with a unilateral implant (both groups).[22] Blood Co and Cr levels increased (p<0.001) in both groups after surgery until six months postoperatively, with stable concentrations thereafter. Co concentrations were higher for RHA patients than for THA patients only at 3 months (p<0.001, r=–0.50) and 6 months (p=0.006, r=–0.35). Co levels stabilized after 6 months in the RHA group, and the initially statistically significant difference between groups could no longer be detected at 12 months (p=0.1) and 24 months (p=0.1). Cr concentrations were also higher in the RHA group, but this time at all time points until 24 months and with a large effect size (p<0.001, r=–0.50). We could not establish any correlation between metal ion concentration and gender, femoral component diameter, or age.

Four patients (three in the RHA group and one in the THA group) had extremely high levels of metal ions at 12 and 24 months (Figure 3). At these time points they had good clinical scores with HHS of 98 (95–100), OHS of 13 (12–16), and a median UCLA activity score of 6.5 (6–8). These patients will be monitored closely.

Table 3 Whole-blood cobalt and chromium concentrations, values (µg/L) are median (range)

	Pre-operative		6 months		12 months		24 months	
	RHA	THA	RHA	THA	RHA	THA	RHA	THA
Unilateral implants	(n=33)	(n=29)	(n=33)	(n=29)	(n=33)	(n=28)	(n=16)	(n=17)
Co	0.1 (0.1-0.8)	0.1 (0.1-0.6)	1.3 [a] (0.1-23)	0.85 [a] (0.1-4.0)	1.25 (0.6-8.3)	1.0 (0.1-4.2)	1.2 (0.5-22)	0.9 (0.1-2.7)
Cr	0.1 (0.1-1.4)	0.1 (0.1-0.1)	1.1 [a] (0.1-15)	0.1 [a] (0.1-2.9)	1.0 [a] (0.1-6.1)	0.5 [a] (0.1-2.0)	1.2 [a] (0.1-10)	0.5 [a] (0.1-2.1)
Bilateral implants	(n=5)	(n=4)	(n=5)	(n=4)	(n=5)	(n=4)	(n=3)	(n=4)
Co	0.3 (0.1-1.1)	0.1 (0.1-1.8)	1.7 (1-7.9)	0.85 (0.5-2.2)	1.9 (0.9-11)	1.15 (0.8-1.3)	2.0 (0.7-6.0)	1.4 (0.7-1.8)
Cr	0.1 (0.1-0.9)	0.1 (0.1-0.8)	1.7 (0.1-3.8)	0.25 (0.1-1.5)	2.2 (0.1-4.9)	0.5 (0.1-0.8)	1.5 (0.1-2.3)	0.75 (0.6-0.8)

[a] Significant difference between resurfacing (RHA) and conventional (THA) hip arthroplasty ($p \leq 0.05$).

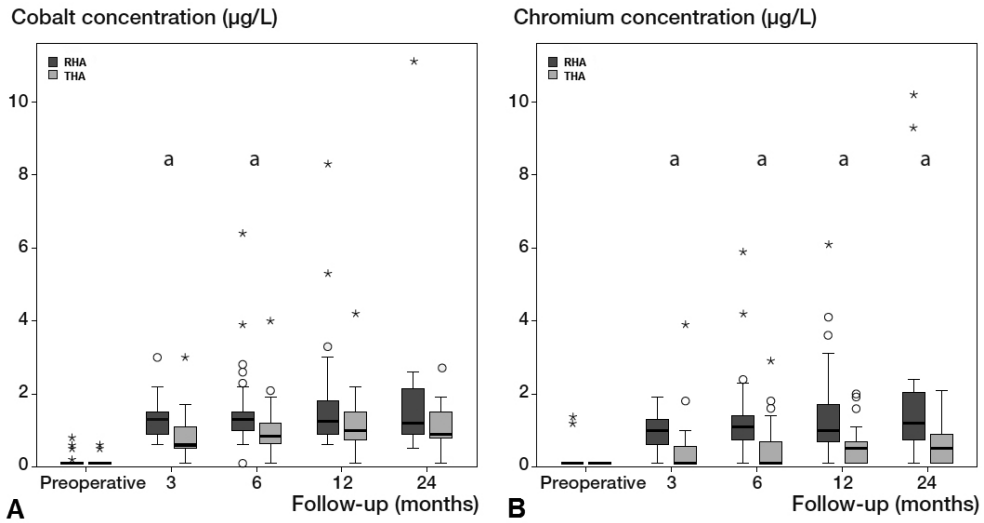


Figure 3 A Boxplot Co concentrations of unilateral prosthesis in blood in µg/L. Two extreme outliers are not represented for clarity purposes, this concerns two RHA patients at 6 and 24 months with Co concentration of respectively 22.80 and 22.00 µg/L. **B** Boxplot Cr concentrations of unilateral prosthesis in blood in µg/L. One extreme outlier was not represented for clarity purposes, this concerns an RHA patient at 6 months with a Cr concentration of 14.90 µg/L. [a] Significant differences between the RHA and THA groups.

The subgroup of bilateral metal-on-metal implants did not have statistically significantly higher metal ion concentrations than the unilateral group, but it should be noted that the bilateral subgroup was small (Table 3). One extreme outlier of Co with a concentration of 10.6 µg/L at 12 months was encountered in a male patient (RHA) with a bilateral implant. This patient had a high UCLA activity score of 9, HHS of 98, and an excellent satisfaction score of 95/100. There were no statistically significant differences between unilateral and bilateral prostheses regarding Co levels (p=0.2) and Cr levels (p=0.8) at 12 months.

Complications

There were three THA patients with recurrent dislocation, for which two patients had an early re-intervention with cup insert and head exchange, and there were no dislocations afterwards. In addition, two early deep infections were encountered in the THA group without recurrence of infection after lavage. In the RHA group, one early revision was encountered; an early aseptic loosening from avascular necrosis of the femoral head dictated conversion to an intramedullary stem with a large femoral head. The metal acetabular cup was kept since the patient had been pain-free for two years and the whole-blood Co level was 2.3 µg/L prior to revision.

Discussion

The most important findings of this exploratory study were that after one and two years,

Cr concentrations were higher in patients with resurfacing hip arthroplasty, and Co concentrations were comparable with those in patients with a conventional arthroplasty. The functional results improved substantially in both groups without any major differences between groups.

The functional results — tested by validated functional scales — showed a highly significant postoperative improvement in both groups, which is in line with other studies.[2,3,6-8,12,18,23] A limitation of some of these studies was that the pre-operative values of the resurfacing group were different from those in the control group.[2,6,7] In our RCT, this confounding factor was not apparent, as the pre-operative HHS and OHS values were similar. In spite of the randomized nature of the present study, the pre-operative UCLA activity score and SF-12 score were higher in the RHA patients. The pre-operative values of the SF-12 in the THA group were lower, and the mental part of the SF-12 accounted for this difference. The difference in pre-operative SF-12 is difficult to explain; perhaps the THA patients were less satisfied with the implant allocated to them. Obtaining the SF-12 result before informing the patient about the implant allocated to him or her could perhaps have prevented this confounding variable. This idea is also supported by our experience that inclusion for randomization proved to be extremely difficult. Generally speaking, patients tended to prefer a resurfacing arthroplasty. It was only after considerable explanation that we managed to include 82 patients. The difficulty we encountered in performing a well-designed RCT was also illustrated by the relatively high number of exclusions after randomization in the THA group; four patients still decided to have further treatment at another hospital and withdrew from the study after having been allocated to total hip arthroplasty.

Some functional outcome scores showed a statistically significant difference in favor of the RHA group at certain time points. For example, satisfaction by VAS at 12 months favored the RHA group; however, this difference was inapparent at the 24-month follow-up. The OHS was also significantly better in the RHA group at 6 and 24 months, with a medium effect size, whereas there was no significant difference in the pre-operative baseline levels. The UCLA activity score was significantly higher for the RHA group at each time point until 24 months, however, it has been noted that this difference also already applies for the pre-operative scores, despite the randomization procedure. These findings correspond to those in earlier studies. From their large, retrospective comparative study Stulberg et al.[23] reported an initial advantage in HHS from resurfacing at 6 and 12 months, but the results were comparable after 24 months. Higher UCLA activity scores after five to seven years were also described for resurfacing in another matched cohort study with THA patients.[8] There has only been one other RCT comparing resurfacing with conventional metal-on-metal hip arthroplasty.[5] The authors also reported initial UCLA activity scores in favor of the RHA group. However, in a recent three to six year follow-up report of the same study, the statistical significance of this difference was no longer apparent.[18] In their matched control study, Mont et al. also found a significantly better activity level after three years, and no significant differences in HHS and satisfaction. They claimed that the activity scores were influenced by higher baseline levels

and selection bias from targeted choice of implant.[7] Selection bias was excluded in our study by randomization; however, patient outcome can still be influenced by patients having received their 'preferred' implant.

With three patients having a re-intervention, the percentage of early revision in this study was 4%. Of these three patients, two in the THA group underwent a relatively simple insert exchange for recurrent dislocation and one RHA patient had a femoral component revision because of early aseptic loosening from avascular necrosis. Three patients in the THA group of 33 patients suffered a dislocation, which is an unusually high percentage. We do not have a clear explanation for this phenomenon, and do not recognize this high number from our own practice/experience. In two patients, a stabilizing insert exchange was performed after CT scanning had revealed proper implant positioning; no dislocations occurred after this exchange of insert.

Besides functional results as a measurement of postoperative outcome, determination of metal ion levels is becoming increasingly common after metal-on-metal arthroplasties and serves as an indicator of bearing performance and device safety.[11] High metal ion concentrations may lead to adverse biological reactions including local soft tissue toxicity; hypersensitivity reactions; impaired renal, endocrine, and immune function; bone loss; and risk of carcinogenesis.[14,16] In the present study, initially, resurfacing gave a larger increase in Co and Cr concentrations than a 28-mm metal bearing hip arthroplasty. After their respective run-in phases, Co blood levels were similar between the two groups at 12 months. Only Cr blood levels remained statistically significantly higher in the RHA group at all time points. Since Co is known to be relatively toxic compared to Cr, it is important to have established that blood Co levels (specifically) stabilize after a run-in phase of six months, and that the difference in blood levels with the THA group in this study could only be established during the first six months of follow-up. As compared to most of the published case-controlled or retrospective reports on the performance of several types of resurfacing implants,[10,11,24] the metal ion levels after unilateral resurfacing in our study appeared to be rather low — with median blood levels of Co of 1.3 µg/L and of Cr of 1.2 µg/L. This observation may be an implant-related phenomenon.

The relationship between relatively high metal ions and the need for revision surgery after resurfacing has already been explored.[25] In spite of this recognized association between elevated Co and Cr levels in blood and malfunctioning implants, there is limited information about the range of acceptable metal ion concentrations and where toxicity is introduced. The best-defined reference values are the *exposure equivalent of carcinogenic substances* (EKA values)[26] for industrial workers and those in the Mayo Medical Laboratories interpretive handbook.[22] The EKA upper limits for Co have been defined to be 5 µg/L in whole blood and those for Cr to be 17 µg/L in erythrocytes (as no whole blood upper limits have been reported). From their own clinical series with malfunctioning resurfacing implants, De Smet et al. proposed an upper acceptable limit of 4.4 µg/L for Co and 5.1 µg/L for Cr in serum.[27]

The median ion levels in the present study were well below this limit, although a few outliers were encountered. Since a strong correlation between high metal ion concentrations and component wear has been established, forthcoming early revisions can still be expected in our group of patients with longer follow-up.[25]

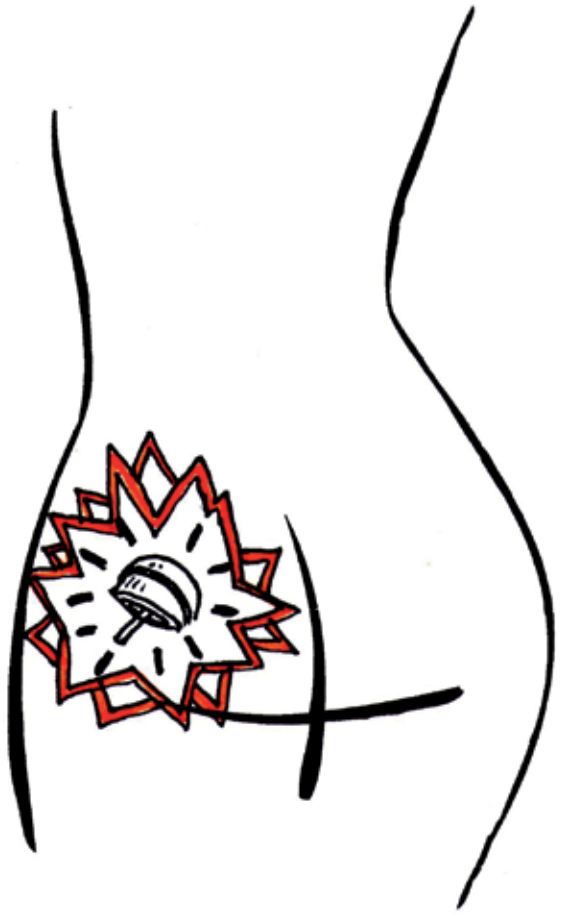
On theoretical grounds,[17] the wear of small- and large-diameter bearings — and therefore the metal ion concentrations — should be equal. In the present study, this applied to Co, but not to Cr. This is partially consistent with results from the literature.[10,13] The medium-term follow-up of Moroni et al. showed that after five years there were no differences in metal ion concentrations between large-diameter resurfacing hip arthroplasty and small-diameter metal-on-metal hip arthroplasty.[13] Differences found at 3 and 6 months between RHA patients and THA patients (28-mm) for Co — and at all time intervals for Cr — may be attributed to a run-in phase. Interestingly, the run-in phase of the small-diameter head in hip arthroplasty appeared to be longer, with a peak at 12 months, while the large-diameter head concentrations peaked at 6 months and stabilized thereafter.

In conclusion, we believe that the results of our study are supported by the only other published RCT comparing resurfacing with a 28-mm conventional hip arthroplasty.[18] The strength of our study compared to that study is that we combined clinical follow-up with prospective evaluation of metal ion levels. In addition, two independent RCT's with comparable outcome lead to an increase in the level of evidence of the findings. On the other hand, there are also clear limitations to our study. Inclusion of patients proved to be extremely difficult, and the number of patients available was therefore limited. Due to the limited number of patients, we can only present our data as an exploratory trial, mainly because it had insufficient power to allow us to draw firm conclusions, but also because the report deals with a short-term follow-up. Especially in the light of reports in the literature on a peak in revisions after resurfacing at three years of follow-up,[25] we can expect that more revisions in the RHA group will appear. Also, from the fact that at 24 months after surgery we encountered some clinically well-functioning resurfacings with relatively high levels of metal ions, these patients may still become symptomatic in the near future and the revision rate may increase. We will continue to monitor these patients with repeated metal ion measurements and functional assessment. Longer follow-up of these two groups of patients may help us to understand the potential advantages and disadvantages of resurfacing compared to conventional arthroplasty.

References

1. Amstutz HC, Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA for patients younger than 50 years: Results of 2- to 9-year followup. *Clin Orthop Relat Res.* 2007;460:159-164.
2. Vail TP, Mina CA, Yergler JD, Pietrobon RMD. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. *Clin Orthop Relat Res.* 2006;453:123-131.
3. Lavigne M, Therrien M, Nantel J, Roy A, Prince F, Vendittoli P-A. The John Charnley Award: The functional outcome of hip resurfacing and large-head THA is the same: A randomized, double-blind study. *Clin Orthop Relat Res.* 2010;468(2):326-336.
4. Smolders JMH, Hol A, Rijnders T, van Susante JLC. Changes in bone mineral density in the proximal femur after hip resurfacing and uncemented total hip replacement: A prospective randomized controlled study. *J Bone Joint Surg Br.* 2010;92-B(11):1509-1514.
5. Vendittoli PA, Lavigne M, Roy AG, Lusignan D. A prospective randomized clinical trial comparing metal-on-metal total hip arthroplasty and metal-on-metal total hip resurfacing in patients less than 65 years old. *Hip Int.* 2006;4:73-81.
6. Fowble VA, dela Rosa MA, Schmalzried TP. A comparison of total hip resurfacing and total hip arthroplasty - patients and outcomes. *Bull NYU Hosp Jt Dis.* 2009;67(2):108-112.
7. Mont M, Marker D, Smith J, Ulrich S, McGrath M. Resurfacing is comparable to total hip arthroplasty at short-term followup. *Clin Orthop Relat Res.* 2009;467(1):66-71.
8. Pollard TCB, Baker RP, Eastaugh-Waring SJ, Bannister GC. Treatment of the young active patient with osteoarthritis of the hip: a five to seven-year comparison of hybrid total hip arthroplasty and metal-on-metal resurfacing. *J Bone Joint Surg Br.* 2006;88-B(5):592-600.
9. Bisseling P, Smolders JMH, Hol A, van Susante JLC. No clear influence of preference bias on satisfaction and early functional outcome in resurfacing hip arthroplasty. *Acta Orthop.* 2011;82(2):161-165.
10. Antoniou J, Zukor DJ, Mwale F, Minarik W, Petit A, Huk OL. Metal ion levels in the blood of patients after hip resurfacing: A comparison between twenty-eight and thirty-six-millimeter-head metal-on-metal prostheses. *J Bone Joint Surg Am.* 2008;90(Suppl 3):142-148.
11. Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin Orthop Relat Res.* 2005;438:177-181.
12. Garbuz D, Tanzer M, Greidanus N, Masri B, Duncan C. The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: A randomized clinical trial. *Clin Orthop Relat Res.* 2010;468(2):318-325.
13. Moroni A, Savarino L, Cadossi M, Baldini N, Giannini S. Does ion release differ between hip resurfacing and metal-on-metal THA? *Clin Orthop Relat Res.* 2008;466(3):700-707.
14. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: A review of current knowledge and future strategies. *J Bone Joint Surg Br.* 2007;89-B(5):567-573.
15. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90(7):847-851.
16. Shimmin AJ, Bare J, Back D. Complications associated with hip arthroplasty. *Orthop Clin North Am.* 2005;36(2):187-193.
17. Smith SL, Dowson D, Goldsmith AA. The effect of femoral head diameter upon lubrication and wear of metal-on-metal total hip replacements. *Proc Inst Mech Eng H.* 2001;215(2):161-170.
18. Vendittoli PA, Ganapathi M, Roy AG, Lusignan D, Lavigne M. A comparison of clinical results of hip resurfacing arthroplasty and 28 mm metal on metal total hip arthroplasty: a randomised trial with 3-6 years follow-up. *Hip Int.* 2010;20(01):1-13.

19. Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid surface arthroplasty. Surgical technique. *J Bone Joint Surg Am.* 2006;88(1_suppl_2):234-249.
20. Hol A, van Grinsven S, Lucas C, van Susante J, van Loon C. Partial versus unrestricted weight bearing after an uncemented femoral stem in total hip arthroplasty: recommendation of a concise rehabilitation protocol from a systematic review of the literature. *Arch Orthop Trauma Surg.* 2010;130(4):547-555.
21. Daniel J, Ziaee H, Pynsent PB, McMinn DJ. The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. *J Bone Joint Surg Br.* 2007;89(6):736-741.
22. Serum Cobalt (80084) and Serum Chromium (8638) [Web page] New England, Massachusetts: *Mayo Medical Laboratories.* 2010; Available from: http://www.mayomedicallaboratories.com/test-catalog/alphabetical/C.
23. Stulberg BN, Fitts SM, Bowen AR, Zadzilka JD. Early return to function after hip resurfacing: Is it better than contemporary total hip arthroplasty? *J Arthroplasty.* 2010;25(5):748-753.
24. Moroni A, Savarino L, Hoque M, Cadossi M, Baldini N. Do ion levels in hip resurfacing differ from metal-on-metal THA at midterm? *Clin Orthop Relat Res.* 2011;469(1):180-187.
25. De Smet K, De Haan R, Calistri A, Campbell PA, Ebramzadeh E, Pattyn C, et al. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. *J Bone Joint Surg Am.* 2008;90 Suppl 4:202-208.
26. Morgan MS, Schaller KH. An analysis of criteria for biological limit values developed in Germany and in the United States. *Int Arch Occup Environ Health.* 1999;72(4):195-204.
27. De Smet K, Campbell PA, Van Orsouw M, Backers K, Gill HS. Interpretation of metal ion levels after metal-on-metal resurfacing. *Proc AAOS.* 2010;Poster Presentation Number: P100.



No clear influence of preference bias on satisfaction and early functional outcome in resurfacing hip arthroplasty

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Abstract

Background and purpose Hip resurfacing arthroplasty (RHA) is done in patients who often have a high preference for the method. This preference can influence the clinical outcome and satisfaction. We evaluated the potential influence of this preference bias.

Patients and methods From an ongoing randomized trial comparing RHA with total hip arthroplasty, 28 consecutive patients (28 hips) who had been allocated to an RHA were characterized as the 'randomized' group. Twenty-two other patients (24 hips) who had refused participation and had especially requested an RHA were characterized as the 'preference' group. Harris hip score (HHS), Oxford hip score (OHS), University of California at Los Angeles activity scale (UCLA), Short Form 12 (SF-12), and visual analog scale satisfaction score (VAS) were assessed in both groups.

Results Both groups had a high implant satisfaction score (97/100 for the 'preference' group and 93/100 for the 'randomized' group) at 12 months. The HHS, OHS, and UCLA were similar at baseline and also revealed a similar improvement up to 12 months ($p<0.001$). Regarding the SF-12, the 'preference' group scored lower on the mental subscale pre-operatively ($p=0.03$), and there was a greater increase after 12 months ($p=0.03$).

Interpretation We could not show that there was any influence of preference on satisfaction with the implant and early clinical outcome in patients who underwent RHA. The difference in mental subscale scores between groups may still indicate a difference in psychological profile.

Introduction

The outcome of any surgical treatment is influenced by several factors. Apart from the surgical intervention itself, co-morbidities and postoperative rehabilitation — and also factors such as patients' perception, confidence, and expectations — contribute to the final result and patient satisfaction. Nowadays, most patients have access to the internet and other sources of information, and are well-informed. Their conceptions will lead beliefs and expectations, which will in turn lead to preferences. Preference for a specific treatment can influence the outcome,[1-6] and can introduce bias into assessments of satisfaction and acceptability. This might be a confounding factor in a trial, and may affect the validity of the results. To obtain hard evidence of any possible preference effects is problematic, as it is difficult to reliably distinguish between simple therapeutic effects and preference effects mediated through psychological pathways in experiments.[7]

The dilemma of a possible influence of preference is frequently encountered in studies in orthopedic surgery. For example, the interest in resurfacing hip arthroplasty (RHA) has grown in the past 15 years8-10 and has received much international attention. The results reported regarding the short-term and long-term follow-up of RHA appear to correspond with the results of conventional total hip arthroplasty (THA)[11-16] and the satisfaction rates reported have been 90–100%.[14,15,17] Hip resurfacing surgeons generally deal with patients with a profound preference for this particular implant. We have not found any studies that have incorporated the possible influence of preference of the patient for an RHA into their results, and it can be speculated whether these results are influenced by this preference and perception on the part of the patients.

In an ongoing randomized trial comparing RHA with conventional THA, we encountered — as expected — some difficulty in recruiting patients for inclusion, since several patients had a specific demand for RHA. In this way, RHA's were performed in two groups of patients: (1) an unbiased 'randomized' group without any preferences, willing to participate in the ongoing trial, and simply allocated to RHA; and (2) a 'preference' group of potentially biased patients with a specific demand for RHA and who declined participation in the trial. We could therefore evaluate the potential role of preference bias on implant satisfaction and early clinical outcome. We hypothesized that patients in the 'preference' group would be more satisfied than the patients in the 'randomized' group. On the other hand, patients with a high degree of preference could have such high expectations of the treatment that they might be difficult to fulfill, which would lead to lower satisfaction compared to patients without any preference.

Patients and methods

From April 2007 through March 2010, patients under 65 years with primary osteoarthritis of the hip were evaluated for eligibility to enter the randomized controlled trial (RCT) comparing

RHA with THA. After having given informed consent, patients with a strong preference for RHA (and who were therefore unwilling to be randomized) entered the prospective cohort study — the 'preference' group. Patients with no preference were enrolled in the RCT to receive either an RHA or a THA. The current study included all patients in the 'preference' group and all patients in the RCT who were allocated to RHA, with a minimum follow-up of 6 months.

The criteria for inclusion in both the RCT and the cohort were identical: patients between 35 and 65 years old, eligible for primary hip replacement because of osteoarthritis, congenital hip dysplasia, or posttraumatic arthritis. Patients were excluded in case of (previous) infection of the hip, hip fracture, avascular necrosis with collapse, osteoporotic bone mineral density index levels of the involved hip (t-score <2.5), renal failure, or hip revision of the primary index procedure.

All patients received a Conserve® Plus RHA (Wright Medical Technology, Arlington, TN). The operations were performed through a standard posterolateral approach by a senior hip surgeon with considerable experience in RHA implants.[18] Both groups received identical antibiotic prophylaxis, periarticular ossification prophylaxis, and thrombosis prophylaxis during hospital admission, and six weeks afterwards. The patients had identical rehabilitation protocols with unrestricted weight bearing according to individual tolerance, starting on the first postoperative day.

Table 1 Demographics of patients

	'Preference' group (n=24)	'Randomized' group (n=28)	p-value
Age, median (IQR)	52 (48-56)	58 (52-62)	0.01
Sex ratio (men:women)	15:9	13:15	0.2
Diagnosis (OA/AVN/CHD) [a]	24/0/0	26/1/1	0.5

[a] OA = osteoarthritis; AVN = avascular necrosis; CHD = congenital hip dysplasia.

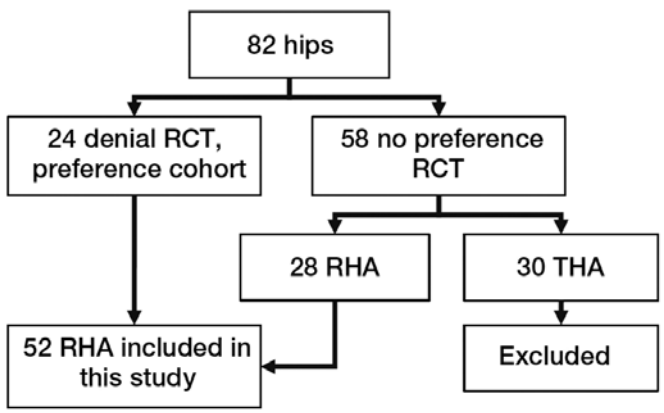


Figure 1 Recruitment of patients to the study.

Fifty patients were included in the study, with 28 implants (28 patients) in the 'randomized' group and 24 implants (22 patients) in the 'preference' group (Table 1 and Figure 1). All patients in the 'preference' group and 22 of the 28 patients in the 'randomized' group completed the follow-up term of 12 months. The remaining six patients had a follow-up of 6 months.

All patients completed a questionnaire that included the Short Form 12 (SF-12) and Oxford hip score (OHS) pre-operatively, at 6 months, and at 12 months. The Harris hip score (HHS) and the University of California at Los Angeles activity scale (UCLA) were assessed by an independent member of the research staff (AH) who collected and registered all the forms. Satisfaction with the implant was measured on a numeric scale (visual analog scale satisfaction score (VAS)) of 0–100 mm, where 100 mm corresponded to being completely satisfied.

Approval for the randomized clinical trial and the cohort follow-up was obtained from the regional ethics committee of the Radboud University Nijmegen Medical Centre, with issue number LTC 419-071206 and date of approval 01/02/2007. All patients agreed to sign an informed consent document. The EudraCT number assigned to the randomized controlled trial was 2006-005610-12.

Statistics

Variables were checked for normal distribution with the Shapiro-Wilk test. A value of <0.05 was defined as the absence of a normal distribution. The mean and standard deviation (SD) were used for normally distributed variables and the median and interquartile range (IQR) for variables without normal distribution. Differences between the groups were determined by the Student's t-test for variables with normal distribution, the Mann-Whitney test for variables without normal distribution, and the Pearson Chi-square test for categorical variables (sex and diagnosis). Variables that were not normally distributed were: age, blood loss, the pre-operative OHS and UCLA scores, the VAS satisfaction score at 12 months, and the change in satisfaction score between 6 and 12 months. These p-values are marked with the superscript ß. Significance was defined as p-values of <0.05. SPSS software version 15.0 was used for statistical analysis.

Results

The characteristics of the patients are given in Table 1. Both groups were similar regarding sex and diagnosis, but the patients in the 'preference' group were younger than in the 'randomized' group. Mean operation time ('preference' group: 81 min (SD 15); 'randomized' group: 76 min (SD 11); p=0.2) and median blood loss ('preference' group: 300 mL (288–313); 'randomized' group: 300 mL (200–300); p=0.4β) were similar in both groups. Similar implants sizes were used in both groups (p=0.70).

The pre-operative HHS, OHS, and UCLA scores were similar in both groups (Figure 2). The SF-12 score, however, was higher (88 (SD 14)), in the 'randomized' group than in the

'preference' group (80 (SD 12)) (p=0.03). This difference mainly originated from intergroup differences in the mental subscale. A mean score of 47 (SD 13) on the mental subscale was found in the 'preference' group, as opposed to 53 (SD 10) in the 'randomized' group (p=0.05).

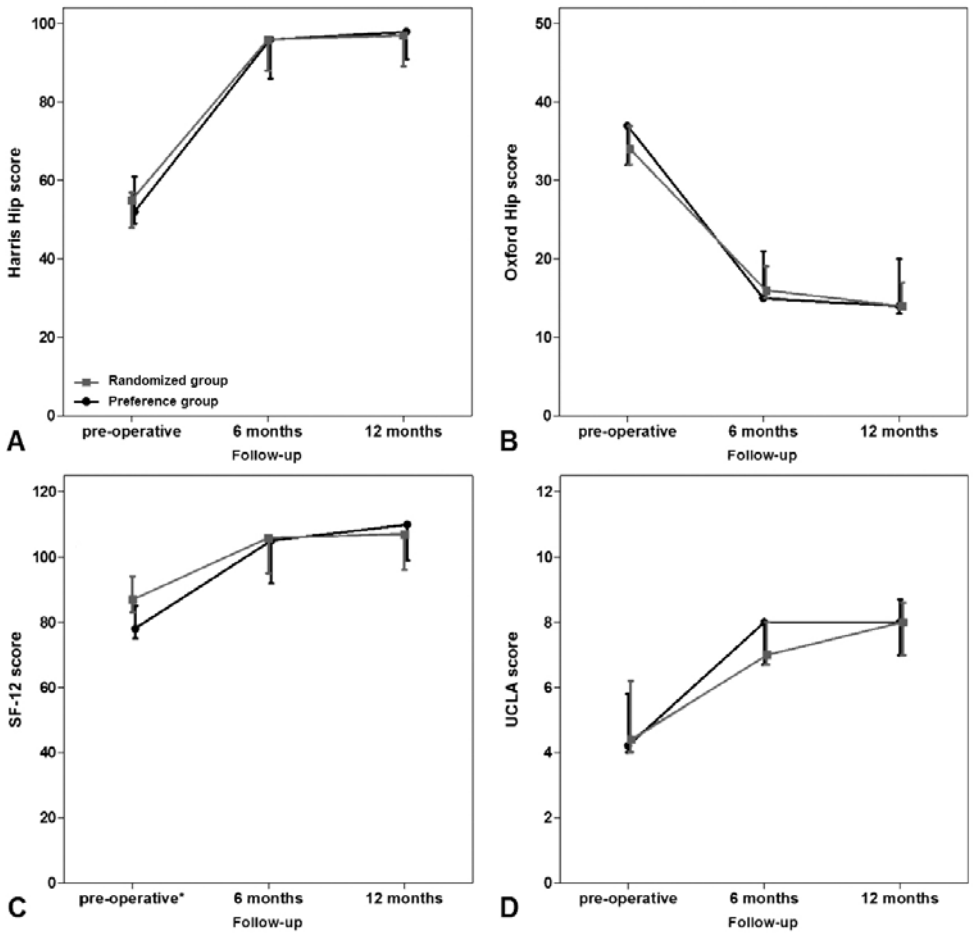


Figure 2 Clinical scores (HHS, Oxford, SF-12 and UCLA) with 95%-confidence interval pre-operatively, at 6 and 12 months. * In the horizontal axis of the SF-12 score represents a significant difference at baseline pre-operative scores (p<0.05).

The HHS, OHS, and UCLA scores all showed a postoperative improvement at 12 months compared to the pre-operative baseline scores for both groups (p<0.001) (Figure 2). These improvements were similar between the groups (p=0.8, p=0.7, and p=0.4, respectively). For the SF-12, however, at 12 months a better recovery was achieved from pre-operative levels in the 'preference' group than in the 'randomized' group (p=0.03). Patient satisfaction (VAS) was assessed at 6 and 12 months for both groups. Both groups had a high satisfaction score, with a median of 97 for the 'preference' group and 93 for the 'randomized' group at the 12-month follow-up (p=0.7β). Similar scores were obtained at the 6-month follow-up.

Two complications occurred in the 'preference' group. One patient had a perioperative collum fissure with a delayed, but uneventful, recovery — and with clinical and satisfaction scores that matched within the interquartile range. Another patient had complaints of possible anterior impingement of the RHA. This patient had clinical and satisfaction scores that dropped below the interquartile range. With exclusion of both patients, the median satisfaction score remained at 97 for the 'preference' group and 93 for the 'randomized' group (p=0.6β). With this exclusion, there were minimal changes in clinical scores, but with no consequences for the differences between the 'preference' group and the 'randomized' group (p=1.0, p=0.9, p=0.3, and p=0.01 for HHS, OHS, UCLA, and SF-12, respectively). The other 50 RHA's all had an uneventful clinical course.

Discussion

In this prospective comparative study, patient satisfaction and early clinical outcome in 'biased' patients with a high preference for resurfacing hip arthroplasty (the 'preference' group) did not differ statistically significantly from the results in unbiased patients who were simply allocated to an RHA after randomization in a separate randomized controlled trial (the 'randomized' group). There was, however, a trend toward better satisfaction in the 'preference' group. Only for the pre-operative SF-12 values, and for the mental subscale in particular, was any statistically significant difference between groups encountered, in favor of the 'randomized' group.

In spite of the fact that the potential bias from treatment preferences is a well-recognized phenomenon in orthopedic practice, there have only been a few studies dealing with this clinical dilemma. Van der Windt et al.,[3] for example, demonstrated a success rate of 85% in patients with shoulder pain who received their preferred therapy compared to a 64% success for those who underwent the same treatment against their preference. In another study,[5] any direct influence of preference for a certain therapy on shoulder pain could not be confirmed; however, the authors revealed that in general patients with a preference before randomization tended to have a better overall outcome than those with no preference.

Randomized controlled trials are usually regarded as the gold standard in comparing two therapeutic treatments, as they diminish possible confounding factors. To study the potential influence of preference bias on the outcome of one and the same surgical procedure, randomization is, however, not a feasible tool for obvious reasons. Our randomized controlled trial on THA and RHA confirmed for us the existence of patient preference for RHA; it was difficult to recruit patients for the trial. Many patients had a preference for RHA even after being informed about the absence of any evidence in the literature of a benefit of RHA over a conventional THA.[15,16] The presence of a cohort of patients with a clear preference for RHA

and a group of patients allocated to RHA after randomization enabled us to gain some insight into the possible role of preference bias.

Our study had some limitations, however. The number of patients in both groups was small, eventually resulting in a power of 59% to detect a clinical significant difference of 10 on the VAS for patient satisfaction in a post hoc power analysis. A power of 80% was calculated to detect a difference of 13 on the VAS for patient satisfaction. Clearly, there was a small difference in outcome between the groups and a larger number of patients may eventually have revealed a statistically significant difference in patient satisfaction between the groups. On the other hand, the power in our study was substantial enough for us to question whether such a difference would have been of clinical importance.

Another limitation of our study may have been the short follow-up. However, Khan et al. evaluated the Birmingham hip arthroplasty in a five to eight year follow-up study and demonstrated that the satisfaction rate did not change substantially after the first postoperative year.[14] Lingard et al. also showed a ceiling effect after one year.[17] In addition, it is debatable whether a potential difference in satisfaction after one year would be influenced by preference, because expectations would be most manifest in the short period after the operation.

Two patients with a bilateral prosthesis were included. One must assume that the outcome of two prostheses in the one patient cannot be interpreted independently. The result of the first prosthesis can either positively or negatively influence the outcome of the second, and vice versa.[19] Study outcome in general may be biased by this phenomenon; however, the number of bilateral prostheses in our study was low and exclusion of the two patients with bilateral prostheses did not have any consequences for our findings (data not shown).

Apart from the presence or absence of a profound preference for an RHA, both groups matched regarding most demographic features and pre-operative functional scores. The size of the femoral component of the implant was similar in both groups. This is important, as component size is known to influence the outcome of RHA.[20,21]

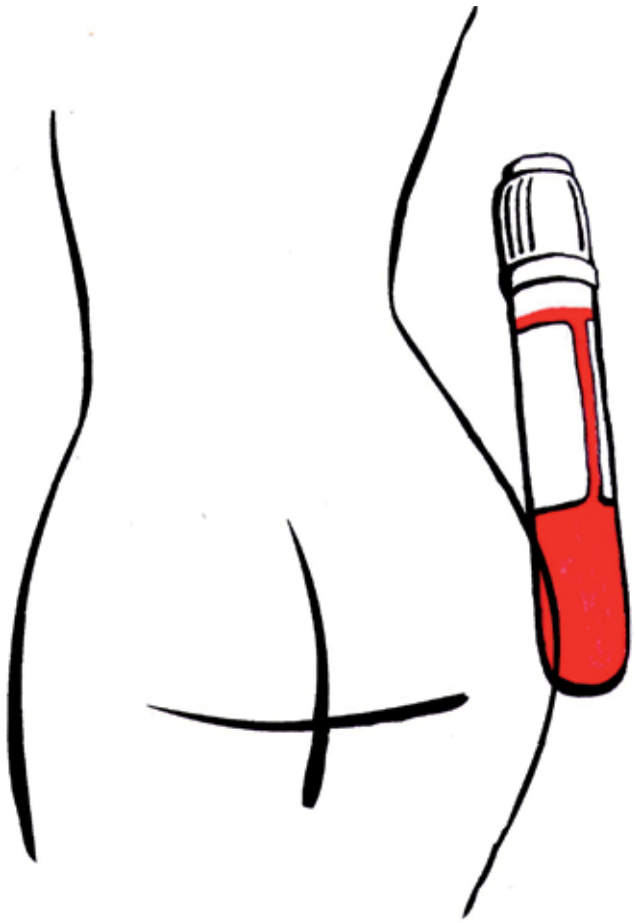
The only differences between the groups were age and pre-operative SF-12 score. The difference in age between the groups suggests that younger patients are less willing to participate in a randomized clinical trial. As for the SF-12, and for the mental subscale in particular, patients in the 'preference' group had a lower pre-operative score. There were no outliers that could explain this difference between the groups. One could argue whether there is reason to believe that patients with a high preference for a certain treatment generally have a different psychological profile than patients who are willing to participate in a randomized trial. This finding has been recognized before.[2]

In conclusion, we could not demonstrate any influence of preference on implant satisfaction and early clinical outcome in patients with an RHA. A trend towards a relatively higher degree of satisfaction was nevertheless established for patients with a specific request for RHA. The significant difference in mental subscale scores encountered between groups may indicate a difference in psychological profile.

References

1. Torgerson DJ, Klaber-Moffett J, Russell IT. Patient preferences in randomised trials: threat or opportunity? *J Health Serv Res Policy.* 1996;1(4):194-197.
2. McPherson K, Britton AR, Wennberg JE. Are randomized controlled trials controlled? Patient preferences and unblind trials. *J R Soc Med.* 1997;90(12):652-656.
3. van der Windt DA, Koes BW, van Aarst M, Heemskerk MA, Bouter LM. Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. *Br J Gen Pract.* 2000;50(454):371-374.
4. McPherson K, Britton A. Preferences and understanding their effects on health. *Qual Health Care.* 2001;10 Suppl 1:i61-66.
5. Thomas E, Croft PR, Paterson SM, Dziedzic K, Hay EM. What influences participants' treatment preference and can it influence outcome? Results from a primary care-based randomised trial for shoulder pain. *Br J Gen Pract.* 2004;54(499):93-96.
6. Klaber Moffett JA, Jackson DA, Richmond S, Hahn S, Coulton S, Farrin A, et al. Randomised trial of a brief physiotherapy intervention compared with usual physiotherapy for neck pain patients: outcomes and patients' preference. *BMJ.* 2005;330(7482):75.
7. McPherson K, Chalmers I. Incorporating patient preferences into clinical trials. Information about patients' preference must be obtained first. *BMJ.* 1998;317(7150):78; author reply 78-79.
8. National Joint Registry for England and Wales. 1st Annual report. Hemstead, England: *The National Joint Registry (NJR) Centre.* 2004; Available from: http://www.njrcentre.org.uk/njrcentre/Aboutthe NJR/Publicationsandreports/Annualreports/tabid/86/Default.aspx.
9. Chen S, Marin M, Estabrooks T, Amuah J, Zhu N. Hip resurfacing arthroplasty: Findings from the Canadian Joint Replacement Registry. Toronto, Canada: *Canadian Institute for Health Information.* 2009; Available from: http://secure.cihi.ca/cihiweb/en/downloads/cjrr_coa_poster_200907_e.pdf.
10. National Joint Registry for England and Wales. 6th Annual report. Hemstead, England: *The National Joint Registry (NJR) Centre.* 2009; Available from: http://www.njrcentre.org.uk/njrcentre/Aboutthe NJR/ Publicationsandreports/Annualreports/tabid/86/Default.aspx.
11. Pollard TCB, Baker RP, Eastaugh-Waring SJ, Bannister GC. Treatment of the young active patient with osteoarthritis of the hip: a five to seven-year comparison of hybrid total hip arthroplasty and metal-on-metal resurfacing. *J Bone Joint Surg Br.* 2006;88-B(5):592-600.
12. Vail TP, Mina CA, Yergler JD, Pietrobon RMD. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. *Clin Orthop Relat Res.* 2006;453:123-131.
13. Amstutz HC, Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA for patients younger than 50 years: Results of 2- to 9-year followup. *Clin Orthop Relat Res.* 2007;460:159-164.
14. Khan M, Kuiper JH, Edwards D, Robinson E, Richardson JB. Birmingham hip arthroplasty: five to eight years of prospective multicenter results. *J Arthroplasty.* 2009;24(7):1044-1050.
15. Mont M, Marker D, Smith J, Ulrich S, McGrath M. Resurfacing is comparable to total hip arthroplasty at short-term followup. *Clin Orthop Relat Res.* 2009;467(1):66-71.
16. Lavigne M, Therrien M, Nantel J, Roy A, Prince F, Vendittoli P-A. The John Charnley Award: The functional outcome of hip resurfacing and large-head THA is the same: A randomized, double-blind study. *Clin Orthop Relat Res.* 2010;468(2):326-336.
17. Lingard EA, Muthumayandi K, Holland JP. Comparison of patient-reported outcomes between hip resurfacing and total hip replacement. *J Bone Joint Surg Br.* 2009;91(12):1550-1554.
18. Witjes S, Smolders JM, Beaule PE, Pasker P, Van Susante JL. Learning from the learning curve in total hip resurfacing: a radiographic analysis. *Arch Orthop Trauma Surg.* 2009;129(10):1293-1299.

19. Bryant D, Havey TC, Roberts R, Guyatt G. How many patients? How many limbs? Analysis of patients or limbs in the orthopaedic literature: a systematic review. *J Bone Joint Surg Am.* 2006;88(1):41-45.
20. Crowninshield RD, Maloney WJ, Wentz DH, Humphrey SM, Blanchard CR. Biomechanics of large femoral heads: what they do and don't do. *Clin Orthop Relat Res.* 2004(429):102-107.
21. Prosser GH, Yates PJ, Wood DJ, Graves SE, de Steiger RN, Miller LN. Outcome of primary resurfacing hip replacement: evaluation of risk factors for early revision. *Acta Orthop.* 2010;81(1):66-71.



Metal ion interpretation in resurfacing versus conventional hip arthroplasty and in whole blood versus serum. How should we interpret metal ion data?

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Abstract

Metal ions generated from joint replacements are a cause for concern. There is no consensus on the best surrogate measure of metal ion exposure, both serum and whole blood measurements are used in clinical practice. This study provides a guideline for interpretation of metal ion analysis in clinical practice. In a prospective trial comparing hip resurfacing (RHA) with a conventional metal-on-metal (MoM) total hip arthroplasty (THA) cobalt and chromium levels were determined for whole blood and serum in 343 paired samples at regular intervals up to 24 months postoperatively. Cobalt whole blood and serum levels increased significantly after either implant. Cobalt concentrations were significantly higher for the RHA group, as compared to the THA group, at 3, 6 and 12 months for whole blood and serum. At 24 months cobalt levels decreased and differences between RHA and THA were no longer significant. In contrast, chromium whole blood levels remained significantly higher for RHA until 24 months. Whole blood and serum levels could not be used interchangeably. The mean difference for cobalt and chromium between blood and serum values were +0.13 µg/L and -0.91 µg/L respectively. Regression analysis provided a formula for conversion from serum to blood of *0.34 + [0.88 * Co serum]* for cobalt and *0.14 + [0.58 * Cr serum]* for chromium, with an acceptable prediction error below ±1.0 µg/L. Cobalt and chromium levels were significantly higher for RHA versus THA, especially during the run-in phase of one year. Overall, the metal ion levels were well below 5 µg/L. We cannot recommend the use of whole blood over serum measurements or vice versa. The provided conversion formula between whole blood and serum in combination with the presented practical guidelines may be useful for clinical practice.

Introduction

Hip resurfacing (RHA) has been re-introduced as an attractive bone preserving treatment option for young patients with osteoarthritis. In addition, 'in vitro' studies on the metal-on-metal (MoM) articulation revealed a twenty-fold reduction of volumetric wear in comparison with metal-on-polyethylene.[1,2] The relatively small size of these metal particles (6-834nm)[3] accounts for this decrease in volumetric wear, since the total number of particles is higher. Liberated metal ions may bind to proteins and cells[1,4] and can be transported elsewhere, resulting in elevated levels in blood, serum and urine.[2,5-7] These elevated systemic metal ion levels are a cause for concern. Reports of hypersensitivity reactions,[8,9] osteolysis[9,10] and the growth of liquid or solid soft tissue reactions[11,12] are available. There is increasing evidence that elevated levels of metal ions (especially cobalt) may have adverse long term systemic effects including polyneuropathy, cardiomyopathy and hypothyroidism.[13,14] The uncertainty about the consequences of these elevated metal ion levels has raised concerns and diminished the use and acceptance of MoM bearings.

In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA) has produced guidelines regarding the monitoring of systemic ion levels, and assay is recommended in cases with pain, adverse radiological abnormalities and small component head size. Metal ion measurements and a knowledge of their interpretation have thus become important.

Various matrices, such as whole blood (WB), serum (SE) and urine can be used. Analyses in whole blood or serum is preferable, since urine requires a 24-hour collection and the levels seem to be more variable due to variation in hydration of the patient.[15] Metal ion levels after different MoM hip implants have been reported.[16-19] However, most studies report on either metal ion concentrations in whole blood or serum, and data on repeated measurements over time are scarce, resulting in a lack of knowledge of how levels evolve over time. There may be superiority of serum over whole blood measurements, but whether these two levels can be correlated is not fully understood.

The aim of our study was to present prospective follow-up of cobalt (Co) and chromium (Cr) levels in both whole blood and serum in a group of patients with an RHA versus a conventional MoM total hip arthroplasty (THA). In addition, a conversion formula was generated to calculate serum from whole blood metal ion levels and practical guidelines were developed for clinical use in the interpretation of metal ion levels.

Patients and methods

Between May 2007 and April 2010 97 patients were prospectively followed in either a randomized controlled trial (RCT) comparing an RHA to a conventional MoM THA, or they participated in the cohort of RHA patients. Approval for both RCT and cohort was obtained from the regional ethics committee of the Radboud University Nijmegen Medical Centre (LTC 419-071206).

All patients agreed to sign an informed consent.

Table 1 Demographic data of the study population

	RHA (n=60)	THA (n=32)	p-value
Gender (men:women)	36:24	20:12	1.000 [b]
Median age in years (range)	55.3 (25-65)	59.1 (36-65)	0.106 [c]
Mean body mass index in Kg/m^2 (SD)	26.6 (4.8)	27.9 (5.2)	0.243 [d]
Pre-operative diagnosis (OA/AVN/CHD) [a]	57/1/2	30/0/2	0.786 [e]
Charnley category (A/B1/B2)	36/14/10	23/5/4	0.285 [e]
Mean operating time in minutes (SD)	78.1 (12.9)	55.5 (12.0)	<0.001 [d]
Median blood loss in mL (range)	300 (100-600)	275 (100-900)	0.653 [c]

[a] OA = osteoarthritis; AVN = avascular necrosis; CHD = congenital hip dysplasia. [b] Fisher's exact probability test, [c] Mann-Whitney U test, [d] Student's t-test. [e] Kruskall-Wallis test.

Table 2 Demographic data of specimens

	Cobalt (n=79)	Chromium (n=72)
Gender (men:women) (p-value)	48:31 (0.056)	39:33 (0.480)
Median femoral component size of RHA (range)	48 (42-54)	48 (42-54)
Total number of specimen	343	343
Number of specimen included	213	191
Below detection limit	130	152
Conserve/Metasul/Bilateral/No prosthesis	149/58/53/6	147/40/45/4

All patients under the age of 65 were asked to participate in the ongoing RCT. Patients who preferred not to participate but who requested RHA were followed in a separate cohort. Co and Cr levels were prospectively analysed in both whole blood and serum at consecutive time intervals. In the RHA group a resurfacing prosthesis was implanted with both components made of a cast, heat-treated solution-annealed Co-Cr alloy (Conserve® Plus; Wright Medical Technology, Arlington, Tennessee, USA). Mean resurfacing femoral head size was 48 mm (range 42-54). In the THA group, an uncemented tapered stem and a threaded titanium cup with a polyethylene insert with a metal liner was inserted (Zweymüller® Classic; Zimmer Orthopaedics, Warsaw, Indiana, USA) together with a metal 28 mm head (Metasul®; Zimmer Orthopaedics, Warsaw, Indiana, USA). A total of 343 paired whole blood and serum specimen were collected pre-operatively and at 3, 6, 12 and 24 months in 97 patients. 92 patients had a follow-up of more than 3 months. Metal ion levels below the detection limit of

0.5 µg/L were excluded in the statistical evaluation of the correlation between whole blood and serum levels and in generating a conversion formula. After exclusion of these baseline levels below the detection limit 213 Co specimens and 191 Cr specimens remained in 79 and 72 patients respectively. Demographic data of the study population and specimens are given in Table 1 and 2.

Cobalt and chromium blood levels

Blood samples were collected in metal-free vacutainers, the first 5 mL blood being discarded to eliminate metal contamination from the needle. A 6 ml BD 'EDTA' and a 5 ml 'SST II Advance' vacutainer system (Franklin Lakes, New Jersey, USA) was used for blood collection. After blood collection the tube with clot activator was set at rest for a minimum of 30 minutes and was then centrifuged at 3600 rpm for ten minutes. Both tubes were stored at a maximum of 4°C and sent within 7 days to the laboratory of Toxicology of the University Hospital Ghent (Belgium) for analysis. The metal ion levels in serum and whole blood were determined using an inductively-coupled plasma mass spectrometer (ICP-MS) on a Perkin Elmer Elan DRC-e, equipped with a standard cross-flow nebuliser and a Dynamic Reaction Cell (Perkin Elmer SCIEX, Canada).

Statistical analysis

Since metal ion data are not normally distributed they are represented by the median, and a non-parametric test (Mann-Whitney U) was used for analysis. The agreement between whole blood and serum levels was assessed with mean difference, regression analysis and the Bland-and-Altman limits-of-agreement between methods of measurement with multiple observations per individual, as is proposed by Bland-and-Altman.[20] In this study several measurements in the same patients were used. Therefore we used the modification from Bland-Altman with adjustment for the repeated measurements.[21]

The multiple observations per individual can have influence on the regression analysis. Therefore prior to this analysis a mixed model analysis was used to analyse the influence of the repeated measurements on the linear regression. The Null Model Likelihood Ratio Test showed a p-value of >0.05 for all tests, indicating that there is no significant difference between a regression with ignorance of the repeated measurements and the regression with adjustment for the repeated measurements. As a result the simple linear regression with the equation 'whole blood level = $\alpha+\beta$*serum level' was used for all analyses in this study. To validate our regression equation we randomly split the database into two. The patients in the first section were used to calculate a regression equation which could be tested on the second section. The data was processed in SPSS (Version 15.0 SPSS Inc. Chicago, IL) and analysed for statistical differences. Statistical significance was set at $p \leq 0.05$.

Results

RHA versus THA metal ion levels

Patient characteristics are described in Table 1. The mean operating time was longer for RHA (p<0.001), but median blood loss was equal between the two groups.

The concentrations of Co and Cr in whole blood and serum for RHA versus THA for each time interval are summarised in Table 3 and Figures 1A and 1B. Baseline pre-operative Co and Cr concentrations were, as expected, below the detection level of 0.5 µg/L for both groups.

Table 3 Cobalt and chromium concentrations

	Pre-operative		6 months		12 months		24 months	
	RHA	THA	RHA	THA	RHA	THA	RHA	THA
Cobalt								
	(n=60)	(n=32)	(n=51)	(n=30)	(n=42)	(n=23)	(n=21)	(n=8)
WB	0.10 (0.1-2.7)	0.10 (0.1-1.8)	1.30 [a] (0.1-10.6)	0.90 [a] (0.1-4.0)	1.40 [a] (0.6-11.5)	1.10 [a] (0.1-2.2)	1.20 (0.7-16.3)	1.00 (0.1-1.6)
SE	0.10 (0.1-2.6)	0.10 (0.1-1.3)	1.20 [a] (0.1-11.4)	0.65 [a] (0.1-4.1)	1.30 [a] (0.1-11.4)	0.80 [a] (0.1-1.9)	1.50 (0.7-17.6)	0.70 (0.1-1.4)
Chromium								
	(n=60)	(n=32)	(n=51)	(n=30)	(n=42)	(n=23)	(n=21)	(n=8)
WB	0.10 (0.1-4.2)	0.10 (0.1-0.8)	1.20 [a] (0.1-5.9)	0.10 [a] (0.1-2.9)	0.90 (0.1-6.0)	0.40 (0.1-1.9)	1.10 [a] (0.1-8.4)	0.55 [a] (0.1-2.1)
SE	0.1 (0.1-2.7)	0.1 (0.1-2.9)	1.90 [a] (0.1-8.8)	0.60 [a] (0.1-4.9)	2.30 [a] (0.1-10.2)	0.90 [a] (0.1-2.9)	1.90 [a] (0.9-14.4)	0.85 [a] (0.1-3.4)

Values (µg/L) are given as the median (range). WB = whole blood, SE = serum. [a] Significant difference between RHA and THA (Mann-Whitney signed-rank).

Co whole blood and serum levels increased after implantation of an RHA (p<0.001) and a THA (p=0.015 (WB) and p=0.002 (SE)). Co concentrations were higher for HR compared to THA at 3, 6 and 12 months for whole blood (p<0.001, p=0.001, p=0.026) and serum (p<0.001, p<0.001, p=0.007). At 24 months Co levels stabilised and the initially statistically significant difference between HR and THA could no longer be detected for whole blood (p=0.082) and serum (p=0.53). Postoperative Cr levels of RHA patients increased compared to the pre-operative levels for whole blood and serum (p<0.001). The THA patients showed a solitary increase for serum (p<0.001), while whole blood concentrations remained stable (p=0.243). Cr concentrations were higher for RHA at 3, 6 and 24 months for whole blood (p<0.001, p<0.001, p=0.021), and at all follow-up intervals for serum (p<0.001).

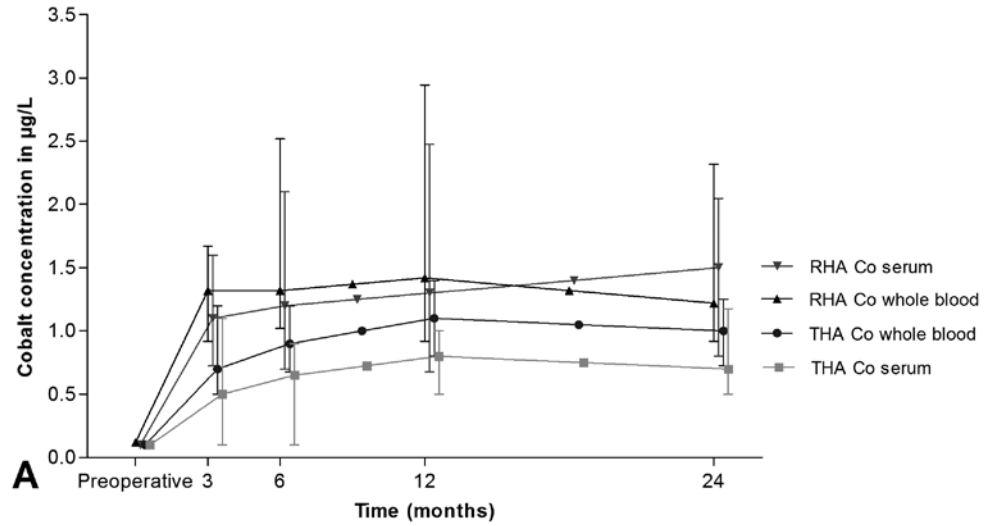


Figure 1 A Error-plot (median and IQR) cobalt concentrations in whole blood and serum in µg/L. **B** Error-plot (median and IQR) chromium concentrations in whole blood and serum in µg/L.

Whole blood versus serum

Demographics of specimen-specific patient data are given in Table 2. The mean difference between serum and whole blood was +0.13 µg/L for Co (95%-CI:0.03;0.22) and -0.91 µg/L for Cr (95%-CI:-1.05;-0.77). There was a statistically significant difference between whole blood and serum levels for Co (p=0.01) and Cr (p<0.001). Despite this difference, Co and Cr levels in whole blood and serum were highly correlated: Co R=0.936 (p<0.001) and Cr R=0.937 (p<0.001).

A Bland-and-Altman analysis showed limits-of-agreement of +1.5 µg/L and -1.25 µg/L

with a mean difference of +0.13 µg/L for Co (Figure 2A). This means that Co levels in whole blood are on average +0.13 µg/L higher compared to serum and that 95% of these differences between blood and serum levels appeared to be between +1.5 µg/L and -1.25 µg/L. For Cr the correlation between whole blood and serum levels was obscured by an increase in difference at higher mean concentrations. There was a mean difference between whole blood and serum of -0.91 µg/L with relatively wide limits-of-agreement between +0.95 µg/L and -2.85 µg/L. The tendency of an increase in difference between whole blood and serum at higher mean concentrations is visualised by a diagonal trend in the Bland-Altman plot (Figure 2B).

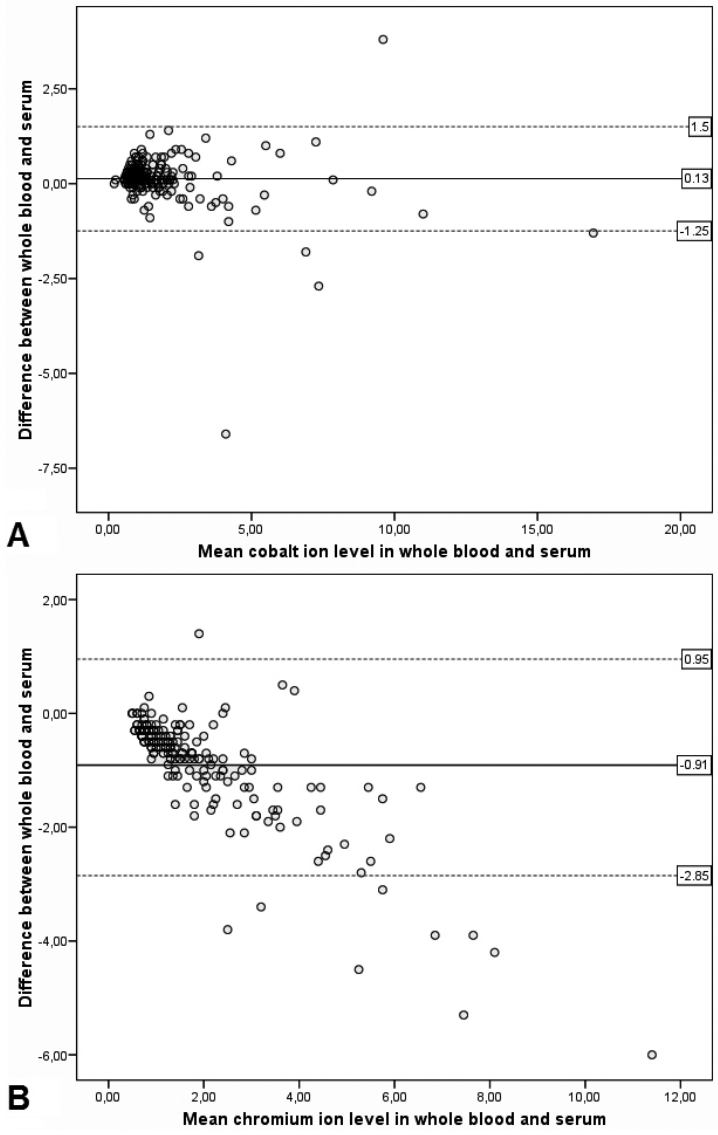


Figure 2 A Cobalt standard Bland-Altman plot. **B** Chromium standard Bland-Altman plot. In both graphs the black line illustrates the mean difference between metal ion levels in serum and whole blood and the two gray parallel lines illustrate subsequently indicate the 1.96 standard deviation of this difference or 'limits-of-agreement'.

We calculated a conversion formula for serum metal ion levels into whole blood metal ion levels by regression analysis. The following formula was established for cobalt: *Co whole blood = 0.34 + [0.88 * Co serum]*, and for chromium: *Cr whole blood = 0.14 + [0.58 * Cr serum]*.

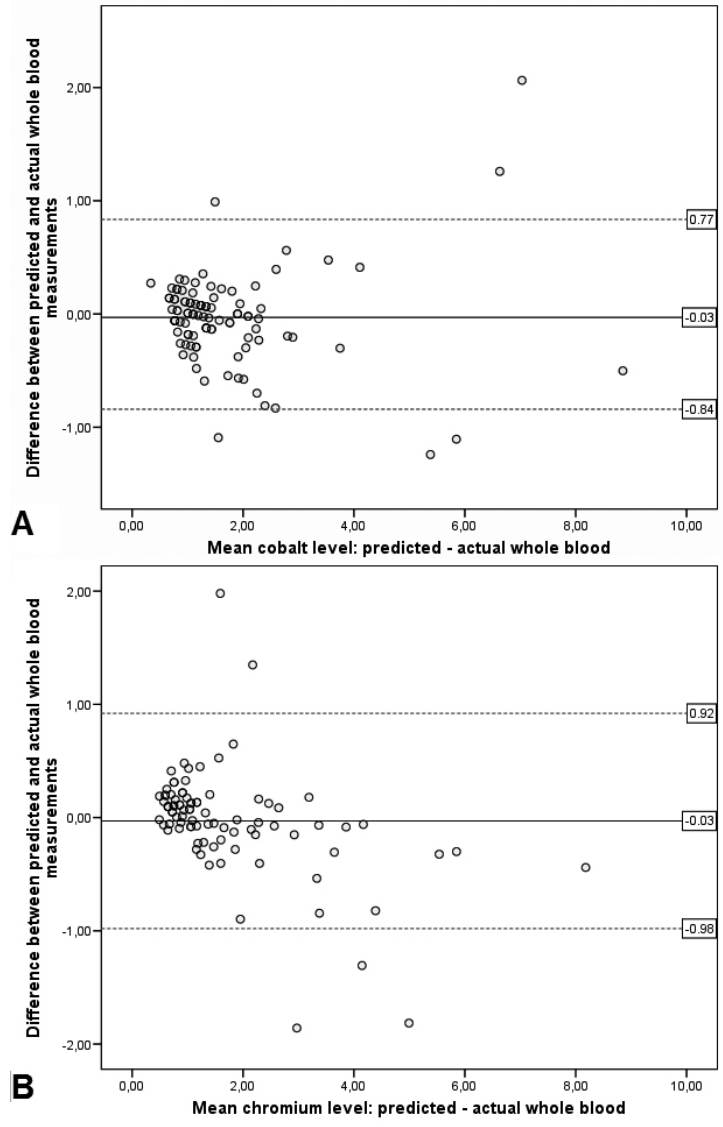


Figure 3 A Predicted cobalt levels compared to the actual blood levels. **B** Predicted chromium levels compared to the actual blood levels. In both graphs the black line illustrates the mean difference between predicted and real metal ion levels in serum and whole blood and the two gray parallel lines illustrate subsequently indicate the 1.96 standard deviation of this difference or 'limits-of-agreement'.

Validation of prediction model blood versus serum

In order to validate the conversion formula, we randomly divided our database in two. A similar regression analysis on half of the database provided a conversion formula which was subsequently tested on the second half of the database. The newly obtained conversion

formulae were *Co whole blood = 0.29 + [0.89 * Co serum]* and *Cr whole blood = 0.21 + [0.54 * Cr serum]*. Serum levels from the second half of the database were used to predict whole blood levels, and compared to the actual measured values. The Bland-Altman test was computed as the difference between the measured and predicted value (Figures 3A and B). The mean difference between measured and predicted values of Co and Cr was 0.0 µg/L. Limits-of-agreement for the difference between predicted and measured Co whole blood levels were +0.77 µg/L and -0.84 µg/L. In relation to Cr these limits were +0.92 µg/L and -0.98 µg/L. There was no difference between predicted and actual measured whole blood values of Co (p=0.411) and Cr (p=0.561).

Discussion

The evaluation of metal ion levels is becoming increasingly important after a MoM hip arthroplasty and serves as an indicator of bearing performance and device safety.[19] In this study, RHA revealed a higher initial increase in Co and Cr concentrations than a conventional MoM 28mm THA. After a run-in phase, this difference in Co levels between the two groups resolved, but Cr levels were still higher for the RHA group. Because Co is known to be a relatively toxic ion,[13,22] it is important to note that Co levels decrease after a run-in phase of 12 months.

It is clear from our observations that increased metal ion levels are not exclusively seen in RHA patients, and over time metal ion levels after RHA may approach values following a MoM THA. These findings are consistent with previous reports; which suggest that after five years there is no difference in metal ion concentrations following large-diameter resurfacing and a small-diameter MoM THA.[17]

Unlike some reports following the use of a variety of RHA devices, the metal ion levels following both RHA and THA used in our study appeared to be rather low.[16,17,19] Implant-related differences are present in metal ion release and this should be taken into account as one of the confounding factors in the interpretation of our results. Furthermore, it has to be recognised that the mechanism and source of metal debris may also be different for RHA compared to MoM THA. In general metal ions and particles are generated both by wear from the articulation and by corrosion. In addition to metal ion release from the bearings, a THA may create metal debris from the taper junction with the head. This may thus have influenced metal ion concentrations in peripheral blood in the THA group However, the source of metal ion release should not influence the relationship between metal ion levels in serum versus whole blood as evaluated in our study. Metal ion levels may be influenced by renal excretion, protein binding and transport, and extremely high levels of Co may occur in patients with renal dysfunction, and therefore MoM bearings are contraindicated in these patients.[23] High levels can also be related to other sources of metal ion release, such as mechanical heart valves, orthodontic implants, medical or nutritional supplements containing metal ion 'equivalents' or environmental and/or occupational sources of metal contamination. All patients in our study were carefully monitored for the potential presence of these other sources of metal

ions. These confounding factors should always be taken into consideration when confronted by high metal ion levels, and remain an obstacle in the interpretation of metal ion levels.

Regarding the differences between serum and whole blood, Co serum levels were slightly lower or equivalent to whole blood, which was represented by a mean difference of only +0.13 µg/L. For Cr, serum levels were relatively high compared to whole blood, indicated by a mean difference of -0.91 µg/L. Our results correspond with earlier data from Walter et al, who found little difference between whole blood and serum for Co, but higher serum levels compared to whole blood for Cr.[6] Studies that examine the difference between metal traces in whole blood and serum are rare. Daniel et al. studied the suitability of whole blood and serum for measurement of ion levels, but the limits-of-agreement between whole blood and serum for Co and Cr were relatively wide as compared to our data with +3.8 µg/L; -2.2 µg/L for Co and +8.4 µg/L; -4.2 µg/L for Cr.[7] This finding may be explained by differences in collection and processing of the samples, and the fact that Daniel et al. studied a group of miscellaneous types of resurfacing implants each with unique metallurgy.[24,25]

Daniel et al. suggested whole blood as a superior matrix over serum metal ion measurements,[7] but from our data we cannot recommend whole blood over serum or 'vice versa'. From a practical point of view, the use of whole blood may be preferred, since whole blood can be sent to the laboratory without separation of serum, a step which can introduce pollution to the sample. The option of a conversion formula to extrapolate serum to whole blood metal ion levels is attractive for obvious reasons. Based on the wide limits-of-agreement of the Bland-Altman plot we do not believe that the two blood fractions can be used interchangeably. However, conversion between whole blood and serum remains possible. The conversion formulae, as provided in this study, can be used with limits-of-agreement that are within acceptable range (Figures 3A and B). For both metal ions the whole blood and serum levels could be predicted from one another with a prediction error below 1.0 µg/L. The prediction error is obtained from testing on a homogeneous group of patients, and verification on a heterogeneous group might be helpful. The conversion formula is best used for the lower boundary of metal ion levels and may offer reassurance to the clinician in interpreting metal ion levels. The provided levels can subsequently be balanced to the upper acceptable limits. Higher values cannot be predicted without accepting a greater prediction error, but we believe that prediction of these values from serum to whole blood is of less clinical significance since the values are usually already in the pathological range, and indicative of malfunctioning of the implant.

There are some weaknesses in our study. The number of available samples at 24 months was limited, which may have contributed to the observed non-significant difference in Co levels between both implants. Further follow-up of these patients will eventually resolve this. Co has a smaller variability compared to Cr, but is recognised to be more toxic both in particle and ion form. It is therefore important to follow Co ion levels closely. We also recognise some limitations in the conversion formulae presented. The conversion formula is particularly

valuable for the concentrations in the range of 2-5 µg/L, both because its prediction error is lowest in the lower range and because the lower values are of clinical importance for the evaluation of implant performance. Since the vast majority of metal ions should be below 5 µg/L it may not be clinically relevant to be able to predict a serum or whole blood level knowing that it is already in the higher range. The formulae can be used for reassurance in clinical practice. A low serum level, for example, will never be correlated with a high whole blood level. Only one clinical sample (either whole blood or serum) can be used to conform to safety guidelines referring to serum or whole blood levels.

It is extremely important in clinical practice to know the upper acceptable levels for metal ions. The best-defined reference values are the *exposure equivalent of carcinogenic substances* (EKA values)[26] for industrial workers and the Mayo Medical Laboratories interpretive handbook.[27] The upper limits are defined for Co at 5 µg/L in whole blood and for Cr at 17 µg/L in erythrocytes (no whole blood upper limits reported).[26] In addition to these reference values, De Smet et al. analysed metal ion levels in patients with a well-functioning versus a malfunctioning RHA and proposed that serum Co and Cr levels up to respectively 4.4 µg/L (odds ratio for revision 6.0) and 5.1 µg/L (odds ratio for revision 4.3) are acceptable as upper limits. Metal ion levels higher than twice these upper limits are very likely to be associated with poor clinical outcome.[28] The median ion levels of our study are well below this limit, although a few outliers were still encountered. The North Tees group (UK) state that patients with Co values between 2-5 µg/L have to be followed clinically and patients with Co values above 5 µg/L have to be evaluated with cross-sectional imaging.[29] In patients with clearly elevated levels, revision should be considered or anticipated.

We have summarised our results together with data from the literature in an attempt to produce some guidelines (Table 4) which may help the orthopaedic surgeon regarding the use and interpretation of metal ion levels in patients with a MoM hip arthroplasty. It is important to emphasise again that these guidelines can only be seen as an aid to the clinician in decision making and certainly not as an absolute reference tool. Numerous limitations exist, but since the topic of the interpretation of metal ion levels is becoming increasingly important we believe our study may help the clinician towards understanding of this difficult topic.

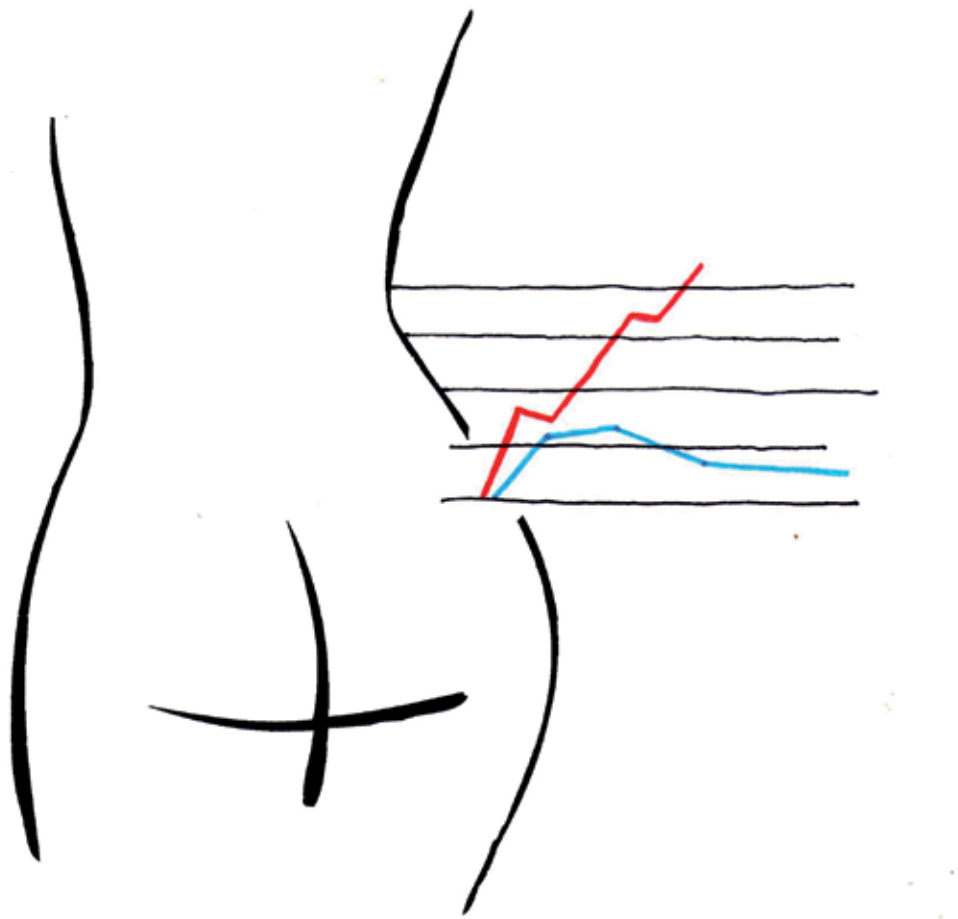
Table 4 Practical guidelines for the interpretation of metal ion levels in patients with a MoM hip arthroplasty

Type of Analysis	No superiority of whole blood or serum; whole blood may be favored for practical reasons depending on local preference Inductively-coupled plasma mass spectrometer (ICP-MS) method of first choice
RHA versus THA [a]	Metal ion levels are significantly higher for RHA versus THA. This difference decreases after the run-in phase, in particular for cobalt
Metal ion measurement	Serum ≠ whole blood Toxicity: Cobalt > Chromium
Cobalt	Serum > and < whole blood Co blood = Co serum + 0.13 µg/L (95%-CI:0.03;0.22) Conversion formula (prediction error <1 µg/L): Co whole blood = 0.34 + [0.88 * Co serum]
Chromium	Serum (in general) > whole blood Cr blood = Cr serum - 0.91 µg/L (95%-CI:-1.05;-0.77) Conversion formula (prediction error <1 µg/L): Cr whole blood = 0.14 + [0.58 * Cr serum]
Confounding Factors	Renal impairment 'Contamination' by nutritional supplements, medication, other metal implants Implant type and positioning
High levels	Associated with an increased risk of a malfunctioning implant. Close monitoring is indicated with levels: - Cobalt serum concentration >4.4 µg/L - Chromium serum concentration >5.1 µg/L

[a] This conclusion applies for the implants used in this study and may differ for other implants.

References

1. Amstutz HC, Campbell P, McKellop H, Schmalzreid TP, Gillespie WJ, Howie D, et al. Metal-on-metal total hip replacement workshop consensus document. *Clin Orthop Relat Res.* 1996(329 Suppl):S297-303.
2. Sieber HP, Rieker CB, Kottig P. Analysis of 118 second-generation metal-on-metal retrieved hip implants. *J Bone Joint Surg Br.* 1999;81(1):46-50.
3. Doorn PF, Campbell PA, Worrall J, Benya PD, McKellop HA, Amstutz HC. Metal wear particle characterization from metal-on-metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. *J Biomed Mater Res.* 1998;42(1):103-111.
4. Case CP, Langkamer VG, James C, Palmer MR, Kemp AJ, Heap PF, et al. Widespread dissemination of metal debris from implants. *J Bone Joint Surg Br.* 1994;76(5):701-712.
5. Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. *Clin Orthop Relat Res.* 1996(329 Suppl):S233-243.
6. Walter LR, Marel E, Harbury R, Wearne J. Distribution of chromium and cobalt ions in various blood fractions after resurfacing hip arthroplasty. *J Arthroplasty.* 2008;23(6):814-821.
7. Daniel J, Ziaee H, Pynsent PB, McMinn DJ. The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. *J Bone Joint Surg Br.* 2007;89(6):736-741.
8. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. *J Biomed Mater Res.* 2001;56(3):427-436.
9. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am.* 2005;87(1):28-36.
10. Park YS, Moon YW, Lim SJ, Yang JM, Ahn G, Choi YL. Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg Am.* 2005;87(7):1515-1521.
11. Boardman DR, Middleton FR, Kavanagh TG. A benign psoas mass following metal-on-metal resurfacing of the hip. *J Bone Joint Surg Br.* 2006;88(3):402-404.
12. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90(7):847-851.
13. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: A review of current knowledge and future strategies. *J Bone Joint Surg Br.* 2007;89-B(5):567-573.
14. Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M. Polyneuropathy caused by cobalt–chromium metallosis after total hip replacement. *Muscle Nerve.* 2010;42(1):140-143.
15. MacDonald SJ, Brodner W, Jacobs JJ. A consensus paper on metal Ions in metal-on-metal hip arthroplasties. *J Arthroplasty.* 2004;19(8 suppl. 3):12-16.
16. Antoniou J, Zukor DJ, Mwale F, Minarik W, Petit A, Huk OL. Metal ion levels in the blood of patients after hip resurfacing: A comparison between twenty-eight and thirty-six-millimeter-head metal-on-metal prostheses. *J Bone Joint Surg Am.* 2008;90(Suppl 3):142-148.
17. Moroni A, Savarino L, Hoque M, Cadossi M, Baldini N. Do ion levels in hip resurfacing differ from metal-on-metal THA at midterm? *Clin Orthop Relat Res.* 2011;469(1):180-187.
18. Garbuz D, Tanzer M, Greidanus N, Masri B, Duncan C. The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: A randomized clinical trial. *Clin Orthop Relat Res.* 2010;468(2):318-325.
19. Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin Orthop Relat Res.* 2005;438:177-181.
20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1(8476):307-310.
21. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat.* 2007;17(4):571-582.
22. Kwon YM, Xia Z, Glyn-Jones S, Beard DJ, Gill HS, Murray DW. Dose-dependent cytotoxicity of clinically relevant cobalt nanoparticles and ions on macrophages in vitro. *Biomed Mater.* 2009;4(2):[Epub].
23. Hur CI, Yoon TR, Cho SG, Song EK, Seon JK. Serum ion level after metal-on-metal THA in patients with renal failure. *Clin Orthop Relat Res.* 2008;466(3):696-699.
24. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br.* 2008;90-B(10):1291-1297.
25. Griffin W, Nanson C, Springer B, Davies M, Fehring T. Reduced articular surface of one-piece cups: A cause of runaway wear and early failure. *Clin Orthop Relat Res.* 2010;468(9):2328-2332.
26. Morgan MS, Schaller KH. An analysis of criteria for biological limit values developed in Germany and in the United States. *Int Arch Occup Environ Health.* 1999;72(4):195-204.
27. Serum Cobalt (80084) and Serum Chromium (8638) [Web page] New England, Massachusetts: *Mayo Medical Laboratories.* 2010; Available from: http://www.mayomedicallaboratories.com/test-catalog/alphabetical/C.
28. De Smet K, Campbell PA, Van Orsouw M, Backers K, Gill HS. Interpretation of metal ion levels after metal-on-metal resurfacing. *Proc AAOS.* 2010;Poster Presentation Number: P100.
29. Langton DJ, Jameson SS, Joyce TJ, et al. Accelerating failure rate of the ASR total hip replacement secondary to taper junction failure. *J Bone Joint Surg Br.* 2011;93(8):1011-1016



Metal ion trend may be more predictive for malfunctioning metal-on-metal implant than single metal ion measurement

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Hip International, in press

Abstract

Forty-eight unilateral hip resurfacing arthroplasty patients were evaluated for cobalt and chromium levels. The metal ion trend of 42 well-functioning patients was compared with 6 sub-optimal functioning patients. Median metal ion levels were significantly higher for the sub-optimal group. For the well-functioning implants, the percentage of patients with increasing cobalt/chromium levels between two consecutive time-intervals ('risers') gradually decreased from 90/86% (0-3 months) to 22/22% (24-36 months). The percentage of patients with increasing metal ion levels was higher in the sub-optimal group. The median absolute increase of this 'risers' subgroup was significantly lower for the well-functioning group at 12-24 months. Sub-optimal functioning MoM-implants have a different metal ion trend than well-functioning implants, a higher chance of 'risers' and a larger absolute increase in time.

Introduction

Hip resurfacing arthroplasty (RHA) is an attractive treatment option for young and active patients with osteoarthritis, however, over the last few years increasing concern has been raised. Exposure to metal ions over an extended period are a major cause of concern, as there are reports on hypersensitivity reactions, osteolysis and soft tissue reactions.[1-3] In addition to these local effects, there is increasing evidence that elevated levels of metal ions, may have adverse long term systemic effects like polyneuropathy, cardiomyopathy and hypothyroidism.[4-5]

The uncertainty about the consequences of these elevated metal ion levels in most patients, together with the occasionally encountered serious adverse events, has raised concerns and tempered the use and acceptance of metal-on-metal (MoM) bearings. In response, the Medicines and Healthcare products Regulatory Agency (MHRA, UK) recommends in an official alert to control cobalt (Co) and chromium (Cr) blood levels at least once postoperatively and/or perform cross-sectional imaging if these levels are above 7 ppb (or µg/L).[6] Metal ion measurements have thereby become an important tool in the diagnostic work-up of a malfunctioning MoM implant and the orthopaedic surgeon is expected to know how to interpret them.

In spite of abundant ongoing research on defining the best cut off level to differentiate between well-functioning and sub-optimal functioning implants, to date there is no consensus on which levels are acceptable.[6,7] In addition to this confusion there is literature available on well-performing implants with relatively high levels of metal ions and malfunctioning implants with low values.[8-14] In summary we must conclude that we do not fully understand the clinical significance of a single metal ion measurement and its interpretation. However, on the other hand clinicians are confronted with guidelines urging at least one metal ion analysis and with patients subsequently asking whether their values are too high or not.

We hypothesize that the trend in these metal ion levels in time may be more informative then single measurements alone, since the latter frequently raise more questions then they answer. Several studies already reported on repeated metal ion measurements after RHA,[15-18] however, there are none with a specific trend evaluation. The aim of this study was therefore to present a prospective follow-up of Co and Cr levels in a cohort of unilateral RHA's and potentially identify differences in the trend characteristic in the short-term between patients with well versus sub-optimal functioning implants.

Patients and methods

Study design

Between May 2007 and June 2012 sixty patients with an RHA were prospectively followed in either a randomized controlled trial (RCT) comparing an RHA to a conventional MoM THA, or in a cohort of RHA patients.[22,23] Approval for both RCT and cohort was obtained from the regional ethics committee (LTC 419-071206). All patients agreed to sign an informed consent. All patients under the age of 65 were asked to participate in the ongoing RCT; patients who denied participation and had a profound preference for an RHA were followed in a separate cohort.

Twelve patients were excluded from the study because of; bilateral RHA (n=7), missing metal ion measurements (n=4) and evident femoral loosening (n=1). The latter case was excluded because in this study we were interested in a possible difference in metal ion trend in patients with suboptimal clinical scoring and otherwise normal radiographs. Because the decision for revision in this patient was already made based on his evident radiographic loosening, the metal ion measurement may have biased our findings. This study will therefore present the results of 48 patients with a unilateral RHA and a minimum (and median) follow-up of 24 months. Based on their most recent Harris Hip Score (HHS) we divided the study patients in well and sub-optimal functioning. A HHS ≥90 was defined as 'well-functioning' (n=42), a HHS <90 was defined as 'sub-optimal functioning' (n=6). The clinical outcome was measured preoperatively and at 6, 12, 24 and 36 months by Oxford Hip Score (OHS), satisfaction on visual analogue scale (VAS), University of California Los Angeles (UCLA) activity score and 12-item Short Form Health Survey (SF-12). In this study the outcome score at most recent follow-up was used.

Surgical technique

Preoperative digital templating for positioning of the implant was implemented in all patients. All operations were performed by three experienced hip surgeons through a posterolateral approach. The surgical technique has been described earlier.[18,19] The resurfacing prosthesis was made of a cast, heat-treated solution-annealed Co-Cr alloy (Conserve® Plus; Wright Medical Technology, Arlington, Tennessee, USA; FDA approved). The femoral component was cemented and the hydroxyapatite (HA)-coated acetabular component, underreamed by 1 mm, was press-fitted in the acetabulum. Antibiotic prophylaxis with Cephalosporin preoperative and 24 hours postoperative, periarticular ossification prophylaxis by three days of Diclophenac, and thrombosis prophylaxis with Nadroparine during hospital admittance and six weeks after were given. Patients were rehabilitated with immediate unrestricted weight bearing according to patient's tolerance.

Metal ion blood levels

Blood samples were collected and assessed on Co and Cr serum concentrations preoperatively and at consecutive time intervals until 36 months postoperatively (3, 6, 12, 24 and

36 months). Blood samples were collected in metal-free vacutainers and taken using a standardized technique to minimize the risk of contamination: a plastic intravenous cannula was inserted, the metal needle removed and the first 5 mL blood was discarded to eliminate metal contamination. Serum blood tubes were stored at 4°C, send the same day to the laboratory of Toxicology of the University Hospital Ghent (Belgium) and analyzed within seven days.

Metal ion analysis

The metal ion levels in serum were determined using an inductively-coupled plasma mass spectrometer (ICP-MS). The trend line of median values was calculated, and presented in Table 2 and plotted in Figure 2. To obtain a 'percentage of patients with an increase in their metal ion level' we determined at each time-interval between subsequent analyses whether Co or Cr concentration for each patient increased, stabilized or decreased. This way for each time interval between two analyses the percentage of 'risers' could be calculated. This metal ion increase percentage is graphically presented in Figure 3. In addition, the actual 'quantitative increase' was also calculated for each time interval by taking the median value of the elevation in metal ion level for this subgroup of 'risers'. The quantitative increase of both Co and Cr in the subgroups of 'risers' for both groups of well and sub-optimal functioning patients is presented in Table 3.

Statistical analysis

Metal ion data distributions were asymmetric and therefore expressed as a group median with range. Symmetrical data are represented by a mean and standard deviation (SD). The following formal null hypothesis was used: there is no difference in metal ion trend between patients with a well- or sub-optimal functioning hip resurfacing. To test this null hypothesis the Mann-Whitney U test was used. Concerning study characteristics no a priori power analysis could be performed and combined with the small number of patients in the sub-optimal functioning group, this study can be considered an exploratory trial. Differences were considered statistically significant at $p<0.05$. All statistical analyses were performed using SPSS software (Version 18.0).

Results

Patient characteristics are presented in Table 1: age, BMI, gender en peroperative factors were comparable between the two groups. Clinical outcome scores were plotted against Co values per time interval in Figure 1. The clinical outcome scores show, in addition to the expected significant difference in HHS (<0.001), a significant difference in OHS (p=0.008), UCLA activity score (p=0.012) and SF-12 (p=0.002), all in favor of the well-functioning implants. There is a trend for less VAS satisfaction in de sub-optimal functioning group, but this was not significant (p=0.069).

Table 1 Patient characteristics and clinical outcome scores, values are median (range)

	Well-functioning (n=42)	Sub-optimal functioning (n=6)	p-value
Patient characteristics			
Gender (women/men)	16/26	3/3	0.581
Mean BMI (SD)	26.3 (2.9)	24.3 (3.5)	0.121
Age at operation in years	55.1 (34-65)	56.5 (44-64)	0.524
Diagnosis (OA/CHD) [a]	41/1	5/1	0.105
Femoral head size	49 (42-54)	48 (42-52)	0.558
Clinical outcome at latest follow-up			
HHS	100 (91-100)	78 (59-89)	<0.001
OHS	13 (12-27)	21 (13-25)	0.008
VAS Satisfaction	94 (62-100)	68 (30-100)	0.069
UCLA Activity score	8 (3-10)	5.5 (3-8)	0.012
SF-12 Total score	110 (71-117)	89 (81-103)	0.002

[a] OA = osteoarthritis; CHD = congenital hip dysplasia.

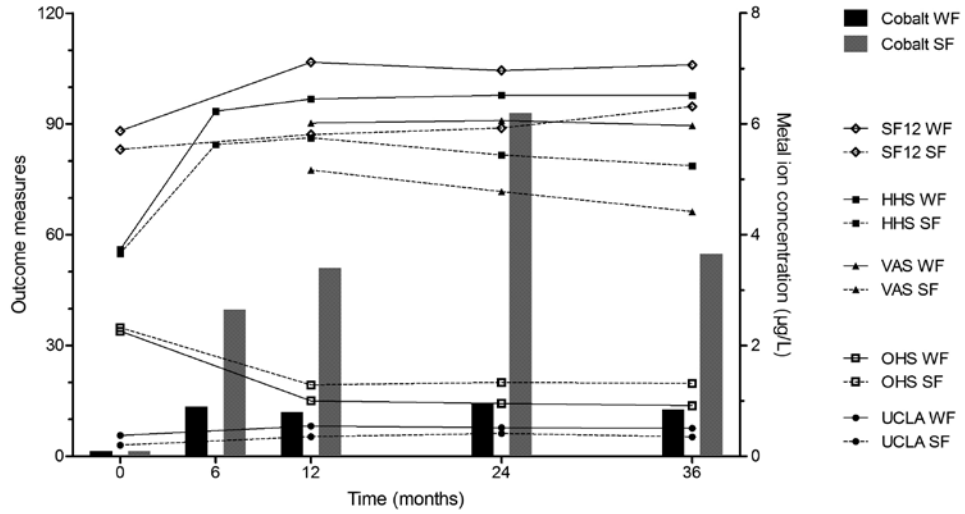


Figure 1 Representation of the median clinical outcome scores (left y-axis) and cobalt concentration (right y-axis) per time interval per group. WF = Well-functioning group; SF = Sub-optimal functioning group; SF-12 = 12-item short form health survey; HHS = Harris hip score; VAS = Satisfaction on visual analogue scale; OHS = Oxford hip score; UCLA = University of California Los Angeles activity score.

Trend in metal ion levels

pre-operative median metal ion concentrations were 0.1 µg/L for both metal ions (Co and Cr) in both groups. Both well-functioning and sub-optimal implant groups show stable median Co concentrations from 3 to 36 months (p=0.436; p=0.062), but significant differences occur between the groups. From three months on the median Co concentrations significantly differ between groups with higher levels in the sub-optimal functioning group (Table 2). At 24 months the median Co concentration, for the well-functioning group, is 0.95 µg/L (0.1-9.3; 42 patients) versus 6.2 µg/L (2.0-29.30; 6 patients) for the sub-optimal functioning group (p<0.001); at 36 months 0.85 µg/L (0.1-7.0; 18 patients) versus 3.65 µg/L (0.1-21.2; 6 patients) respectively (p=0.015) (Table 2, Figure 2).

Table 2 Median metal ion concentrations (range)

	Well-functioning	Sub-optimal functioning	p-value
Cobalt			
pre-operative (n=42/6)	0.10 (0.1-1.0)	0.10 (0.1-2.6)	0.305
3 months (n=42/6)	0.90 (0.1-2.2)	1.90 (0.8-7.8)	0.012
6 months (n=42/6)	0.90 (0.1-5.7)	2.65 (0.5-5.6)	0.015
12 months (n=42/6)	0.80 (0.1-4.7)	3.40 (0.1-7.7)	0.029
24 months (n=42/6)	0.95 (0.1-9.3)	6.20 (2.0-29.3)	<0.001
36 months (n=18/6)	0.85 (0.1-7.0)	3.65 (0.1-21.2)	0.015
Chromium			
pre-operative (n=42/6)	0.10 (0.1-0.7)	0.10 (0.1-1.3)	0.637
3 months (n=42/6)	1.30 (0.1-3.5)	3.10 (0.7-6.1)	0.096
6 months (n=42/6)	1.45 (0.1-5.8)	4.15 (0.1-7.2)	0.047
12 months (n=42/6)	1.70 (0.1-4.9)	4.15 (0.7-10.2)	0.024
24 months (n=42/6)	1.70 (0.6-13.3)	4.70 (2.9-17.5)	0.001
36 months (n=18/6)	1.70 (0.5-8.5)	4.30 (0.6-16.0)	0.022

For Cr both groups (well and sub-optimal functioning) also show stable median Cr concentrations from 3 up to 36 months (p=0.059 and p=0.417) with differences between the groups. At six months (and further) the differences between the two groups for median Cr concentrations are significant, again with higher levels in the sub-optimal functioning group (Table 2). At 24 months the median Cr concentration is 1.7 µg/L (0.6-4.9; 42 patients) versus 4.7 µg/L (2.9-17.5; 6 patients) (p=0.001), and at 36 months 1.7 µg/L (0.5-8.5; 18 patients) versus 4.3 µg/L (0.6-16.0; 6 patients) for the well versus sub-optimal functioning group respectively (p=0.022) (Table 2, Figure 2).

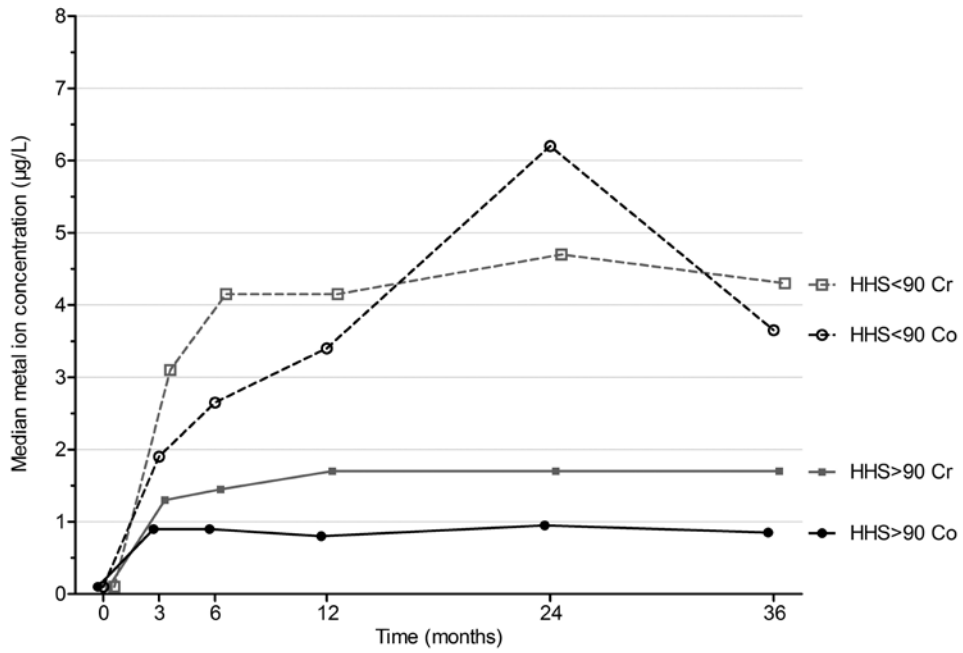


Figure 2 Median Co (black) and Cr (grey) serum concentrations in µg/L for the well-functioning (straight line) and sub-optimal functioning (dashed line) implants.

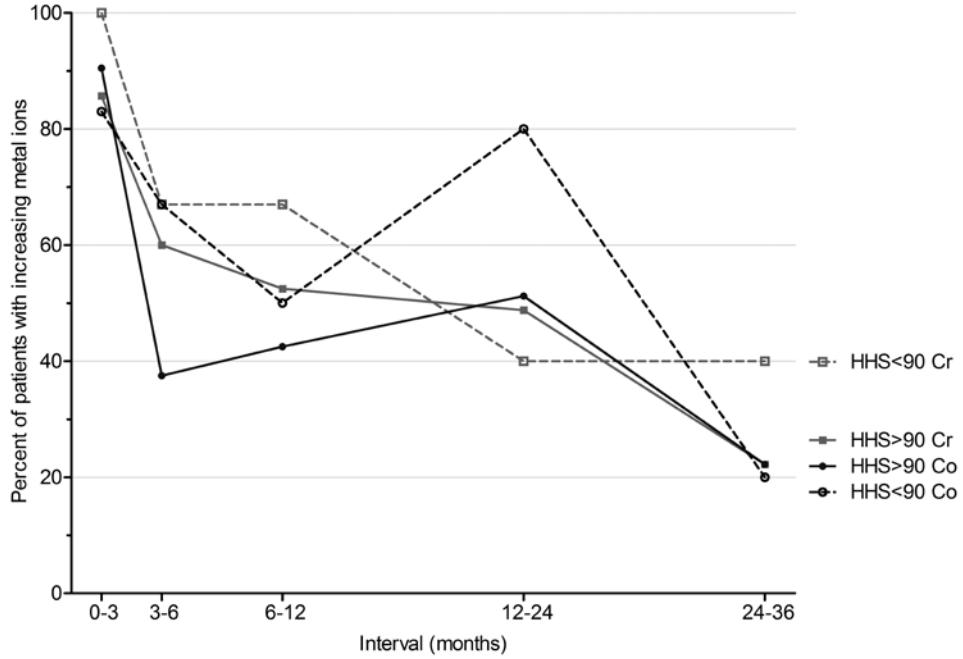


Figure 3 Metal ion increase percentage of patients with increasing Co (black) or Cr (grey) concentrations in serum, for the well-functioning (straight line) and sub-optimal functioning (dashed line) implants.

Percentage of patients with increasing metal ion levels

Figure 3 shows the percentage of patients who have increasing Co or Cr concentrations at each interval between two subsequent measurements. For the well-functioning implants, the percentage of increasing Co levels between two time intervals gradually decreased from 90% for 0-3 months, to 22% for 24-36 months; for Cr these percentages were respectively 86% and 22%. The trend for sub-optimal functioning implants revealed higher percentages of increasing metal ions between time-intervals with a peak difference between the two groups at 12-24 months; increasing Co values in 80% and 40% for Cr (Figure 3).

Quantitative increase

The median absolute increase in the subgroup of patients with an increase in their metal ion levels ('risers') for each time-interval of the well-functioning group from 0 to 36 months are shown in Table 3. For Co these median values at several time-intervals lies between 0.30 and 0.80 µg/L and for Cr between 0.55 and 1.50 µg/L. On the other hand, for the 'risers' in the sub-optimal functioning group a median increase from preoperative to 24 months of Co lies between 0.40 and 6.65 µg/L and of Cr between 0.10 and 11.60 µg/L (Table 3). The highest median increase for the sub-optimal functioning group occurs at the 12 to 24 months interval, for Co 6.65 µg/L (2.9-23.7) and Cr 11.60 µg/L (11.0-12.2). This was significantly different for both metal ions (Co p=0.002; Cr p=0.009) as compared to the median increase for the risers from the well-functioning group at the same 12 to 24 months interval.

Table 3 Median elevation of metal ion concentrations of rising cases only (range)

	Well-functioning	Sub-optimal functioning	p-value
Cobalt			
0-3 months	0.80 (0.1-2.1)	2.10 (0.6-7.7)	0.049
3-6 months	0.30 (0.1-5.1)	0.75 (0.2-3.3)	0.411
6-12 months	0.50 (0.1-3.3)	1.10 (0.4-2.7)	0.305
12-24 months	0.70 (0.1-4.6)	6.65 (2.9-23.7)	0.002
24-36 months	0.75 (0.4-1.2)	0.40 (0.4-0.4)	0.400
Chromium			
0-3 months	1.50 (0.4-3.4)	2.40 (0.6-6.0)	0.297
3-6 months	0.55 (0.1-3.8)	1.35 (0.9-4.3)	0.012
6-12 months	0.70 (0.1-3.0)	0.90 (0.2-3.2)	0.642
12-24 months	0.80 (0.1-8.9)	11.6 (11.0-12.2)	0.009
24-36 months	0.70 (0.1-1.9)	0.10 (0.1-0.1)	0.267

Discussion

In this study the metal ion trend of well- versus potentially malfunctioning unilateral resurfacing implants is presented. The interpretation of metal ions focused on, besides individual metal ion trend, on the odds of a metal ion increase at each time-interval and the absolute quantitative value of a specific increase.

Although we already know which Co and Cr levels are of clinical concern, there is no consensus which absolute cut off levels should be used. In spite of the recognized relationship between elevated Co and Cr blood levels and malfunctioning implants, there is limited knowledge on the range of acceptable metal ion concentrations and where toxicity is introduced. Research so far concludes that Co concentrations higher than 19 µg/L and Cr concentrations higher than 17 µg/L were likely to be associated with metallosis at revision surgery.[9] De Smet et al. proposed (AAOS poster, 2010) that serum Co and Cr levels up to respectively 4.4 µg/L and 5.1 µg/L are acceptable as upper limits. Hart et al. defined a threshold level of 7 µg/L for both Co and Cr[20] (which the UK MHRA adopted for their safety alert of April 2010)[6] and recently lowered it to a cut off level of 4.97ppb.[7] All these previous studies focus on attempts to formulate a recommendation based on single metal ion measurement. Several studies found high blood metal ion levels at the intermediate term and correlated this with increased wear.[8,9,11-13] On the contrary, others reject this correlation and the use of metal ion measurements as solitary screening tool or surgical trigger.[10,14] The divergent results of all these studies emphasize the need for a different use and interpretation of metal ions. We feel that better information about implant functioning may be obtained from repeated metal ion measurements and trend evaluation. For example, in our opinion a single measurement Co level of 5 µg/L at 12 months raises more questions than it answers. An additional 24 months measurement of 3 µg/L would be rather reassuring, while 6 µg/L would indicate a potentially malfunctioning implant. Although there are no reports of test retest variation from metal ion measurements by ICP-MS, it is the authors opinion that an increase of 1 µg/L after 24 months would be a reason for concern and an indication for repeated measurements or other investigations.

The chronological follow-up of metal ion concentrations of the well-functioning implants exhibits a mild increase in Co and Cr levels up to 12 months. Subsequently, the median metal ion values remain at an acceptable and relatively low level until the end of follow-up at 36 months. These low median metal ion concentrations are in agreement with several other studies, as is the 'running-in phase' of the metal ions until six to twelve months with stabilizing values thereafter.[11,17,18] However, the 12 and 24 months median Co and Cr concentrations of the well-functioning patients in our study are three to six times lower than the ones reported by Allen et al. and deSouza et al.[15,16] The reason for this difference is not clear, however this might be implant or surgical technique related.[13] The chronological metal ion trend for the potentially malfunctioning implants differed significantly from the well-functioning group with

higher levels at all times. As the range of both trend lines is wide, the interpretation of a single ion measurement might still be difficult when it is positioned within both trend lines. In such cases interpretation may become more reliable with a second measurement and knowledge about the odds of increasing levels in time and acceptable increase limits.

From three months on, the odds of an increase in Co and Cr concentration decreases for both groups. Although both groups show a comparable course of this metal ion increase percentage, the 12-24 months interval shows a greater percentage of increasing values for the sub-optimal functioning group (Figure 3). Since this group was relatively small, this high percentage of 'risers' was not significantly different and only a trend can be concluded at this point. This trend might be indicative for a transition point of Co and Cr concentrations in serum at 12 months. If metal ion levels increase structurally after 12 months, this might be an indication of increasing wear and a potentially malfunctioning implant. When looking at the actual quantitative amount of increase in Co or Cr concentration, there was a significant difference between the groups. In well-functioning patients the median increase in metal ion concentrations, if present, was always below 1 µg/L for both metal ions. For patients from the sub-optimal group the observed increase in metal ion levels was significantly higher, especially at the 12-24 months interval with median increase values up to 6.65 µg/L (Co) and 11.6 µg/L (Cr). Thus, the difference between the two groups lies, besides significantly higher median metal ion concentrations, in a trend towards higher odds for an increase together with a significant higher absolute increase for the sub-optimal functioning patients.

We recognize the limitations of our study. We only present a relative small group with a median follow-up of 24 months, with a maximum of 36 months. However, the failures related to high wear and therefore high metal ion concentrations seem to occur between 8 to 85 months[21] and thus short term follow-up studies are still appropriate since we are dealing with a problem of early failures. A HHS above 90 is considered an excellent result, therefore this was chosen as cut off point. There might unfortunately be test retest variations, however, according to two studies the intraclass correlation of the HHS are well over 0.75 and can therefore be considered excellent.[22,23] We are interested if consecutive measurements in a bigger cohort will validate the conclusions from this exploratory study, however to date there are no reports on this specific matter. Furthermore it is recognized that test retest and design-related differences are present in metal ion release[13] and we only studied a single resurfacing design. However, as we present a trend assessment, the increase or decrease is more important than the absolute value of metal ion release and thus the potential influence of design specific differences is minimized.

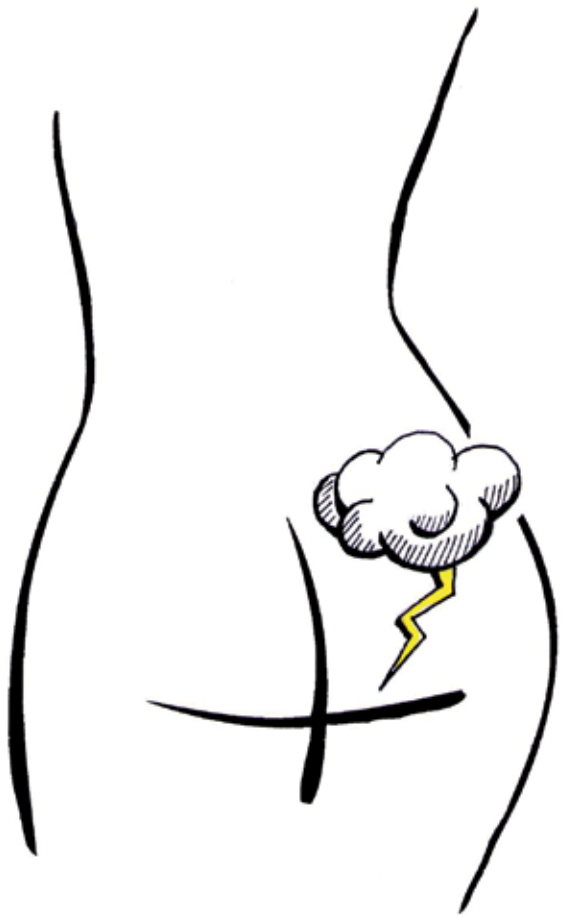
The evaluation of metal ion levels is becoming increasingly important after a MoM hip arthroplasty and serves as an indicator of bearing performance and device safety. Determination how to use and interpret Co and Cr concentration is essential for the general orthopaedic surgeon who will be confronted with the follow-up of patients with MoM implants. For well-functioning patients, it appears that the odds of an increase in metal ion levels is minimal after

two years. If an increase after six months is still encountered, the absolute value of this increase can be considered to be low (below 1 µg/L). On the contrary, for the sub-optimal functioning patients we found a notably 'different trend' with significantly higher metal ion levels at all time-intervals, even after the running-in period. In addition, the odds of increasing metal ions levels were higher in this group, together with significantly higher absolute values of this increase from 12 to 24 months. Although one would prefer a longitudinal measurement of each individual patient, the widespread use is limited by the high costs of analysis. From the results of the trend evaluation in our study we recommend a low threshold for repeated metal ion measurement after the running-in period, as it can help to clarify if an implant is failing.

References

1. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am.* 2005;87(1):28-36.
2. Park YS, Moon YW, Lim SJ, Yang JM, Ahn G, Choi YL. Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg Am.* 2005;87(7):1515-1521.
3. Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90(7):847-851.
4. Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M. Polyneuropathy caused by cobalt–chromium metallosis after total hip replacement. *Muscle Nerve.* 2010;42(1):140-143.
5. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: A review of current knowledge and future strategies. *J Bone Joint Surg Br.* 2007;89-B(5):567-573.
6. *MHRA.* Medical Device Alert: All metal-on-metal (MoM) hip replacements MDA/2012/008. 2012(28 february 2012).
7. Hart AJ, Sabah SA, Bandi AS, et al. Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. *J Bone Joint Surg Br.* 2011;93-B(10):1308-1313.
8. Daniel J, Ziaee H, Kamali A, Pradhan C, McMinn D. What are the risks accompanying the reduced wear benefit of low-clearance hip resurfacing? *Clin Orthop Relat Res.* 2012;470(10):2800-2809.
9. De Smet K, De Haan R, Calistri A, et al. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. *J Bone Joint Surg Am.* 2008;90 Suppl 4:202-208.
10. Griffin WL, Fehring TK, Kudrna JC, et al. Are metal ion levels a useful trigger for surgical intervention? *J Arthroplasty.* 2012;27(8 Suppl):32-36.
11. Heisel C, Silva M, Skipor AK, Jacobs JJ, Schmalzried TP. The relationship between activity and ions in patients with metal-on-metal bearing hip prostheses. *J Bone Joint Surg Am.* 2005;87(4):781-787.
12. Jacobs JJ, Skipor AK, Campbell PA, Hallab NJ, Urban RM, Amstutz HC. Can metal levels be used to monitor metal-on-metal hip arthroplasties? *J Arthroplasty.* 2004;19(8 Suppl 3):59-65.
13. Langton DJ, Joyce TJ, Jameson SS, et al. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. *J Bone Joint Surg Br.* 2011;93(2):164-171.
14. Macnair RD, Wynn-Jones H, Wimhurst JA, Toms A, Cahir J. Metal ion levels not sufficient as a screening measure for adverse reactions in metal-on-metal hip arthroplasties. *J Arthroplasty.* 2013;28(1):78-83.
15. Allan DG, Trammell R, Dyrstad B, Barnhart B, Milbrandt JC. Serum cobalt and chromium elevations following hip resurfacing with the Cormet 2000 device. *J Surg Orthop Adv.* 2007;16(1):12-18.
16. deSouza RM, Parsons NR, Oni T, Dalton P, Costa M, Krikler S. Metal ion levels following resurfacing arthroplasty of the hip: serial results over a ten-year period. *J Bone Joint Surg Br.* 2010;92(12):1642-1647.
17. Isaac GH, Siebel T, Oakeshott RD, et al. Changes in whole blood metal ion levels following resurfacing: serial measurements in a multi-centre study. *Hip Int.* 2009;19(4):330-337.
18. Smolders JM, Hol A, Rijnberg WJ, van Susante JL. Metal ion levels and functional results after either resurfacing hip arthroplasty or conventional metal-on-metal hip arthroplasty. *Acta Orthop.* 2011;82(5):559-566.
19. Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid sur-

face arthroplasty. Surgical technique. *J Bone Joint Surg Am.* 2006;88(1_suppl_2):234-249.
20. Hart AJ, Skinner JA, Winship P, et al. Circulating levels of cobalt and chromium from metal-on-metal hip replacement are associated with CD8+ T-cell lymphopenia. *J Bone Joint Surg Br.* 2009;91(6):835-842.
21. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AVF. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement. *J Bone Joint Surg Br.* 2010;92-B(1):38-46.
22. Soderman P, Malchau H, Herberts P. Outcome of total hip replacement: a comparison of different measurement methods. *Clin Orthop Relat Res.* 2001(390):163-172.
23. Wright JG, Young NL. A comparison of different indices of responsiveness. *J Clin Epidemiol.* 1997;50(3):239-246.



High incidence of pseudotumors after hip resurfacing even in low risk patients; results from an intensified MRI screening protocol

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Abstract

We intensified our screening protocol for the presence of pseudotumors in a consecutive series of patients with a hip resurfacing arthroplasty (RHA), to establish whether we should be alert to the presence of 'silent' pseudotumors. Patients categorized with high risk (11 hips) and low risk (10 hips) for pseudotumor development and a control group (23 hips) were screened with metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI). The Anderson classification to grade any metal-on-metal (MoM) disease present on MARS-MRI images was used. In 15 out of 44 MRI scans pseudotumors were observed (34.1%), of which six were graded with mild (13.6%), eight with moderate (18.2%) and one with severe MoM disease (2.3%). Twelve pseudotumors were present in asymptomatic patients (27.3%). Metal ion levels were normal in 80% of the MARS-MRI screened patients. As a consequence of our intensified screening protocol, one patient was revised for pseudotumor formation and another patient was scheduled for revision. Silent pseudotumors were observed in all three groups. Before our intensified screening protocol was initiated, no pseudotumors were encountered in our cohort of 289 RHA's. We concluded that clinical outcomes and plain radiographs for screening MoM patients underestimates the presence of pseudotumors in MoM patients. The true clinical relevance of these pseudotumors is still unclear.

Introduction

Metal-on-metal (MoM) bearings have been widely used in hip arthroplasty. Although wear rates are low, these bearings still release cobalt (Co) and chromium (Cr) particles which may result in a periprosthetic soft tissue reaction, requiring revision surgery.[1,2] This periprosthetic soft tissue damage, known as adverse reaction to metal debris (ARMD) compromises aseptic lymphocytic vasculitis-associated lesions (ALVAL), metallosis and pseudotumor formation.[3] Revision surgery for pseudotumors is sometimes difficult and post-revision surgery clinical outcomes are less satisfying.[4] The reported incidence of pseudotumors varies, depending on patient characteristics, type of follow-up and implant design features.[5,6] Earlier MoM hip arthroplasty studies relied on clinical outcome scores and radiographs of large case series to report on good implant performance and excellent functional outcomes.[7-9]

Recently published data, however, report on a much higher incidence of pseudotumors in patients with MoM implants after all patients have been screened for the presence of these adverse peri-prosthetic reactions with metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI) or ultrasound.[10,11] Suspicion arises that there may be a relatively large number of 'silent' pseudotumors present in otherwise well-functioning implants. There is reason to believe that the occurrence of pseudotumors is not solely observed with malpositioned implants with relatively high metal ion levels and poor clinical outcome.[11] From this growing unease we decided to intensify our screening protocol for the presence of pseudotumors in a consecutive series of patients with RHA. The aim of this study was to clarify whether we should be alert to the presence of 'silent' pseudotumors in our cohort of hip resurfacing patients. According to previously defined patient and implant characteristics,[6,11] we categorized high and low risk patients for pseudotumor development, together with a non-stratified control group. Subsequently, in all three groups MARS-MRI screening for pseudotumors was performed.

Patients and methods

Patients

Between September 2004 and September 2010 we included 298 consecutive RHA procedures (240 patients) in a prospective cohort study. Females <60 years of age and males <65 years of age were the primary candidates for RHA if diagnosed with end stage osteoarthritis and had an active lifestyle. Older patients with sufficient bone quality and an active lifestyle were considered for RHA on an individual basis. Dual energy X-ray absorptiometry was used to exclude patients with osteoporosis. Patients with renal failure, femoral cysts, avascular necrosis (AVN) of the femoral head and female patients trying to conceive were also excluded. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. After informing the patient on the expected benefits and risks associated with RHA,

informed consent on the surgery procedure and on study participation was obtained. Our study was approved by the Institutional Review Board (IRB nr. 08.013, 18th December 2008).

Implant system

All procedures were performed by one of two experienced hip arthroplasty surgeons (TS, HH). The ReCap hip resurfacing system (Biomet Inc, Warsaw, USA) was implanted by a posterolateral approach. The press-fit acetabular component and the cemented femoral component are manufactured from 'as-cast' cobalt-chromium (Co-Cr-Mo) with a high carbon content (>0.2%) without any heat treatment. The acetabular outside is a full hemisphere design and has four pairs of small fins for initial rotational stability. It has a titanium porous plasma spray surface coating facilitating bone ingrowth. The system offers 2 mm increment sizing. The surgical technique has been described earlier by Gross and Liu.[12] All patients received antibiotic prophylaxis with a Cephalosporin pre-operatively and 24 hours post-operatively, three days of Indometacin for periarticular ossification prophylaxis, Diclophenac for pain management and thrombosis prophylaxis with Dalteparine 5000 units for six weeks postoperatively. Patients were rehabilitated with immediate unrestricted weight bearing according to the patient's tolerance. All bilateral procedures were staged interventions with at least a three month interval.

Table 1 Patient characteristics, values are median (min-max)

	High risk ARMD	Low risk ARMD	Routine FU group
Patients/hips	11/12	10/10	19/22
Male/female	0/11	10/0	16/3
Femoral component size in mm (median)	46 (44-50)	52 (50-56)	52 (46-54)
Cup inclination angle	60° (55-70)	41° (35-44)	51.5° (36-64)
Bilateral MoM	5	0	3
HHS score	89 (79-95)	89 (83-91)	80 (48-91)
HHS pain score (none/slight/moderate)	7/2/2	10/0/0	9/8/3
Age in years	53.1 (41-61)	54 (40-66)	54 (28-69)
Follow up in years	3.8 (1-7)	4.5 (2.3-6.9)	4.0 (1.6-6.9)

Study design

To evaluate the occurrence and incidence of pseudotumor formation we defined three different groups of patients. The first group had a perceived high risk for pseudotumor formation based on gender, component size and cup inclination angle.[6,11,13] Cup inclination angle was measured on the latest available standard anteroposterior radiograph using earlier described methods.[14] Eventually we allocated eleven female patients with a cup inclination angle

>45° and a femoral component size <50 mm to this 'high risk' group. Five patients in this group had bilateral RHA; one patient fulfilled all high risk criteria bilaterally, four patients only unilaterally, and therefore twelve hips were included in the high risk group for MARS-MRI screening. The 'low risk' group consisted of ten asymptomatic male patients with a unilateral RHA, cup inclination angle <45° and femoral component size >50 mm. The third group consisted of 19 patients (22 hips) who, regardless of risk factors, were scheduled for routine follow-up between November 2011 and May 2012 and acted as a 'control' group without risk stratification (Table 1).

In all three groups, blood serum samples were collected and assessed on Co and Cr concentrations. Samples were collected in metal-free vacutainers; the first 5 mL blood was discarded to eliminate metal contamination from the needle. Tubes were stored at 2-8°C and sent to an external laboratory (Ziekenhuis Groep Twente, Hengelo, Netherlands) for analysis. The metal ion levels in whole blood were determined using Atomic Absorption Spectrophotometry (AAS) analysis. Co levels were classified according to guidelines by the Dutch Orthopaedic Society[15] with normal Co <40 nmol/L, slightly elevated 40-85 nmol/L, elevated 85-170 nmol/L and extremely elevated >170 nmol/L. All MARS-MRI examinations were performed on a 1,5T MRI (Philips Medical Systems, Best, Netherlands). Scan parameters are listed in Table 2.

Table 2 MARS-MRI details

	Coronal PDW	Coronal STIR	Transverse PDW	Transverse	Sagittal STIR
TE (ms)	30	40	30	40	40
TR (ms)	3000	8645	3576	105000	9570
TI (ms)		130		130	130
Slice thickness	2.5	2.5	3	3	3
FOV (mm)	230 x 197	230 x 198	240 x 199	280 x 198	230 x 230
Matrix	328 x 220	256 x 168	344 x 198	280 x 152	256 x 189
BW (HZ/pixel)	435	437	437	435	438
Coil	Sense body 16 ch	Sense body 16 ch	Sense body 16 ch	Sense body 16 ch	Sense body 16 ch

All MARS-MRI images were judged by an experienced musculoskeletal radiologist (KB) and validated by a second musculoskeletal radiologist (RH), who were both unaware of the clinical status of the patients. We used the description by Matthies et al. of a pseudotumor being a sterile inflammatory lesion found in the soft tissues surrounding a MoM hip arthroplasty.[16] Grading of MARS-MRI findings was based on the method described by Anderson et al.

(Table 3).[17] Since Harris hip scores (HHS),[18] Oxford hip scores (OHS)[19] and anteroposterior and lateral radiographs were collected yearly as part of routine follow-up, these were available for all patients. The OHS results were calculated using the original scoring system (12 points being best possible score, 60 points being the worst possible score).

Table 3 Anderson classification for MoM disease on MARS-MRI[17]

Grade	Description	Criteria
A	Normal or acceptable	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 disease	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 disease	Peri-prosthetic 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 external rotator or (2) bone marrow edema: hyperintense on STIR.
C3	Severe MoM disease	Any of the following: (1) fluid-filled cavity extending through deep fascia, (2) a tendon avulsion, (3) intermediate T1W soft tissue cortical or marrow signal, (4) fracture.

Statistical analysis

Descriptive statistics were used to compare the three study groups. Metal ion data distributions were asymmetric and are expressed as a group median with range. Symmetrical data are represented by a mean and standard deviation (SD). The significant level is defined as $p \leq 0.05$ in this study. A post hoc analysis was used to measure the statistical power of the observed difference in pseudotumor occurrence between groups. SPSS software (SPSS Statistics, version 17.0, IBM Corporation, Somers USA) was used for all statistical analyses.

Results

Patient characteristics are shown in Table 1. Before the intensified screening protocol was implemented, no pseudotumors had been detected in our cohort of 298 RHA's. With the MARS-MRI screening completed, pseudotumors were observed in all three groups (Table 4). The risk for pseudotumor development in the high risk group was 0.45, 0.33 in the low risk group and 0.30 in the control group. However, the statistical power to detect a true significant difference in risk ratios between groups was low (p=0.11). Overall, in 15 cases of the 44 MARS-MRI available for analysis, pseudotumor formation had occurred. In total 29 MARS-MRI images were classified as grade A, none as grade B, six as grade C1, eight as grade C2 and one grade as C3. In contrast to the MARS-MRI images, the Co levels were normal in 80% of the patients. Two patients had slightly elevated metal ion levels, four patients had elevated levels and two patients had extremely elevated levels. The median Co level for all patients was 24 nmol/L (min-max 11-1897 nmol/L).

Table 4 Incidence and characterization of pseudotumor formation and cobalt levels (min-max)

	High risk ARMD	Low risk ARMD	Routine FU group
Patients/hips	11/12	10/10	19/22
Pseudotumor	5	3	7
Grade C1/C2/C3	2/2/1	3/0/0	1/6/0
Pseudotumor size in cm (mean)	5.2 (1.9-10.5)	3.3 (1.8-5.0)	4.4 (1.9-8.0)
Cobalt in nmol/L (median)	27 (19-1897)	18 (11-36)	24 (12-407)

Out of the 15 pseudotumors which were observed on MARS-MRI, there were 12 silent pseudotumors. These patients did not complain of any pain or other symptoms and had excellent clinical outcome scores (HHS >90, Oxford Hip Score <16) with normal radiographs.

One female patient from the high risk group with severe MoM disease underwent revision surgery, and one male patient from the control group with moderate MoM disease is scheduled for revision. The revised patient had bilateral RHA: seven years after implantation on her right, six years on her left side. There was no pseudotumor observed on her right side but on her left side she had a pseudotumor measuring 105 mm craniocaudal, 71 mm anteroposterior and 80 mm mediolateral (Figure 1).

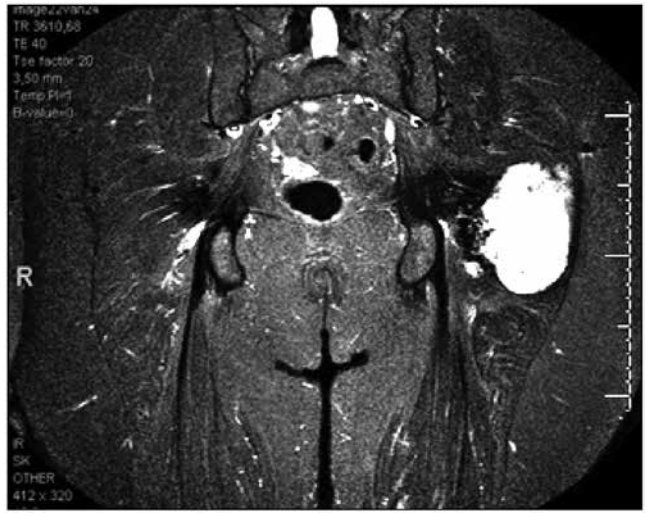


Figure 1 Large fluided filled cyst left hip, indicating Anderson grade C2 MoM disease.

Her Co level was extremely elevated (1897 nmol/L). Her HHS score was 91 points and she never complained of pain after RHA. She did however regularly noticed squeaking on the left side, something we had not observed in any other patient from our series. Both cups had a steep inclination angle (left 70°, right 59°). During revision surgery a large fluid filled cyst was excised, extending from the lateral side to the anterior part of the hip joint.

Discussion

In our study group of patients with a Recap RHA the prevalence of pseudotumors appeared to be high, with pseudotumor occurrence even in the group defined as having a low risk for ARMD. With an established pseudotumor incidence of 34.1 percent in this concise exploratory study group, we can expect another 87 pseudotumors using an intensified MARS-MRI screening protocol on our entire group of 298 resurfacing hip arthroplasties. Of these 87 pseudotumors, an expected 17 would classify as a grade C2 or C3 pseudotumor with an increased revision risk.

As confirmed by other authors, pain was not a very useful indicator for pseudotumor occurrence.[20,21] Compared to the extent of damage noticed on MARS-MRI and at revision surgery, one has to wonder by which mechanism pseudotumors develop relatively pain free. Mild symptoms and relatively low metal ion levels can contribute to the difficulty of convincing patients to have their RHA revised. However, recent media attention about the negative effects of MoM bearings has scared many MoM patients, who even ask for revision surgery in absence of any symptoms.

Although several authors report on pseudotumor rates, the number of studies using other imaging modalities than plain radiographs to detect pseudotumor occurrence is very limited. High rates of pseudotumor occurrence have been found in other studies which used MARS-MRI or computer tomography (CT) scanning. Wynn-Jones reported a similar pseudotumor rate of 36% using the ASR resurfacing device.[21] Compared to MoM hip resurfacing, higher pseudotumor rates are reported for MoM total hip arthroplasty. Mistry et al. reported a 58.3% pseudotumor rate using the Ultima TPS design[20] and Bosker et al. found a 39% pseudotumor rate in MoM THA patients who received the M2a-Magnum femoral head and ReCap acetabular component.[10] Langton et al. described a 13.6% revision rate for ARMD with the ASR design, but use of MRI or CT scanning was not reported in this paper.[6] Malviya et al. found a pseudotumor incidence of just 0.15% using the BHR resurfacing device, although it is not clear from his paper if all patients routinely were scanned using MARS-MRI.[22]

To our knowledge, there are no other studies which have investigated the prevalence of pseudotumors with this particular RHA design using imaging modalities other than plain radiographs. The studies by Baad- Hansen et al. and Gagala et al. were limited to 23 and 25 RHA patients respectively with a maximum follow-up of 24 months.[23,24] Gross and Liu recently published a case series of 740 consecutive procedures with the ReCap RHA design with a follow-up of seven years maximum.[25] The reported Kaplan-Meier survivorship with any

revision as an end point was 96.4% at seven years, with only two revisions (0.3%) for adverse wear. Follow-up was limited to clinical outcomes and plain radiographs, but as the possibility of more adverse wear failures was acknowledged by the authors, they started taking metal ion samples routinely.

There remains uncertainty on the risk factors for pseudotumor formation with current MoM hips. Studies have suggested that edge-loading resulting from adverse cup orientation and implant design leads to a higher wear of the components and subsequently increases blood metal ion levels.[26,27] Clinical studies and reports from arthroplasty registers also implicate smaller components in connection with increased metal ion levels.[13,28] Based on these finding, the use of MoM prostheses is supported for appropriately trained surgeons who select appropriate patients.[29] Recently, studies have debated risk factors for pseudotumor formation. Kwon et al. and Mistry et al. showed that pseudotumors can be observed in asymptomatic patients with well-positioned and well-functioning prostheses.[11,20] Recently, Matthies et al. reported that pseudotumors are common in well-positioned MoM prosthesis.[16] These results are confirmed by our study in which pseudotumors were commonly found in asymptomatic patients with well-positioned, large components. This suggests that development of pseudotumors is more likely to be dependent on patient susceptibility than on factors such as component size, component positioning or implant design. The risk for pseudotumor formation is higher for any patient with any MoM prosthesis than previously thought.

Until now, clinical signs, radiographic evaluation and metal ion levels have been used to identify patients at risk for pseudotumor formation. The best protocol for detecting pseudotumors is not yet defined, but ultrasound scans, CT or MARS-MRI scans are commonly used. Our study indicates that follow-up methods of clinical outcomes and radiographs underestimate the prevalence of pseudotumors after MoM RHA. Moreover, metal ion levels alone are also not sufficient to detect all cases of ARMD. Our findings, especially those from the low risk ARMD group, have prompted us to start using MARS-MRI scans for our whole MoM cohort. Our findings suggest that radiographic screening with MARS-MRI, CT or ultrasound on all patients with a hip resurfacing might be the only option to discover the real magnitude of pseudotumor formation after MoM arthroplasty.

There are several limitations of our study. Most importantly, the number of patients is small since we report on an exploratory study at this stage. In spite of this limited number of patients we still feel the need to report on our preliminary findings of the high number of pseudotumors found on MARS-MRI even in low risk patients with few or no symptoms. In our study group, there were quite a few patients with a steep cup inclination angle, which is considered the only risk factor for ARMD by some authors.[30] However, despite the fact that we differentiated amongst other factors between high and normal cup inclination, we still found pseudotumors with normally inclined cups.

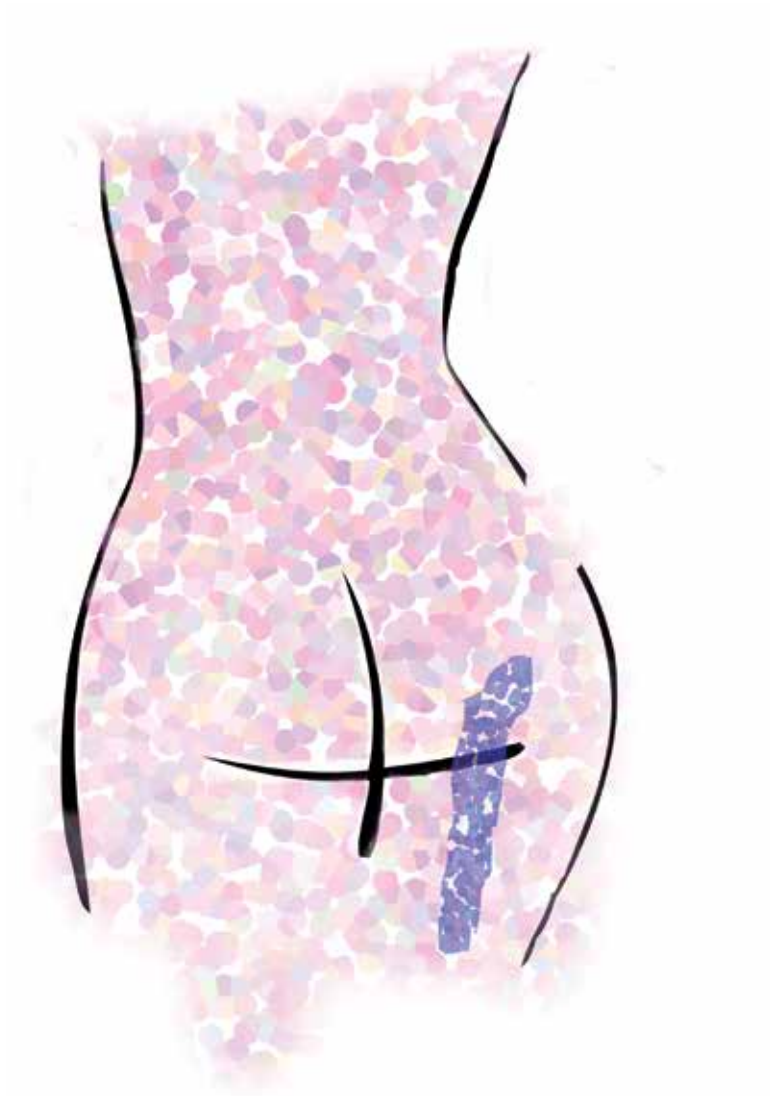
We believe that conventional radiological and clinical follow-up together with metal ion analyses will underestimate the true prevalence of MoM-disease. An intensified screening

protocol for pseudotumors with MRI, CT scan or ultrasound is likely to become unavoidable. There is no consensus yet on the clinical relevance of pseudotumors and it may be possible that only some become problematic. There is increasing evidence that the incidence of pseudotumor formation with large diameter (>36 mm) MoM may be higher than assumed so far and the use of these implants has been suspended in the Netherlands.

References

1. Mabilleau G, Kwon YM, Pandit H, Murray DW, Sabokbar A. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. *Acta Orthop.* 2008;79(6):734-747.
2. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90(7):847-851.
3. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AVF. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement. *J Bone Joint Surg Br.* 2010;92-B(1):38-46.
4. Grammatopolous G, Pandit H, Kwon YM, Gundle R, McLardy-Smith P, Beard DJ, et al. Hip resurfacings revised for inflammatory pseudotumour have a poor outcome. *J Bone Joint Surg Br.* 2009;91(8):1019-1024.
5. Fary C, Thomas GE, Taylor A, Beard D, Carr A, Glyn-Jones S. Diagnosing and investigating adverse reactions in metal on metal hip implants. *BMJ.* 2011;343:d7441.
6. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, et al. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. *J Bone Joint Surg Br.* 2011;93(2):164-171.
7. Amstutz HC, Le Duff MJ. Eleven years of experience with metal-on-metal hybrid hip resurfacing: a review of 1000 conserve plus. *J Arthroplasty.* 2008;23(6 Suppl 1):36-43.
8. De Smet KA. Belgium experience with metal-on-metal surface arthroplasty. *Orthop Clin North Am.* 2005;36(2):203-213, ix.
9. Khan M, Kuiper JH, Edwards D, Robinson E, Richardson JB. Birmingham hip arthroplasty: five to eight years of prospective multicenter results. *J Arthroplasty.* 2009;24(7):1044-1050.
10. Bosker BH, Ettema HB, Boomsma MF, Kollen BJ, Maas M, Verheyen CC. High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. *J Bone Joint Surg Br.* 2012;94(6):755-761.
11. Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS, Murray DW. "Asymptomatic" pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. *J Arthroplasty.* 2011;26(4):511-518.
12. Gross TP, Liu F. Minimally invasive posterior approach for hip resurfacing arthroplasty. *Techniques in Orthopaedics.* 2010;25(1):39-49 10.1097/BTO.1090b1013e3181d1091e1076b.
13. Prosser GH, Yates PJ, Wood DJ, Graves SE, de Steiger RN, Miller LN. Outcome of primary resurfacing hip replacement: evaluation of risk factors for early revision. *Acta Orthop.* 2010;81(1):66-71.
14. Beaule PE, Lee JL, Le Duff MJ, Amstutz HC, Ebramzadeh E. Orientation of the femoral component in surface arthroplasty of the hip. A biomechanical and clinical analysis. *J Bone Joint Surg Am.* 2004;86-A(9):2015-2021.
15. *Nederlandse Orthopaedische Vereniging*. Advies metaal-op-metaal (MOM) articulerende implantaten van de NOV 9 juni 2011. Available from: http://www.orthopeden.org/uploads/3d/Uh/ 3dUhx2N-fVxjLe-Kdd-unfA/Nov-Advies-MoM-eindversie-16-juni-2011-tbv-Email-alert.pdf.
16. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop Relat Res.* 2012;470(7):1895-1906.
17. Anderson H, Toms AP, Cahir JG, Goodwin RW, Wimhurst J, Nolan JF. Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. *Skeletal Radiol.* 2011;40(3):303-307.
18. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg*

Am. 1969;51(4):737-755.
19. Dawson J, Fitzpatrick R, Carr A, Murray D. Questionnaire on the perceptions of patients about total hip replacement. *J Bone Joint Surg Br.* 1996;78(2):185-190.
20. Mistry A, Cahir J, Donell ST, Nolan J, Toms AP. MRI of asymptomatic patients with metal-on-metal and polyethylene-on-metal total hip arthroplasties. *Clin Radiol.* 2011;66(6):540-545.
21. Wynn-Jones H, Macnair R, Wimhurst J, Chirodian N, Derbyshire B, Toms A, et al. Silent soft tissue pathology is common with a modern metal-on-metal hip arthroplasty. *Acta Orthop.* 2011;82(3):301-307.
22. Malviya A, Holland JP. Pseudotumours associated with metal-on-metal hip resurfacing: 10-year Newcastle experience. *Acta Orthop Belg.* 2009;75(4):477-483.
23. Baad-Hansen T, Storgaard Jakobsen S, Soballe K. Two-year migration results of the ReCap hip resurfacing system-a radiostereometric follow-up study of 23 hips. *Int Orthop.* 2011;35(4):497-502.
24. Gagala J, Mazurkiewicz T. First experiences with total hip resurfacing arthroplasty [Polish article]. *Chir Narzadow Ruchu Ortop Pol.* 2007;72(5):311-317.
25. Gross TP, Liu F. Hip resurfacing with the Biomet Hybrid ReCap-Magnum system: 7-year results. *J Arthroplasty.* 2012;27(9):1683-1689 e1682.
26. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br.* 2008;90-B(10):1291-1297.
27. Morlock MM, Bishop N, Stahmer F, Zustin J, Sauter G, Hahn M, et al. Reasons for failure of hip resurfacing implants. A failure analysis based on 250 revision specimens [German article]. *Orthopade.* 2008;37(7):695-703.
28. Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AVF. The effect of component size and orientation on the concentrations of metal ions after resurfacing arthroplasty of the hip. *J Bone Joint Surg Br.* 2008;90-B(9):1143-1151.
29. Murray DW, Grammatopoulos G, Gundle R, Gibbons CL, Whitwell D, Taylor A, et al. Hip resurfacing and pseudotumour. *Hip Int.* 2011;21(3):279-283.
30. Amstutz HC, Le Duff MJ, Johnson AJ. Socket position determines hip resurfacing 10-year survivorship. *Clin Orthop Relat Res.* 2012;470(11):3127-3133.



Changes in bone mineral density in the proximal femur after hip resurfacing and uncemented total hip replacement. A prospective randomized controlled study

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Abstract

We undertook a randomized prospective follow-up study of changes in peri-prosthetic bone mineral density (BMD) after hip resurfacing and compared them with the results after total hip replacement. A total of 59 patients were allocated to receive a hip resurfacing (n=29) or an uncemented distally fixed total hip replacement (n=30). The BMD was prospectively determined in four separate regions of interest (ROI) of the femoral neck and in the calcar region corresponding to Gruen zone 7 for the hip resurfacing group and compared only to the calcar region in the total hip replacement group. Standardized measurements were performed pre-operatively and after 3, 6 and 12 months. The groups were well matched in terms of gender distribution and mean age. The mean BMD in the calcar region increased after one year to 105.2% of baseline levels in the resurfaced group compared with a significant decrease to 82.1% in the total hip replacement group ($p<0.001$) by 12 months. For the resurfaced group, there was a decrease in bone density in all four ROI of the femoral neck at three months which did not reach statistical significance and was followed by recovery to baseline levels after 12 months. Hip resurfacing did indeed preserve BMD in the inferior femoral neck. In contrast, a decrease in the mean BMD in Gruen zone 7 followed uncemented distally fixed total hip replacement. Long term follow-up studies are necessary to see whether this benefit in preservation of BMD will be clinically relevant at future revision surgery.

Introduction

One of the most common sequelae of total hip arthroplasty (THA) is periprosthetic bone loss. Stress shielding is an important cause of this phenomenon according to the principles of Wolff's law.[1-3] Such bone loss is clinically relevant as it may result in peri-prosthetic fractures and loosening or migration of the implant.

Hip resurfacing arthroplasty is an option for the treatment of arthritis of the hip in young and active patients. This procedure preserves the femoral neck and part of the head and does not invade the femoral canal, thus preserving bone stock. The loading patterns in the femoral neck after hip resurfacing seem to mimic the natural situation,[4,5] although stress shielding seems to occur in the femoral neck according to finite element models.[6,7] Narrowing of the femoral neck has been described as a radiological feature following hip resurfacing arthroplasty,[8,9] and might represent adaptive remodelling to stress shielding. However, the literature to date is inconclusive on this subject.

One of the theoretical advantages of hip resurfacing is preservation of the femoral neck which would simplify future revisions in these young patients. However, for this to be true, the preserved bone of the femoral neck needs to be durable and not susceptible to gradual decline. Loss of bone stock in the femoral neck may then predispose to critical narrowing of the neck and to peri-prosthetic fractures. If this transpired the assumed advantages of hip resurfacing would be limited.

Dual energy X-ray absorptiometry (DEXA) is a reliable method of evaluating changes in bone mineral density (BMD) and can be applied to the femoral neck.[10] Accordingly it can be used to assess the evolution of changes in BMD after hip resurfacing. Earlier studies using DEXA have shown an increase in BMD in Gruen zone 7[11] after hip resurfacing arthroplasty, whereas a decrease in BMD in this zone has been observed after conventional THA.[3,12] However, these studies were performed with early DEXA equipment and today more sensitive software can detect BMD changes in well defined and smaller region of interest (ROI) in the femoral neck. Also, these studies were cohort series and a truly randomized comparison between THR and hip resurfacing arthroplasty for changes in BMD has not been previously described.

We have performed a prospective randomized controlled trial of hip resurfacing arthroplasty compared with metal-on-metal uncemented THA during which we evaluated changes in BMD in several ROI in the femoral neck and proximal femur for the resurfacing procedure and the corresponding region of the calcar in THA.

Patients and methods

The study was designed following a power analysis based on the work of Lian et al.[13] The minimum number of participants needed in each group to obtain a power of 80% with a significance level of $p<0.05$, was determined as 34, with a calculated difference of 2.98%

(SD 6.14) in BMD ratio.

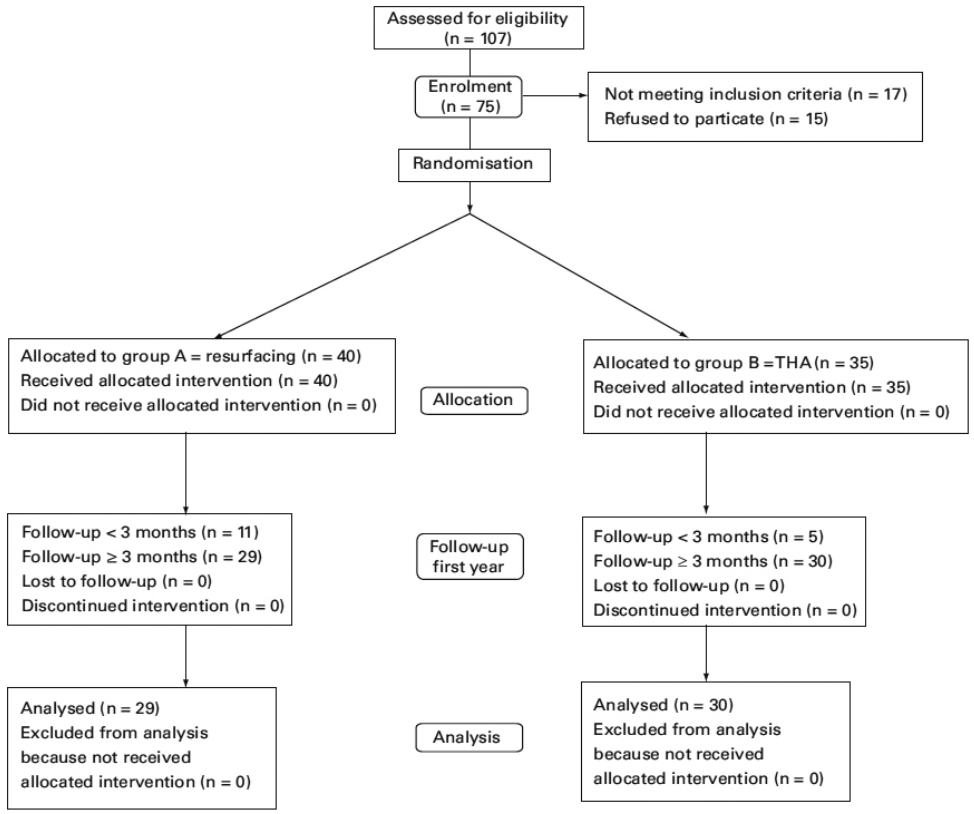


Figure 1 Consort diagram showing patient selection (THA = total hip arthroplasty).

Between June 2007 and December 2008, 75 patients were randomly assigned to receive one of two hip implants, either a hip resurfacing arthroplasty (Conserve® Plus, Wright Medical Technology, Arlington, Tennessee) or a THA (Zweymüller® Metasul®, Zimmer Orthopaedic, Warsaw, Indiana) (Figure 1). Consecutive randomization was employed using a computer-generated variable block schedule. The randomization list was generated by an independent statistician and the resulting treatment allocations were stored in sealed opaque envelopes. Randomization occurred prior to surgery. Due to the nature of the procedure both the patient and the surgeon could not be blinded to the eventual type of implant but neither the patient nor the surgeon could influence the randomization process. Patients were informed in detail about the randomization procedure and accepted the assigned implant in all cases. They were aged between 35 and 65 years old and needed a primary hip replacement because of arthritis, congenital hip dysplasia or posttraumatic arthritis. Patients were excluded if they had a previous history of infection of the hip or other sites, a hip fracture, avascular necrosis with collapse of the femoral head, rapid progressive bone resorption, levels of BMD

indicating osteoporosis of the involved hip, or renal failure. Two patients were excluded after randomization for hip resurfacing since during the operation anatomical deformities were encountered which precluded this procedure and a THA was carried out. Of the randomized patients, 59 had a minimum follow-up of three months. The 29 patients in group A received a resurfacing implant and 30 in group B, an uncemented THA. There were no significant differences between the groups for age and gender (Table 1). The body mass index (BMI) of group A was significantly lower than in group B (Student's t-test, p=0.048), but this difference was small and considered clinically irrelevant.

Approval from the regional ethics committee from the Radboud University Nijmegen Medical Centre was obtained and all patients provided informed consent.

Table 1 Clinical details of the patients in both groups

	Group A (RHA)	Group B (THA)	p-value
Number of patients (hips)	29	30	
Mean follow-up in months (range)	17.3 (4.4-31.3)	16.0 (4.2-27.8)	0.585 [b]
Gender (women:men)	15:14	11:19	0.299 [c]
Mean body mass index (SD)	26.0 (2.7)	28.2 (5.3)	0.048 [d]
Mean age at operation in years (range)	54.8 (24 - 65)	56.6 (37-65)	0.440 [d]
Diagnosis (OA/AVN/CHD) [a]	27/1/1	29/0/1	0.713 [e]
Mean blood loss in mL (range)	258.7 (100-600)	286.4 (100-900)	0.596 [d]
Mean operating time in minutes (SD)	75.1 (10.4)	54.6 (12.9)	<0.001 [b]

[a] OA = osteoarthritis; AVN = avascular necrosis; CHD = congenital hip dysplasia [b] Student's t-test; [c] Fisher's exact probability test; [d] Mann-Whitney U test; [e] Kruskal-Wallis test

Surgical technique

Pre-operative digital templating for positioning of the implant (Easyvision, Philips Medical Systems, Eindhoven, the Netherlands) was carried out in all patients. All operations were carried out by one author (JVS) and two other experienced hip surgeons through a postero-lateral approach. In group A, the Conserve® Plus resurfacing arthroplasty was implanted with both components made of a cast, heat-treated solution- annealed cobalt-chrome alloy. The femoral component was cemented with low-viscosity cement after preparation of the femoral head with multiple subchondral anchor holes, and the hydroxyapatite (HA)-coated acetabular component under-reamed by 1 mm was press-fitted into the acetabulum. The surgical technique has been described in detail before.[14] Cementing around the stem of the femoral component was avoided.

In group B, an uncemented grit-blasted titanium alloy Zweymüller® tapered stem and a threaded acetabular component were implanted. As this trial was designed to minimize confounding variables, a metal-on-metal bearing was also used for THA with a Metasul 28 mm

diameter modular head and a Metasul lined acetabular component. Both groups received identical prophylaxis against infection, periarticular ossification and venous thrombosis during the hospital admission and for six weeks after operation. Patients mobilised without any weight-bearing restriction according to their tolerance.

The BMD was measured by DEXA (Lunar Prodigy, GE Healthcare, Little Chalfont, United Kingdom) with the software package Encore 2007 version 11.30.062. Measurements were performed two weeks pre-operatively and then at three, six and 12 months after surgery. Since the actual ROI could only be defined after implantation of the hip components, these ROI were imported from the three-month DEXA scan to the pre-operatively DEXA scan in order to measure baseline BMD levels in the absence of the implant. The patients were positioned supine on the examination table with their feet attached to a positioning device to obtain a standardised reproducible 20° of internal rotation. Mortimer et al. found that a range of 15° internal to 15° external rotation yields a precision of 1.7%.[15] The software used in our study was designed to measure the periprosthetic BMD in five ROI in the proximal femur in group A and one ROI (Gruen zone 7) in group B with a mean entrance skin dose of 37 mSv per patient (Figure 2).

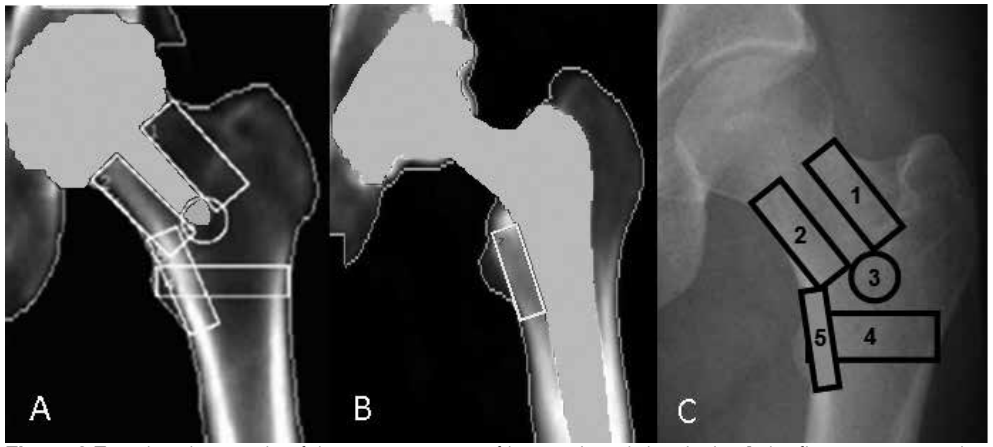


Figure 2 Templated example of the measurement of bone mineral density in: **A** the five separate region of interest (ROI) in hip resurfacing arthroplasty; **B** in total hip arthroplasty; **C** a diagrammatic representation of distribution of the areas of interest.

Tests using phantoms have shown that our DEXA scans are accurate for the determination of peri-prosthetic BMD with an error below 1%.[10] In addition, precision and reproducibility of the DEXA measurements for each ROI were assessed on 15 patients (eleven male, four female, eight hip resurfacing arthroplasty and seven THA) with a mean age of 53 years (34 to 63). They underwent two sequential DEXA examinations of the involved hip, taken on the same day and measured twice by two independent laboratory assistants, with repositioning between each scan. The precision error was then expressed as the coefficient of variation percentage and calculated according to Aldinger et al.[16] The precision in our study (Table 2)

was adequate and consistent with the literature.[16,17] Additional quality controls for the DEXA equipment were undertaken daily according to the manufacturer's guidelines to verify the stability of the system. No change was observed during the entire study period.

Table 2 Percent coefficient of variation (CV%) in ROI 1 to 5

ROI	1	2	3	4	5	Mean (SD)
CV%	1.2	2.1	2.0	2.7	3.5	2.3 (0.7)

Statistical analysis

The BMD data were normally distributed and the differences in each ROI between the two groups pre-operatively and at each follow-up were analysed using a Student's t-test. The change of the BMD in each ROI over each observation period was assessed by repeated analysis of variance (ANOVA) for the two groups. For purposes of clarity the mean change in BMD is described as the percentage relative to the pre-operative mean value. Differences were considered statistically significant with a p-value <0.05. All statistical analyses were performed using SPSS software version 15.0.1 (SPSS Inc., Chicago, Illinois).

Results

The patient characteristics are presented in Table 1. As expected, the mean operating time for group A was significantly longer than for group B (Student's t-test; p<0.001), demonstrating the inherent technical difficulty of the resurfacing procedure. There was no significant difference in pre-operative mean BMD at ROI 5 which matched Gruen zone 7[11] for resurfacing compared with THA (Student's t-test; p=0.785) (Table 3). The mean BMD ratios obtained during the 12-month follow-up, compared with the mean baseline levels, are shown in Table 4.

Table 3 Mean (SD) bone mineral density (g/cm^2) for each group at each study interval

		Pre-operative	3 months	6 months	12 months
	Group A (RHA)	n=29	n=29	n=27	n=20
	Group B (THA)	n=30	n=30	n=28	n=20
ROI 1	Group A	0.88 (0.32)	0.82 (0.29)	0.85 (0.28)	0.93 (0.29)
ROI 2	Group A	1.32 (0.33)	1.31 (0.35)	1.33 (0.35)	1.35 (0.36)
ROI 3	Group A	0.92 (0.31)	0.88 (0.27)	0.90 (0.28)	0.95 (0.28)
ROI 4	Group A	1.28 (0.25)	1.27 (0.25)	1.29 (0.24)	1.34 (0.25)
ROI 5	Group A	1.87 (0.32)	1.92 (0.41)	1.97 (0.39)	1.97 (0.40)
ROI 5	Group B	1.90 (0.39)	1.67 (0.39)	1.57 (0.43)	1.53 (0.40)

Table 4 Mean (SD) bone mineral density ratio (%) for each group at each study interval

		Pre-operative	3 months	6 months	12 months
	Group A (RHA)	n=29	n=29	n=27	n=20
	Group B (THA)	n=30	n=30	n=28	n=20
ROI 1	Group A	100	94.1 (10.4)	97.3 (10.9)	101.3 (10.9)
ROI 2	Group A	100	98.5 (9.8)	100.2 (9.2)	100.9 (7.7)
ROI 3	Group A	100	92.0 (8.0)	95.0 (7.6)	96.6 (7.8)
ROI 4	Group A	100	99.0 (6.1)	100.2 (5.6)	100.5 (4.7)
ROI 5	Group A	100	103.5 (10.0)	105.2 (9.2)	105.2 (9.7)
ROI 5	Group B	100	88.8 (12.7)	84.0 (15.0)	82.1 (14.6)

After resurfacing the BMD values of ROI 1, 2 and 4 revealed a slight, non-significant decrease in BMD during the first three months (Student's t-test; ROI 1 p=0.486, ROI 2 p=0.955, ROI 4 p=0.774), together with a subsequent restoration to the baseline pre- perative values at 12 months (Figure 3). In contrast, in ROI 3 of the tip of the peg of the resurfacing arthroplasty, a significant decrease to 92% of the baseline values (ANOVA; p<0.001) was observed at three months which remained 96.6% (ANOVA; p=0.046) of the mean pre-operative value at 12 months.

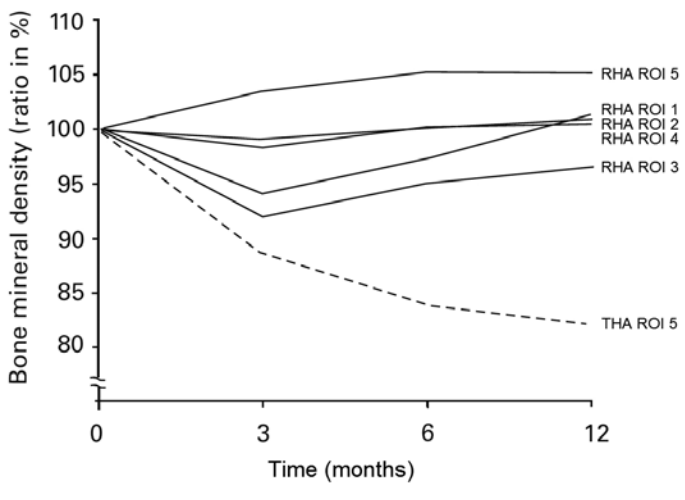


Figure 3 Graph of the mean bone mineral density ratio as a proportion of the pre-operative baseline values (100%) for all region of interest (ROI) in resurfacing hip arthroplasty (RHA) and total hip arthroplasty (THA).

Due to the nature of a resurfacing arthroplasty compared to a THA, only BMD values of ROI 5 representing Gruen zone 7 were available for both implants. The mean BMD ratio in ROI 5 increased to 105.2% of the pre-operative mean values after resurfacing within six months (ANOVA; p=0.012), while in the same ROI the mean BMD ratio for THA decreased significantly to 82.1% (ANOVA; p<0.001). The actual decrease of 17.9% of the mean BMD ratio in Gruen zone 7 for the THA group was most marked in the first six months after surgery and remained stable thereafter. This pattern of difference in BMD changes between the two implants in ROI 5 persisted at one year, with a further reduction in the mean BMD ratio for the THA group which remained significantly different from the findings in the resurfacing arthroplasty patients (Student's t-test; p<0.001).

Discussion

This prospective randomized controlled study indicates that the normal load transfer through the femoral neck is maintained or restored after hip resurfacing arthroplasty and there is an increase in desnity in the proximal femur. In contrast the BMD was reduced after the uncemented THA used in this study.

These results are in accordance with earlier case control studies, which also reported an increase of BMD in the calcar region to 105% at 12 months[3,12] and 111% at 24 months in a resurfacing group,[3] and a decrease of 17% in a THA group. However, both earlier studies were non-randomized case control series with the potential for bias in patient selection. In addition, the studies were small and the metal-on-metal HA-bearing was compared with a ceramic-on-polyethylene bearing couple. Our patients were randomized, producing comparable groups with similar demographics (Table 1) and bearing couples. The more recent DEXA software package used in our study permitted smaller ROI to be examined with greater accuracy, as indicated by the low coefficient of variation (Table 3).

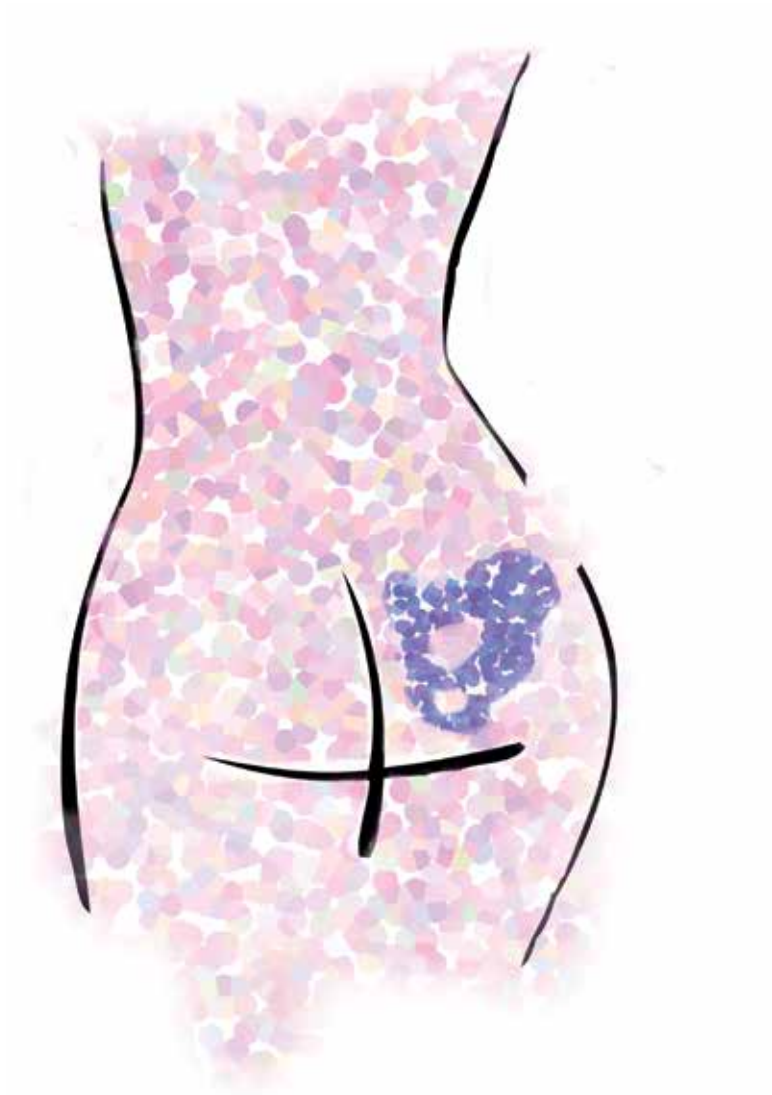
The literature is inconclusive regarding the extent to which stress-shielding affects the proximal femoral bone stock after resurfacing.[4-8,18] The data from our randomized controlled trial clearly indicate preservation of BMD in the femoral neck after resurfacing arthroplasty and a significant increase of BMD in Gruen zone 7. In the control group of uncemented THA's a significant decrease of the BMD in Gruen zone 7 was identified. This loss of BMD in the proximal femur is a consequence of stress-shielding in distally fixed uncemented THA's.[1,2,5,19-22] It has to be recognised that the choice of implant plays an important role in the progress of depletion of peri-prosthetic bone stock and thus may have influenced the observed changes in BMD in our study. However, since earlier studies[3,12] with different types of resurfacing arthroplasty report similar changes, it appears that evidence is accumulating for true preservation of bone density after this procedure.

We have evidence that BMD recovers in the proximal femur after resurfacing arthroplasty, which might be important at a future revision. We recognise the limitations of this study as the follow-up is short. Accordingly, caution must be observed in extrapolating the results at one year of an operation designed to last many years. The significant decrease of ROI 3 might be iatrogenic as the drill hole for the RHA peg extends beyond the peg itself. We looked at a range of aetiologies for the arthritis of the hip but could not perform any analysis of the subgroups as most patients had osteoarthritis.

References

1. Oh I, Harris W. Proximal strain distribution in the loaded femur. An in vitro comparison of the distributions in the intact femur and after insertion of different hip-replacement femoral components. *J Bone Joint Surg Am.* 1978;60(1):75-85.
2. Kröger HPJ, Venesmaa P, Jurvelin J, Miettinen HJA, Suomalainen OT. Bone density at the proximal femur after total hip arthroplasty. *Clin Orthop Relat Res.* 1998(352):66-74.
3. Kishida Y, Sugano N, Nishii T, Miki H, Yamaguchi K, Yoshikawa H. Preservation of the bone mineral density of the femur after surface replacement of the hip. *J Bone Joint Surg Br.* 2004;86-B(2):185-189.
4. Harty J, Devitt B, Harty L, Molloy M, McGuinness A. Dual energy X-ray absorptiometry analysis of peri-prosthetic stress shielding in the Birmingham resurfacing hip replacement. *Arch Orthop Trauma Surg.* 2005;125(10):693-695.
5. Deuel CR, Jamali AA, Stover SM, Hazelwood SJ. Alterations in femoral strain following hip resurfacing and total hip replacement. *J Bone Joint Surg Br.* 2009;91-B(1):124-130.
6. Waal Malefijt MCd, Huiskes R. A clinical, radiological and biomechanical study of the TARA hip prosthesis. *Arch Orthop Trauma Surg.* 1993;112(5):220-225.
7. Watanabe Y, Shiba N, Matsuo S, Higuchi F, Tagawa Y, Inoue A. Biomechanical study of the resurfacing hip arthroplasty: finite element analysis of the femoral component. *J Arthroplasty.* 2000;15(4):505-511.
8. Spencer S, Carter R, Murray H, Meek RM. Femoral neck narrowing after metal-on-metal hip resurfacing. *J Arthroplasty.* 2008;23(8):1105-1109.
9. Shimmin A, Beaule PE, Campbell P. Metal-on-metal hip resurfacing arthroplasty. *J Bone Joint Surg Am.* 2008;90(3):637-654.
10. Kiratli BJ, Heiner JP, MvBeath AA, Wilson MA. Determination of bone mineral density by dual X-ray absorptiomatry in patrients with uncemented total hip arthorplasty. *J Orthop Res.* 1992;10(6):836-844.
11. Gruen TA, McNeice GM, Amstutz HC. 'Modes of failure' of cemented stem-type femoral components. A radiographical analysis of loosening. *Clin Orthop Relat Res.* 1979;Jun(141):17-27.
12. Hayaishi Y, Miki H, Nishii T, Hananouchi T, Yoshikawa H, Sugano N. Proximal femoral bone mineral density after resurfacing total hip arthroplasty and after standard stem-type cementless total hip arthroplasty, both having similar neck preservation and the same articulation type. *J Arthroplasty.* 2007;22(8):1208-1213.
13. Lian Y, Pei F, Yoo M, Cheng J, CY F. Changes of the bone mineral density in proximal femur following total hip resurfacing arthroplasty in osteonecrosis of femoral head. *J Orthop Res.* 2007;26(4):453-459.
14. Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid surface arthroplasty. Surgical technique. *J Bone Joint Surg Am.* 2006;88(1_suppl_2):234-249.
15. Mortimer ES, Rosenthall L, Paterson I, Bobyn JD. Effect of rotation on periprosthetic bone mineral measurements in a hip phantom. *Clin Orthop Relat Res.* 1996;324:269-274.
16. Aldinger PR, Sabo D, Pritsch M, Thomsen M, Mau H, Ewerbeck V, et al. Pattern of periprosthetic bone remodeling around stable uncemented tapered hip stems: A prospective 84-month follow-up study and a median 156-month cross-sectional study with DXA. *Calcif Tissue Int.* 2003;73(2):115-121.
17. Albanese CV, Santori FS, Pavan L, Learmonth ID, Passariello R. Periprosthetic DXA after total hip arthroplasty with short vs. ultra-short custom-made femoral stems. *Acta Orthop.* 2009;80(3):291-297.
18. Hing CB, Young DA, Dalziel RE, Bailey M, Back DL, Shimmin AJ. Narrowing of the neck in resurfacing arthroplasty of the hip: A Radiological Study. *J Bone Joint Surg Br.* 2007;89-B(8):1019-1024.
19. McCarthy C, Steinberg G, Agren M, Leahey D, Wyman E, Baran D. Quantifying bone loss from the proximal femur after total hip arthroplasty. *J Bone Joint Surg Br.* 1991;73-B(5):774-778.

20. Venesmaa PK, Kroger HP, Jurvelin JS, Miettinen HJ, Suomalainen OT, Alhava EM. Periprosthetic bone loss after cemented total hip arthroplasty: a prospective 5-year dual energy radiographic absorptiometry study of 15 patients. *Acta Orthop Scand.* 2003;74(1):31-36.
21. Sköldenberg OG, Bodén HSG, Salemyr MOF, Ahl TE, Adolphson PY. Periprosthetic proximal bone loss after uncemented hip arthroplasty is related to stem size: Dexa measurements in 138 patients followed for 2–7 Years. *Acta Orthop.* 2006;77(3):386-392.
22. Kim Y-H, Yoon S-H, Kim J-S. Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement: Alumina-on-alumina versus alumina-on-polyethylene articulation. *J Bone Joint Surg Br.* 2007;89-B(2):174-179.



Periacetabular bone mineral density changes after resurfacing hip arthroplasty versus conventional total hip arthroplasty. A randomized controlled DEXA study

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Abstract

A randomized controlled trial was performed to evaluate acetabular bone mineral density (BMD) changes after hip resurfacing (RHA) versus an established conventional total hip arthroplasty (THA). A total of 71 patients were allocated randomly to receive either an RHA press-fit Co-Cr cup (n=38) or a THA with a threaded titanium cup and polyethylene-metal-inlay insert (n=33). The BMD in five separate periacetabular regions of interest (ROI) was prospectively quantified pre-operative until 24 months. We conclude that, in contrast to our hypothesis, periacetabular BMD was better preserved after RHA than after placement of a conventional THA. Long term follow-up studies are necessary to see whether this benefit in bone preservation sustains over longer time periods and whether it is turned into clinical benefits at future revision surgery.

Introduction

One of the biggest concerns in total hip arthroplasty is long-term acetabular fixation and preservation of bone stock. According to the Swedish hip register 65% of all re-operations are because of an acetabular component revision.[1] A thirty year follow-up of the Charnley arthroplasty by Callaghan et al.[2] shows that revision of the cup is three times more common than stem revision. Polyethylene wear of acetabular components is a key factor in the development of periprosthetic osteolysis.[3,4] Periprosthetic osteolysis with loosening of the socket frequently opposes the orthopedic surgeon with challenging acetabular bone defect reconstructions.

Metal-on-metal (MoM) hip arthroplasty was introduced as an alternative to overcome polyethylene wear related prosthetic failure. Proposed advantages are a reduction of wear, a subsequent lower incidence of periprosthetic osteolysis and eventually improved prosthetic survival.[5] On the other hand, a resurfacing hip prosthesis needs a rigid and thick shell press-fit socket. Such a relatively thick and rigid socket makes the implant stiffer and more susceptible to localized bone resorption caused by stress shielding behind the implant.[6] These press-fit cups transmit forces sideways to the peripheral cortical bone which induces stress shielding and a subsequent decrease of the cancellous bone mineral density (BMD) behind the cup.[7-9]

The main theoretical benefit of resurfacing is the bone-preserving nature of the technique on the femoral side, however, when stress shielding results in osteolysis behind the cup, this benefit would be ineffective, if not detrimental. Finite element analyses predict medial bone loss up to 50% caused by stress shielding, and a bone gain near the prosthetic rim of press-fit cups (which is the main loading site of the pelvis).[10] Clinical dual energy X-ray absorptiometry (DEXA) studies on metal-on-poly (MoP) conventional THA confirm these results.[11,12] Little is known about periprosthetic acetabular BMD changes around MoM implants and resurfacing hip arthroplasty (RHA) in particular. So far, only one study evaluated the acetabular BMD after RHA.[13] In that study the periacetabular BMD was evaluated one year after an RHA and compared to the BMD in the contralateral non-operated hip, no prospective changes in BMD were recorded in this study.

A randomized comparison between RHA and conventional THA for periacetabular BMD changes has not been previously reported. For this reason, we performed a prospective randomized controlled trial of an RHA versus a conventional MoM THA and evaluated BMD changes in five periprosthetic regions of interest (ROI) of the acetabulum. We hypothesized that due to stress shielding behind the RHA cup a more profound BMD decrease would be encountered as compared to an established threaded conventional THA cup.

Materials and methods

This randomized study was designed to compare, amongst other outcome parameters, the

periprosthetic BMD changes in the acetabulum of patients who received an RHA against a conventional uncemented MoM THA. The BMD of the femoral side of these patients has already been reported by our group,[14] we now present a further recruitment of patients.

From June 2007 till January 2010 82 patients were randomly assigned to receive one of the two hip implants types (RHA versus THA) (Figure 1).

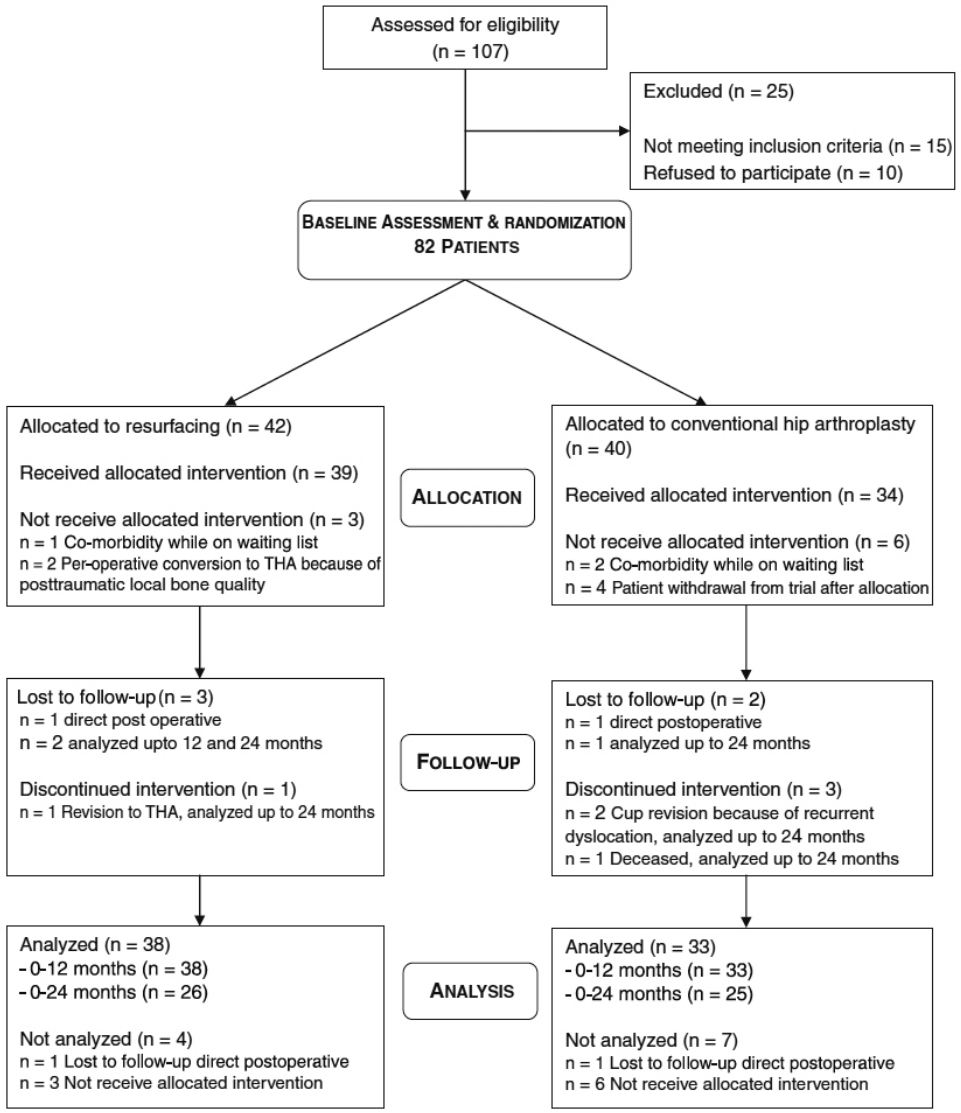


Figure 1 Consort statement: flowchart of participants throughout the study.

A computer-generated variable block schedule was used for randomization. The randomization list was generated by an independent statistician and the resulting treatment allocations were stored in sealed opaque envelopes. Randomization occurred at the outpatient consultation by the orthopedic surgeon at the time of planning the hip arthroplasty. Patient and the surgeon could not be blinded for the eventual type of implant, neither could they influence the randomization outcome. The criteria for inclusion were patients under 65 years, who needed a primary hip replacement for osteoarthritis. Patients were excluded if they had (previous) infection of the hip or other sites, hip fracture, avascular necrosis with collapse, osteoporosis, neoplasm, or renal failure. Inclusion and subsequent follow-up of patients is summarized in the consort statement (Figure 1).

Five patients (three RHA, two THA) were lost to follow-up; directly after operation (n=2), after 12 months (n=1) and after 24 months (n=2). Three patients (one RHA, two THA) did not participate in all follow-up moments because of revision after 24 months, one patient passed away. One RHA was revised for unexplained pain and subtle signs of a periprosthetic adverse reaction to metal debris (ARMD) on MRI scan, in two patients with a THA a relatively simple insert exchange was performed for recurrent dislocation. Seventy-one patients had a follow-up of 12 months; 38 RHA patients, and 33 THA patients, 51 patients had a follow-up of 24 months. There were no significant differences between both groups for age, gender and BMI (Table 1). Approval from the regional ethics committee from the Radboud University Nijmegen Medical Centre was obtained (LTC 419- 071206). All patients agreed to sign an informed consent form. The study was performed in compliance with the Helsinki declaration, and is registered in EudraCT (2006-005610-12).

Table 1 Clinical details of the patients in both groups

	RHA (n=38)	THA (n=33)	p-value
Gender (women:men)	17:21	13:21	0.637 [a]
Mean BMI (SD)	26.1 (3.1)	28.0 (5.1)	0.083 [b]
Median acetabular cup size (range)	54 (48-60)	64 (58-68)	<0.001 [c]
Median age at operation in years (range)	57.5 (40.7)	59.1 (27.8)	0.475 [c]
Diagnosis (OA/AVN/CHD) *	35/1/2	32/0/2	0.639 [d]
Median blood loss in mL (range)	300 (100-600)	250 (100-900)	0.993 [c]
Mean operating time in minutes (range)	75.0 (40)	54.0 (45)	<0.001 [b]

* OA = osteoarthritis; AVN = avascular necrosis; CHD = congenital hip dysplasia. [a] Fisher's exact probability test, [b] Student's t-test, [c] Mann-Whitney U test, [d] Kruskall-Wallis test.

Surgical technique

Pre-operative digital templating (Easyvision, Philips Medical Systems, Eindhoven, the Netherlands) for positioning of the implant was carried out for all patients. All surgeries were carried out by one of the authors (JvS) and two other experienced hip surgeons through

a posterolateral approach. In the RHA group a resurfacing prosthesis was implanted with both components made of a cast, heat-treated solution-annealed Co–Cr alloy (Conserve® Plus; Wright Medical Technology, Arlington, Tennessee, USA) (Figure 2). The femoral component was cemented with low-viscosity cement after preparation of the femoral head with multiple subchondral anchor holes, the 6-mm hydroxyapatite (HA)-coated acetabular component was pressfitted in the acetabulum (underreamed by 1 mm). The surgical technique has been described earlier.15 In the THA group, an uncemented grit-blasted titanium alloy Zweymüller® tapered stem was press-fitted in the femoral canal and a threaded solid backed titanium acetabular component was screwed in the acetabulum without additional screw fixation (Figure 3).

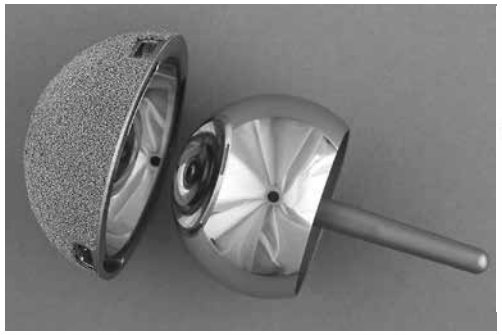


Figure 2 Conserve® Plus hip resurfacing; Wright Medical Technology, Arlington, Tennessee, USA.

Figure 3 Alloclasic Zweymüller® CSF with Metasul inlay; Zimmer Orthopaedics, Warsaw, Indiana, USA.

As this trial was designed to minimize confounding variables, a metal-on-metal bearing was also used for the THA together with a metal 28-mm head (Alloclasic Zweymüller® CSF with Metasul® inlay; Zimmer Orthopaedics, Warsaw, Indiana, USA). Both groups received identical antibiotic prophylaxis with Cephalosporin pre-operative and 24 hours postoperative, three days of Diclophenac for periarticular ossification prophylaxis, and thrombosis prophylaxis with Fraxiparine until six weeks postoperative. Patients were rehabilitated with immediate unrestricted weight bearing according to patient's tolerance.[16]

Bone densitometry

BMD measurements and software have been described previously by our group.[14] Briefly, the BMD was measured by DEXA (Lunar Prodigy, GE Healthcare, United Kingdom) with software package 13.60.033. Measurements were performed two weeks pre-operatively and then at 3, 6, 12 and 24 months after surgery. The patients were positioned supine with their feet attached to a positioning device to obtain a standardized reproducible 20° of internal rotation. Mortimer et al.[17] found that a range of 15° internal to 15° external rotation yields a precision of 1.7%. Five ROI were carefully defined, modified from the regions defined by Wilkinson et al. (Figure 4).[18]

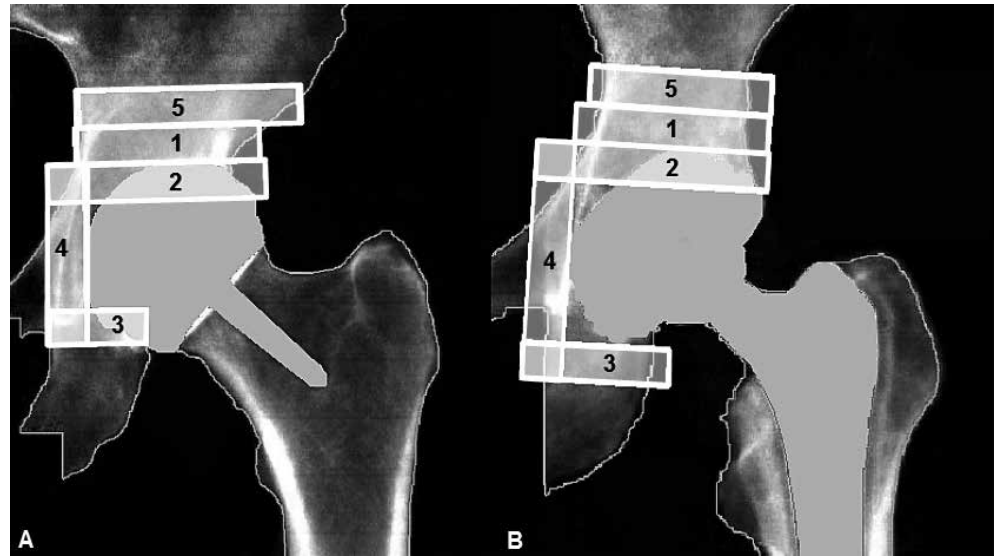


Figure 4 Typical example of the measurement of BMD in the separate ROI's by DEXA of RHA (**A**) and THA (**B**).

For each patient standardized analysis of each ROI was obtained using the manufacturers metal exclusion software. Since the ROI could only be defined after implantation of the hip arthroplasty, these ROI's were imported in the pre-operatively available DEXA scan to measure baseline BMD levels in the absence of the implant. Tests using phantoms have shown that DEXA is accurate for the determination of periprosthetic BMD with an error below 1%.[19] In addition, precision and reproducibility of the DEXA measurements for each region in this study were assessed on fifteen patients (eleven male, four female; eight RHA and seven THA) with a mean age of 53 years (range 34–63). They underwent two sequential DEXA examinations of the involved hip, taken on the same day and measured twice by two independent laboratory assistants, with repositioning between each scan. The precision error was expressed as the coefficient of variation percentage, calculated according to Aldinger et al.[20] The precision in our study (Table 2) was adequate and consistent with the literature.[18,20,21] Additional quality controls for the DEXA equipment were undertaken daily according to the manufacturer's guidelines to verify the stability of the system. No change was observed during the entire study period.

Table 2 Percent coefficient of variation (CV%) in ROI 1 to 5

ROI	1	2	3	4	5	Mean (SD)
CV%	1.3	2.2	3.0	4.0	2.5	2.6 (0.9)

Statistical analysis

We conducted a power analysis based on the article of Lian et al.[22] The minimal number of participants needed in each group, to obtain a power of 80%,was determined at 34 patients,with a calculated difference of 2.98 percent (SD 6.14) in mean relative BMD. All BMD data were normally distributed and the differences in each ROI between the two groups pre-operatively and at 3, 6, 12 and 24 months after surgery were analyzed using a Student's t-test. The change of the BMD in each ROI over each observation period was assessed by repeated analysis of variance for the two groups. To compare the changes between the time intervals, the mean relative BMD as a percentage of the baseline value (presented as 100%) was calculated. All normally distributed data are expressed as group means±SD. When not normally distributed a median and a range are given. Differences were considered statistically significant at $p<0.05$ All statistical analyses were performed using SPSS software (version 18.0).

Results

Patient characteristics are presented in Table 1. The mean operating time for the RHA group was significantly longer than for the THA group ($p<0.001$), demonstrating the inherent technical difficulty of the resurfacing procedure. The acetabular cup of the THA was significantly bigger than the RHA ($p<0.001$). Pre-operatively the BMD of ROI 3 (caudal zone) significantly differed between the two study groups with a higher BMD in the RHA group ($p=0.006$) (Table 3).

Table 3 Mean BMD (in g/cm²) (SD) for both groups in the postoperative period

	Time (months)	Cranial		Medial		Caudal
		ROI 1	ROI 5	ROI 2	ROI 4	ROI 3
RHA						
(n=35)	0	1.78 (0.24)	1.71 (0.31)	2.01 (0.29)	1.48 (0.48)	1.48 (0.47) [a]
(n=38)	3	1.73 (0.29)	1.70 (0.36)	1.54 (0.35)	1.39 (0.52)	1.48 (0.47) [a]
(n=38)	6	1.76 (0.30)	1.72 (0.34)	1.53 (0.37) [a]	1.39 (0.52)	1.45 (0.45) [a]
(n=38)	12	1.75 (0.33)	1.72 (0.36)	1.57 (0.41) [a]	1.39 (0.49)	1.53 (0.51) [a]
(n=26)	24	1.77 (0.41)	1.73 (0.37)	1.54 (0.45) [b]	1.40 (0.54) [b]	1.45 (0.57) [a]
THA						
(n=32)	0	1.78 (0.33)	1.76 (0.39)	2.03 (0.35)	1.34 (0.60)	1.19 (0.35) [a]
(n=33)	3	1.67 (0.29)	1.64 (0.35)	1.46 (0.29)	1.23 (0.56)	1.08 (0.35) [a]
(n=33)	6	1.63 (0.32)	1.67 (0.38)	1.35 (0.28) [a]	1.25 (0.54)	1.07 (0.31) [a]
(n=33)	12	1.61 (0.37)	1.61 (0.37)	1.31 (0.27) [a]	1.21 (0.57)	1.07 (0.27) [a]
(n=25)	24	1.60 (0.35) [b]	1.60 (0.39) [b]	1.34 (0.29) [b]	1.24 (0.46) [b]	1.05 (0.24) [a,b]

[a] Significant difference between RHA and THA ($p\leq.05$). [b] Significant difference against baseline at repeated measures within each ROI ($p\leq0.05$).

There were significant differences between the two groups in mean relative BMD. Twelve months after surgery the mean relative BMD was significantly higher for RHA in all ROI's except for ROI 4 ($p=0.028$, $p=0.001$, $p=0.040$, $p=0.293$, and $p=0.006$, for ROI's 1, 2, 3, 4 and 5 respectively). At 24 months a significantly higher mean relative BMD still existed for ROI's 1, 2 and 5 ($p=0.030$, $p=0.046$, $p=0.013$). In ROI's 1 and 2 there was also a difference at 6 months in favor of RHA ($p=0.017$, $p=0.018$). The pattern of postoperative BMD decrease in ROI 2 was similar in both groups (Figure 5) with a steep decline in BMD from baseline till the first evaluation at 3 months.

A difference of 13.6% between the two groups in mean relative BMD was obtained for the caudal ROI 3, at 12 months. In this region the BMD increased up to 105% for RHA versus a decrease up to 91% for THA ($p=0.040$). At 24 months there were only significant differences between RHA and THA in ROI's 1, 2 and 5; 7.9% ($p=0.030$), 10.4% ($p=0.046$) and 8.1% ($p=0.013$) respectively, in favor of RHA.

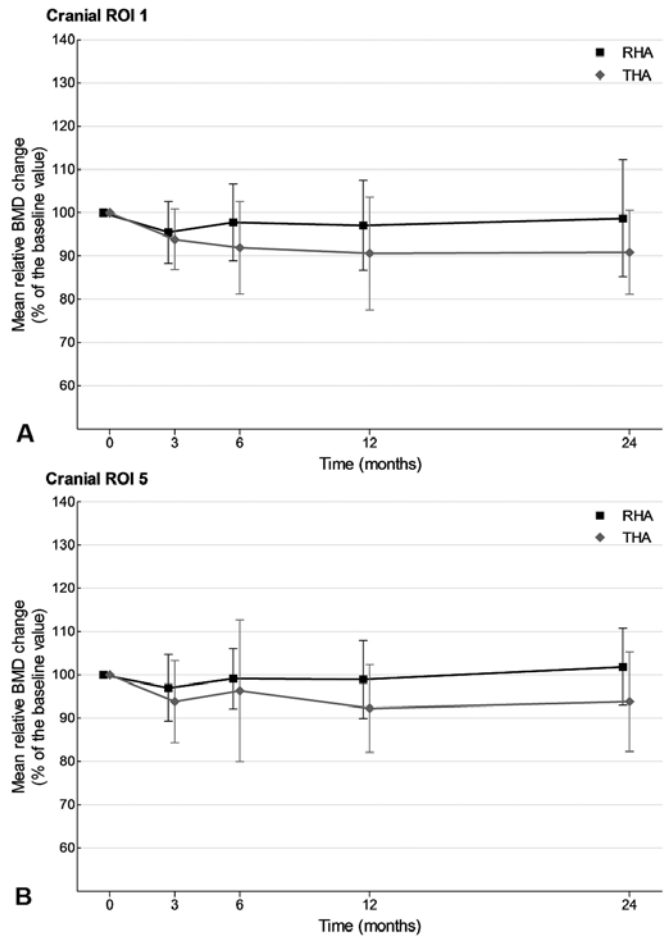


Figure 5 Graph of the mean relative BMD change, as percentage of pre-operative baseline values with error bars indicating one standard deviation for all ROI of RHA (black line) versus THA (gray line).
A Cranial to the acetabular cup ROI 1.
B Cranial to the acetabular cup ROI 5.

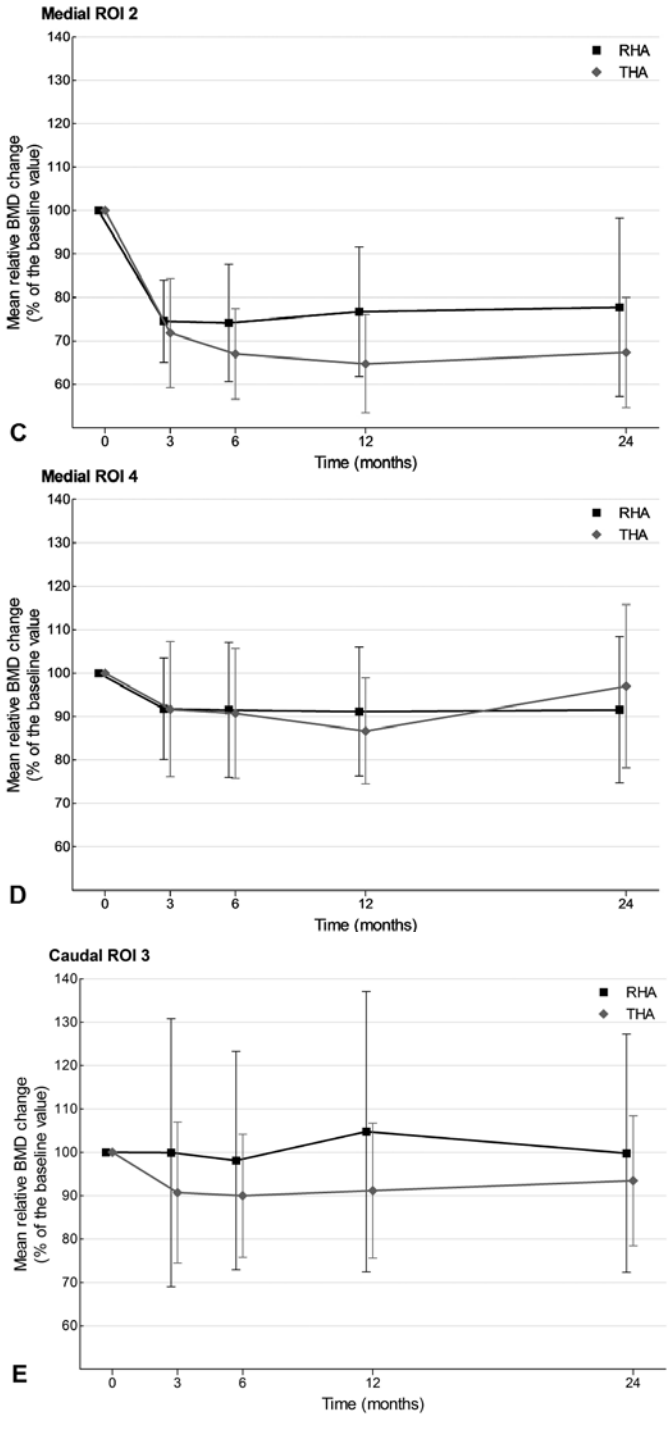


Figure 5 (continued)
C Medial to the acetabular cup ROI 2.
D Medial to the acetabular cup ROI 4.
E Caudal to the acetabular cup ROI 3.

Discussion

This prospective randomized controlled study shows that after an RHA both cranial ROI's remained stable around baseline levels whereas for one cranial ROI the BMD decreased significantly after THA. As for the two medial ROI's, the BMD decreased significantly for both implants ($p<0.05$), in one of these ROI's this difference was in favor of the RHA group. BMD remained stable in the caudal ROI for RHA, whereas a significant decrease was found in the caudal ROI for THA.

These results suggest that, unlike our hypothesis, the acetabular bone was better preserved after the RHA with the rigid press-fit cup. The observed decrease in BMD medial to the cup (ROI's 2 and 4) of 23% and 8.5% for RHA and 32% and 3% for THA at 24 months are in concordance with earlier literature on BMD changes after press-fitted cups of a conventional THA. In clinical[12,23,24] and finite element[10,25] studies a 5% to 50% decrease was found in the ROI medial to the acetabular cup. The BMD preservation of RHA patients was most profound cranial to the cup (ROI's 1 and 5) for RHA patients. This is in accordance with the recent report from Yahia et al.[13] where similar results were found two years postoperative. In contrast to other studies, where a 3% to 35% decrease of cranial acetabular BMD was seen after the placement of a press-fit cup,[7,9,23,26,27] we only found a significant decrease for one of the two cranial ROI's in the THA group. As confirmed in other studies we found the most rapid changes in BMD in the first six months after surgery, but (smaller) BMD changes still occurred until 24 months.[27-29]

Wear and osteolysis are probably the most important factors that limit the survival of metal-on-poly THA. The articulation of the metal ball against the polyethylene cup of the acetabular component creates polyethylene wear debris. The macrophage-mediated response to these implant-derived particulate debris and probably other stimuli, results in local osteoclastic bone resorption.[30] Using a metal-on-metal bearing might prevent this wear-induced osteolysis, but does not overcome stress shielding and subsequent adaptive remodelling. Stress shielding is a major reason for periprosthetic bone loss after THA, because of changes in load distribution as a consequence of the rigidity of an implant.[7,25] Theoretically, the thicker and stiffer press-fit acetabular cup of an RHA may increase periacetabular bone stress shielding.[7-9,13,29] The rationale behind differences in stress shielding for press-fit or threaded cups is based on the elasticity modulus, whereas titanium is half as stiff as cobalt–chromium–molybdenum alloy (modulus of elasticity 114 vs. 214 GPa). Therefore, one would expect that the stiffer and more robust monoblock cobalt-chromium shell would show more bone loss because of increased stress shielding as shown 'in vitro'.[7] We found the opposite, the monoblock shell preserved relatively more cranial acetabular bone compared to the titanium threaded cup. Possibly the differences in modulus of elasticity between the two bearings in vivo were insufficient to effect the same quantitative changes in the BMD over the two years of the study. In our observations, that overall more BMD decline was encountered for THA patients as compared to RHA, we also have to realize that firm conclusions can only

be drawn for the implants used in our study. The use of a metal-on-metal bearing with the THA may for example have stiffened the acetabular component leading to more profound stress shielding and BMD decline. On the other hand we do feel that this potential influence may have been minimal. What we know from our clinical data of these patients is that RHA patients reach a higher activity level then patients with a conventional THA,[31] this might be a possible confounder. This higher postoperative activity level may have contributed to a reduced postoperative bone loss in the RHA group.[32] On the other hand the encountered difference in activity score in favor of RHA patients was only limited and we do not feel that the difference in BMD changes from can be explained by this phenomenon.

A remarkable finding in our study is the major decrease of BMD within the first 3 months of ROI 2 in both groups, whereas in other clinical studies[11,23] a more gradual medial BMD loss between 5% and 17% until one year postoperative has been described. All these studies, however, have their baseline measurements one to six weeks postoperative and therefore all measurements on BMD were performed on the postoperative situation with the implant in situ. One of the strengths of our study was the use of serial BMD measurements which are recorded truly against the pre-operative baseline values, unlike the study of Yahia et al.[11,13] who compared with the contralateral non-operated side only at one time interval. We believe that the steep decline in BMD in the medio-cranial ROI 2 between the pre-operative situation and 3 months after surgery can simply be explained iatrogenic by subchondral reaming and bone removal at the time of implantation and not by stress shielding. There are some remarkable findings in ROI 3 as well. At first, we found a lower pre-operative BMD for the THA patients. We do not have an explanation for this difference, as all other patient characteristics appeared to be matched after randomization. It could have had an influence on the results as there is a significant relationship between periprosthetic femoral bone loss and the pre-operative BMD.[28] Secondly, at 12 months we found an increase in BMD to 105% for RHA, this can be explained by an outlier of 260%. Without this outlier the mean relative BMD would be 100%. Lastly, at all time intervals the standard deviation in ROI 3 of the RHA groups is almost twice as large compared to THA. The reason might be the difficulty of ROI analysis, although the coefficient of variation is only 3%, which is relatively low.

Limitations of this study consist of the fact that patients and reviewing surgeons were not blinded. However, we do not see how these two factors can be overcome and are convinced that this has not biased our results. In RHA patients the cup size used appeared to be significantly larger than for THA patients. This can be explained by the fact that the acetabular preparation was different between the RHA and THA socket. In the THA group a threaded conical cup was screwed in the acetabular socket which mandated removal of a relatively large amount of subchondral acetabular bone. This difference in acetabular preparation and cup size between groups is a confounding factor that theoretically may have affected the subsequently observed change in periprosthetic BMD for both implants, however, we feel that since our change in BMD is recorded against pre-operative baseline levels this influence

can only be very limited. In addition the software used to calculate the actual change in BMD did correct for the iatrogenic bone removal and thus a potential influence from this phenomenon on our results was also avoided. Another limitation is the presentation of the results up to two years, whereas stress shielding is a process of years. Therefore we will continue to follow these patients in time, as these data are part of a larger randomized trial on this matter. On the other hand, we know from the literature that a decrease in BMD after various types of arthroplasty mainly occurs during the first two years.[28,29] Additionally, although DEXA remains a safe and reliable method to evaluate changes in BMD,[19] the method only measures BMD and does not discriminate cancellous from cortical bone, and it is a two-dimensional projection instead of a three-dimensional measurement which can be performed with computed tomography.

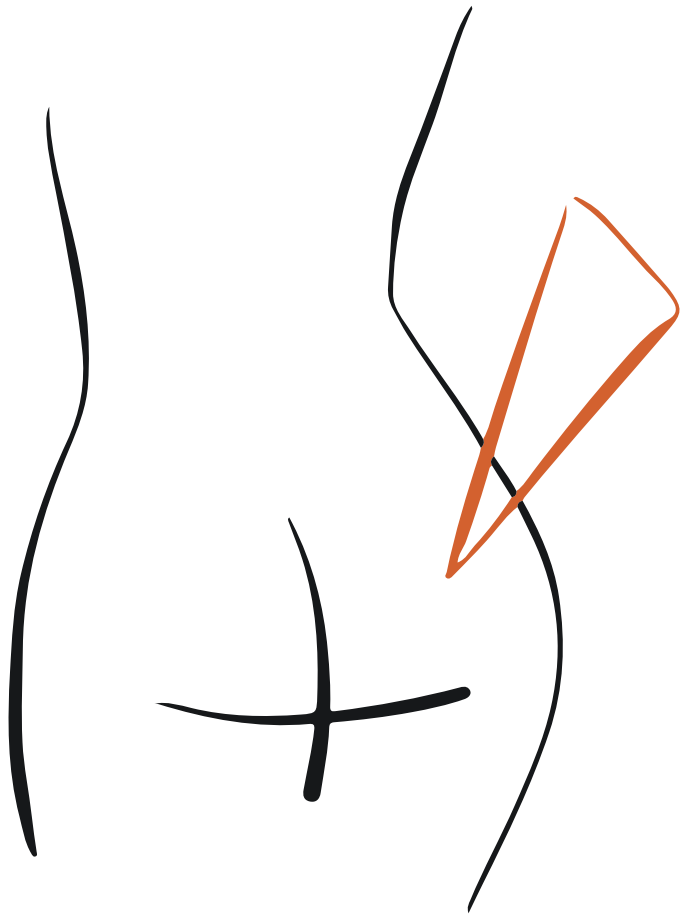
Protection of bone stock after hip arthroplasty is important, especially for the relatively young population, since revision surgery is likely to occur. In this study we focused on periprosthetic BMD changes in the acetabulum after a bone-preserving RHA and the potential pitfall of gradual bone resorption due the effects of an acetabular cup implantation. We found that after placement of a thick press-fit resurfacing cup the supposed decrease of BMD seems not to be as critical as indicated in some finite element studies.[10]

We can conclude that, on the short term, an RHA press-fit cup does not lead to more decline in periprosthetic BMD as compared to an established conventional threaded titanium acetabular component. The RHA used in this study thus appears to be relatively bone preserving, also on the acetabular side, however stress shielding is a process of years and this follow-up so far is limited to 24 months. RHA therefore does not appear to be more susceptible for periprosthetic acetabular bone loss from stress shielding as compared to an established titanium threaded shell with a well-defined clinical track record. Similar findings were already recorded by us for the femoral side[14] and thus we believe that it is safe to conclude that RHA is indeed bone preserving on both the acetabular and the femoral sides. However, as these results are different from our hypothesis, clinical and biomechanical studies are necessary to assess why bone preservation is better around the RHA compared to the conventional THA. A better understanding of periprosthetic bone remodeling may lead to further improvements of hip replacement implants.

References

1. Malchau H, Herberts P, Ahnfelt L. Prognosis of total hip replacement in Sweden: Follow-up of 92,675 operations performed 1978–1990. *Acta Orthop.* 1993;64(5):497-506.
2. Callaghan JJ, Templeton JE, Liu SS, Pedersen DR, Goetz DD, Sullivan PM, et al. Results of Charnley total hip arthroplasty at a minimum of thirty years. A concise follow-up of a previous report. *J Bone Joint Surg Am.* 2004;86(4):690-695.
3. Harris WH. Wear and periprosthetic osteolysis: the problem. *Clin Orthop Relat Res.* 2001;393:66-70.
4. Dumbleton JH, Manley MT, Edidin AA. A literature review of the association between wear rate and osteolysis in total hip arthroplasty. *J Arthroplasty.* 2002;17(5):649-661.
5. Dumbleton JH, Manley MT. Metal-on-metal total hip replacement: What does the literature say? *J Arthroplasty.* 2005;20(2):174-188.
6. Digas G, Thanner J, Anderberg C, Kärrholm J. Bioactive cement or ceramic/porous coating vs. conventional cement to obtain early stability of the acetabular cup Randomised study of 96 hips followed with radiostereometry. *J Orthop Res.* 2004;22(5):1035-1043.
7. Wright JM, Pellicci PM, Salvati EA, Ghelman B, Roberts MM, Koh JL. Bone density adjacent to press-fit acetabular components: A prospective analysis with quantitative computed tomography. *J Bone Joint Surg Am.* 2001;83(4):529-529.
8. Morscher E, Berli B, Jockers W, Schenk R. Rationale of a flexible press fit cup in total hip replacement. 5 year followup in 280 procedures. *Clin Orthop Relat Res.* 1997;341:42-50.
9. Mueller LA, Kress A, Nowak T, Pfander D, Pitto RP, Forst R, et al. Periacetabular bone changes after uncemented total hip arthroplasty evaluated by quantitative computed tomography. *Acta Orthop.* 2006;77(3):380-385.
10. Levenston ME, Beaupré GS, Schurman DJ, Carter DR. Computer simulations of stress-related bone remodeling around noncemented acetabular components. *J Arthroplasty.* 1993;8(6):595-605.
11. Kim Y-H, Yoon S-H, Kim J-S. Changes in the bone mineral density in the acetabulum and proximal femur after cementless total hip replacement: Alumina-on-alumina versus alumina-on-polyethylene articulation. *J Bone Joint Surg Br.* 2007;89-B(2):174-179.
12. Laursen M, Nielsen P, Søballe K. Bone remodelling around HA-coated acetabular cups. *Int Orthop.* 2007;31(2):199-204.
13. Yahia C, Diwanji S, Ganapathi M, Vendittoli P, Lavigne M. Supra acetabular bone mineral density measurements after hip resurfacing arthroplasty at short term follow up. *Hip Int.* 2011;21(4):468-474.
14. Smolders JMH, Hol A, Rijnders T, van Susante JLC. Changes in bone mineral density in the proximal femur after hip resurfacing and uncemented total hip replacement: A prospective randomized controlled study. *J Bone Joint Surg Br.* 2010;92-B(11):1509-1514.
15. Amstutz HC, Beaule PE, Dorey FJ, Le Duff MJ, Campbell PA, Gruen TA. Metal-on-metal hybrid surface arthroplasty. Surgical technique. *J Bone Joint Surg Am.* 2006;88(1_suppl_2):234-249.
16. Hol A, van Grinsven S, Lucas C, van Susante J, van Loon C. Partial versus unrestricted weight bearing after an uncemented femoral stem in total hip arthroplasty: recommendation of a concise rehabilitation protocol from a systematic review of the literature. *Arch Orthop Trauma Surg.* 2010;130(4):547-555.
17. Mortimer ES, Rosenthall L, Paterson I, Bobyn JD. Effect of rotation on periprosthetic bone mineral measurements in a hip phantom. *Clin Orthop Relat Res.* 1996;324:269-274.
18. Wilkinson J, Peel N, Elson R, Stockley I, Eastell R. Measuring bone mineral density of the pelvis and proximal femur after total hip arthroplasty. *J Bone Joint Surg Br.* 2001;83-B:283-288.
19. Kiratli BJ, Heiner JP, MvBeath AA, Wilson MA. Determination of bone mineral density by dual X-ray absorptiomatry in patrients with uncemented total hip arthorplasty. *J Orthop Res.* 1992;10(6):836-844.
20. Aldinger PR, Sabo D, Pritsch M, Thomsen M, Mau H, Ewerbeck V, et al. Pattern of periprosthetic bone remodeling around stable uncemented tapered hip stems: A prospective 84-month follow-up study and a median 156-month cross-sectional study with DXA. *Calcif Tissue Int.* 2003;73(2):115-121.
21. Albanese CV, Santori FS, Pavan L, Learmonth ID, Passariello R. Periprosthetic DXA after total hip arthroplasty with short vs. ultra-short custom-made femoral stems. *Acta Orthop.* 2009;80(3):291-297.
22. Lian Y, Pei F, Yoo M, Cheng J, CY F. Changes of the bone mineral density in proximal femur following total hip resurfacing arthroplasty in osteonecrosis of femoral head. *J Orthop Res.* 2007;26(4):453-459.
23. Digas G, Kärrholm J, Thanner J. Different loss of BMD using uncemented press-fit and whole polyethylene cups fixed with cement: Repeated DXA studies in 96 hips randomized to 3 types of fixation. *Acta Orthop.* 2006;77(2):218-226.
24. Stepniewski AS, Egawa H, Sychterz-Terefenko C, Leung S, Engh Sr CA. Periacetabular bone density after total hip arthroplasty: A postmortem analysis. *J Arthroplasty.* 2008;23(4):593-599.
25. Huiskes R. Finite element analysis of acetabular reconstruction: Noncemented threaded cups. *Acta Orthop.* 1987;58(6):620-625.
26. Pitto R, Bhargava A, Pandit S, Munro J. Retroacetabular stress-shielding in THA. *Clin Orthop Relat Res.* 2008;466(2):353-358.
27. Baad-Hansen T, Kold S, Nielsen PT, Laursen MB, Christensen PH, Soballe K. Comparison of trabecular metal cups and titanium fiber-mesh cups in primary hip arthroplasty. *Acta Orthop.* 2011;82(2):155-160.
28. Kröger HPJ, Venesmaa P, Jurvelin J, Miettinen HJA, Suomalainen OT. Bone Density at the Proximal Femur After Total Hip Arthroplasty. *Clin Orthop Relat Res.* 1998(352):66-74.
29. Venesmaa PK, Kroger HP, Jurvelin JS, Miettinen HJ, Suomalainen OT, Alhava EM. Periprosthetic bone loss after cemented total hip arthroplasty: a prospective 5-year dual energy radiographic absorptiometry study of 15 patients. *Acta Orthop Scand.* 2003;74(1):31-36.
30. Archibeck M, Jacobs J, Roebuck KA, Glant T. The basic science of periprosthetic osteolysis. *Instr Course Lect.* 2001;50:185-195.
31. Smolders JM, Hol A, Rijnberg WJ, van Susante JL. Metal ion levels and functional results after either resurfacing hip arthroplasty or conventional metal-on-metal hip arthroplasty. *Acta Orthop.* 2011;82(5):559-566.
32. Rosenbaum TG, Bloebaum RD, Ashrafi SB, Lester DK. Ambulatory activities maintain cortical bone after total hip arthroplasty. *Clin Orthop Relat Res.* 2006;450:129-137.

Summary and general discussion



Summary

Total hip arthroplasty (THA) is a very successful treatment for end-stage osteoarthritis of the hip. There is a trend towards increasing hip replacement surgeries,[1] not only because of an increasing number of patients with osteoarthritis of the hip, but because the lower age limits are also stretched. The working age patient (with high hip activity demands) with end-stage osteoarthritis demands to be treated with the same successful treatment as the older age group. Unfortunately, these younger patients are very likely to outlive a conventional metal-on-polyethylene (MoP) THA because of polyethylene wear and related consequences. This is the rationale behind the search for other bearing materials, and the revival of the metal-on-metal (MoM) implants. MoM hip resurfacing (RHA) is an old concept, with an improved design and metallurgy (since the 1990s and 2000s). MoM bearings claims to be more wear resistant, and are therefore expected to show less osteolysis and aseptic loosening. The overall aim of this thesis was to obtain an objective comparison between RHA and THA and confirm or reject the proposed (dis)advantages of RHA with respect to clinical outcome, metal ion and bone mineral density evolution. This chapter will summarize the outcomes after RHA, which will be discussed following the seven aims laid out in Chapter 1.

To determine the single surgeon learning curve of RHA

From a surgical perspective, hip resurfacing is a more demanding procedure than THA. Component positioning is a factor under the surgeon's control and, in particular, acetabular position is an important determinant of the ten year survivorship.[2,3] Pitfalls are a relatively steep cup position and a femoral component position in the posterior one-third of the collum. A poor cup orientation can lead to edge loading (a phenomenon whereby the femoral component comes into contact with the edge of the acetabular component), and as a consequence increased wear and metal debris accumulation. According to retrieval studies, the latter can lead to pseudotumor formation, which is four times more likely with a cup not positioned in the safe zone.[4]

To determine whether a learning curve was present, the radiological results of the first forty patients who underwent RHA in our clinic (divided in four subsequent cohorts of ten patients), were studied. The results are presented in Chapter 2. For each patient six established radiographic parameters on implant positioning[5] were measured on the pre-operative planning template with the optimal implant positioning. These parameters were compared with those of the actual implant positioning on postoperative standardized radiographs. In the last cohort, on average 10 min shorter operation time was needed compared to the first cohort ($p<0.013$). The optimal radiological position of an RHA is less than fifty degrees of acetabular abduction and a slightly valgus orientation central in the collum of the femoral component. The subsequent four cohorts showed a trend towards a less steep cup placement, a progressive valgus orientation of the stem and a highly reproducible cup-head angle. In each

subsequent cohort the difference was reduced between the pre-operative planned position and the final postoperative implant position. A clear trend towards optimal stem positioning in the central third of the femoral neck in two radiographic planes was detected throughout the four cohorts. A reproducible optimal implant position was achieved within forty patients, if performed by an experienced hip surgeon, and proves to be an acceptable learning curve for RHA.

To compare RHA and 28-mm MoM THA with regard to short-term metal ion evolution, functional results and complications

The short-term results of the randomized controlled trial (RCT) between the Conserve® Plus RHA (Wright Medical Technology, Arlington, Tennessee, USA) and Zweymüller® Classic Metasul® THA (Zimmer Orthopaedics, Warsaw, Indiana, USA) are presented in Chapter 3. From June 2007 till January 2010 seventy-one patients were randomized for either implant (38 RHA; 33 THA) and forty patients had a follow-up of at least 24 months (19 RHA, 21 THA) at the time of this manuscript. Patient characteristics were comparable, except for operation time, which was longer for the RHA patients ($p<0.001$). The main reason for hip replacement was end-stage osteoarthritis. As expected, in both groups the functional outcome scores improved significantly after surgery. RHA patients scored at 12 months significantly higher on University of California Los Angeles (UCLA) activity score (8 vs 7) and Visual Analogue Scale (VAS) satisfaction (95 vs 85) and at 24 months on UCLA (8 vs 7) and Oxford Hip Score (OHS) (13 vs 16). Chromium whole blood levels in the unilateral patients were significantly higher for RHA ($p<0.001$), whereas cobalt concentrations were comparable to those in THA. At 24 months median chromium concentrations were 1.2 µg/L (0.1-2.3) vs 0.5 µg/L (0.1-2.1), for cobalt this was 1.2 µg/L (0.5-2.2) vs 0.9 µg/L (0.1-2.7) for RHA and THA respectively. In the THA group there were three patients with recurrent dislocation, two of them had a simple cup insert exchange. No dislocations occurred in the RHA group. One RHA was revised for early aseptic loosening because of avascular necrosis of the femoral head; the cobalt level in this patient prior to revision was 2.3 µg/L.

Cobalt and chromium levels correlate with linear and volumetric wear of the femoral component.[6,7] High metal ion concentrations can be caused by continuous elevated wear as a result of edge loading from a steep acetabular positioning or a lower coverage angle design.[6,8] Excessive release of cobalt and chromium particles may result in Aseptic Lymphocytic Vasculitis-Associated Lesions (ALVAL), metallosis and pseudotumor formation, all also known under the collective term Adverse Reaction to Metal Debris (ARMD), requiring revision surgery.[9-11] The reported incidence of pseudotumors varies, depending on type of follow-up, patient characteristics, and implant design features. This is discussed in Chapter 7. In neither group there was suspicion for pseudotumor formation at the time of latest follow-up. It has to be noted however that cross-sectional imaging screening on the presence of pseudotumor formation was not part of this RCT. After the run-in phase four unilateral (three RHA,

one THA) and one bilateral (RHA) implants were considered extreme outliers, all with good clinical scores. Median metal ion levels were higher for the RHA patients, but remained below the proposed non-deviant limit of 2 µg/L for unilateral implants.[12] OHS, VAS satisfaction and UCLA activity score showed to be somewhat higher in the short-term for RHA patients. However, despite randomization, pre-operative UCLA activity levels were also in favor of RHA.

To assess whether a profound patient preference for RHA did influence clinical outcome and patient satisfaction

Patient satisfaction plays a vital role in outcome scores. A stable, well-positioned implant with low wear characteristics can still be classified a failure if the patient is not satisfied. Postoperative patient satisfaction is influenced by pre-operative expectations. Prior to eventual randomization for the RCT, patients were well informed about the known advantages and disadvantages at the outpatient department. However, randomizing for either RHA or THA in a period when RHA was marketed as 'sport prosthesis' and the ideal solution for the young and/or active patient proved extremely difficult. Patients base their perceptions and expectations, which can be totally inconsistent with known published results, on other sources than their orthopedic surgeon.[13] Certain patients proved to have an extremely high preference for RHA and did not want to participate in the RCT. These patients were followed in a separate cohort of RHA patients with an identical follow-up protocol as the RCT. The differentiation between the cohort (preference) and RCT (randomized) patients was their explicit preference for RHA or not. This gives the opportunity to identify whether preference bias of these cohort patients positively or negatively influenced postoperative satisfaction and clinical results.

The results of the comparison between 22 cohort patients and 28 RCT patients with an RHA are presented in Chapter 4. Both groups had twelve months postoperative a high VAS satisfaction; 97/100 for the preference patients and 93/100 for the randomized patients. Harris Hip Score (HHS), OHS and UCLA activity score revealed a similar significant improvement up to twelve months ($p<0.001$). Regarding the Short-Form-12 (SF-12), the preference patients scored pre-operatively lower on the mental subscale ($p=0.03$) and showed a greater increase after twelve months compared to the randomized patients ($p=0.03$). An influence of preference on patient satisfaction and early clinical outcome after RHA could not be objectified. This contradicts a meta-analysis which did find an influence of preference on treatment effect size, which was hypothesized to rely on better compliance and motivation.[14] Patient compliance might be worse when not receiving the preferred treatment if the treatment protocols differ in medication, rehabilitation or adverse effects, this is not applicable for either hip replacement where patients received an identical rehabilitation protocol.

To determine the interchangeability and provide a conversion formula between serum and whole blood metal ion measurements

The evaluation of metal ion levels is becoming increasingly important after a MoM hip replacement and serves as an indicator of bearing performance and device safety.[15] Metal ion measurements have become an important tool in the diagnostic work-up of a malfunctioning MoM implant and the orthopedic surgeon is expected to know how to interpret them. For the assessment of metal ion levels in patients with a MoM hip prosthesis various matrices, such as whole blood, serum and urine can be used. There is no consensus on the best surrogate measure of metal ion exposure, both serum and whole blood measurements are used.

In Chapter 5 the interchangeability of serum and whole blood metal ion measurements was analyzed. This chapter provides also a guideline for interpretation of metal ion analysis in clinical practice based on 343 specimens from 60 RHA and 32 THA patients, respectively. The median metal ion levels were below 2 µg/L. Cobalt and chromium levels were in accordance with Chapter 2 significantly higher for RHA versus THA, although the differences decrease after the run-in phase. In accordance with Daniel et al. no direct interchangeability between whole blood and serum levels was found.[16] The mean difference between blood and serum values was +0.13 µg/L for cobalt and -0.91 µg/L for chromium. The formula to convert serum into whole blood values was *0.34 + [0.88 * Co serum]* for cobalt and *0.14 + [0.58 * Cr serum]* for chromium, both with an acceptable prediction error less than ±1.0 µg/L. No recommendation for the use of whole blood over serum or vice versa can be given, for practical reasons whole blood may be favored. For the interpretation of metal ion concentrations it is important to be aware of renal impairment, implant design and positioning, and contamination by nutritional supplements, medication or other metal implants. With regard to implant design it is of paramount importance to define which implant brand and category of MoM hip implant it concerns: a MoM hip resurfacing, a large-diameter-head (LDH) MoM THA (greater than 36 mm diameter) or a small-diameter-head (SDH) MoM THA. These different implant designs have a different metal ion release pattern,[10,17,18] the successes and failures cannot be lumped together.

To assess the difference in trend evolution of metal ions after well and sub-optimal functioning RHA

To date there is no consensus on which levels are acceptable as cut off level to differentiate between well-functioning and sub-optimal functioning implants.[19,20] In spite of abundant ongoing research upper metal ion concentration limits are ill defined. The Mayo Medical Laboratories interpretive handbook, addresses 5 µg/L as upper limits for cobalt in whole blood and 17 µg/L in erythrocytes for chromium.[21] In our guideline the values of De Smet et al. were adopted as upper acceptable limits; 4.4 µg/L for cobalt (odds ratio for revision 6.0) and 5.1 µg/L for chromium (odds ratio for revision 4.3).[22] The Medicine and Healthcare products Re-

gulatory Agency (MHRA) recommends to check cobalt and chromium blood levels at least once postoperatively and perform cross-sectional imaging if these levels are above 7 ppb (ppb corresponds to µg/L).[20] The Dutch Orthopaedic Society advices that 2-5 µg/L should result in an outpatient visit; 5-10 µg/L mandates cross-sectional imaging for ARMD; greater than 10 µg/L is an alarm signal and revision surgery should be considered with patient complaints and cross-sectional imaging taken into account. Despite these guidelines, there are uncertainties about the consequences of prolonged elevated metal ion levels in patients and at what level the occasionally encountered events will occur. In addition to this confusion there is literature available on well-performing implants with relatively high levels of metal ions and malfunctioning implants with low values.[6,7,23-27]

At this moment, the clinical significance of a single metal ion measurement and its interpretation is not fully understood. The hypothesis was that the evolution of metal ion levels might be more informative than the currently demanded single measurements alone. The aim of this study presented in Chapter 6 was therefore to present a prospective follow-up of Co and Cr levels in a cohort of 48 unilateral RHA's and potentially identify differences in the trend characteristic in the short-term between patients with well versus sub-optimal functioning implants. Based on the most recent postoperative functional outcome score — Harris Hip Score (HHS), 0 is the worst and 100 the best outcome — the patients were divided in well and sub-optimal functioning. A HHS greater than or equal to 90 was defined as 'well-functioning' (n=42), a HHS smaller than 90 was defined as 'sub-optimal functioning' (n=6). The cobalt and chromium levels and individual trends were analyzed in these patients with a median follow-up of 24 months. The median cobalt and chromium concentration are significantly higher for the sub-optimal group, at 24 months 0.95 µg/L (0.1-9.3) vs 6.2 µg/L (2.0-29.3) and 1.70 µg/L (0.6-13.3) vs 4.70 µg/L (2.9-17.5), respectively. The percentage of well-functioning patients with increasing cobalt and chromium levels between two consecutive time-intervals (risers) gradually decreased from 90/86% (0-3 months) to 22/22% (24-36 months). The percentage of risers was higher in the sub-optimal group, in particular at 12-24 months. The median absolute increase of the subgroup of risers was significantly lower for the well-functioning group at 12-24 months; 0.70 µg/L (0.1-4.6) vs 6.65 µg/L (2.9-23.7) for cobalt and 0.80 µg/L (0.1-8.9) vs 11.6 µg/L (11.0-12.2) for chromium. It was concluded that sub-optimal functioning MoM implants have a different metal ion trend than well-functioning implants, a higher percentage of 'risers' and a larger absolute increase per interval.

From these results a low threshold for repeated metal ion measurement is recommended (in particular cobalt, as this is the most toxic), in addition to patient complaints, physical examination and cross-sectional imaging, it can help to clarify if an implant is failing. For example, a single measurement Co level of 5 µg/L at 12 months is considered a borderline concentration. In a patient without complaints, an additional concentration at 24 months of 3 µg/L would be quite reassuring (as it proves decreasing metal ion concentrations), whereas a concentration of 6 µg/L would indicate a potential malfunctioning implant. For well-functioning patients, it appears that an increase in metal ion levels is minimal after two years.

If metal ion levels increase structurally after 12 months, this might be an indication of increasing wear and a potentially malfunctioning implant. Consecutive measurement after one year and a trend assessment can help in decision-making about revision surgery in patients with mild symptoms and borderline metal ion levels (4-5 µg/L).

To determine the rate of silent pseudotumors in a cohort of hip resurfacing patients

The characteristics associated with a malfunctioning MoM implant and adverse reaction to metal debris (ARMD) include high or rising metal ions, a steep cup positioning and complaints. Currently, clinical signs, conventional radiographic evaluation and metal ion levels are mandated in guidelines to identify patients at risk. If these characteristics are aberrant, cross-sectional imaging by ultrasound, CT or Metal Artifact Reduction Sequence (MARS) MRI scan should be performed to detect pseudotumors. The sensitivity and specificity of the clinical characteristics are not indisputably established yet. It is suggested, that cross-sectional imaging on all patients with a MoM hip implant might be the only option to discover the real magnitude of pseudotumor formation after MoM arthroplasty. However, the clinical implications of the presence of pseudotumors are still unclear.

Anticipating this possible upcoming screening for all patients, the screening protocol for the presence of asymptomatic pseudotumors in a cohort of 289 RHA's was intensified.[28] The aim of this study was to clarify whether one should be alert to the presence of silent pseudotumors (pseudotumors in asymptomatic patients) in our cohort of hip resurfacing patients. Before the intensified screening protocol was initiated, no pseudotumors were suspected in the cohort of 289 RHA's based on the available clinical scoring and conventional radiographs. In Chapter 7 the occurrence of a pseudotumor on MARS-MRI in a high risk (n=11, 12 hips), low risk (n=10, 10 hips) and routine follow-up group (n=19, 22 hips) is described. Female patients with a cup inclination angle greater than 45° and a femoral component size smaller than 50 mm were allocated to the high risk group. The low risk group consisted of asymptomatic male patients with a unilateral RHA, cup inclination angle smaller than 45° and femoral component size greater than 50 mm. The risk for pseudotumor development in the high, low and control group was 0.45, 0.33 and 0.30 respectively, and did not show significant differences between the groups. In 15 of the screened hips (34.1%) pseudotumors were observed, of which six were graded mild, eight moderate and one severe MoM disease. 27.3% of the pseudotumors could be regarded silent, this occurred regardless of risk group. In 80% of the screened patients metal ion levels were normal (below 40 nmol/L). Evaluation of clinical outcome, plain radiographs and metal ion levels underestimate the presence of pseudotumors in MoM patients and are not sensitive enough to detect all cases of ARMD. In conclusion, without cross-sectional imaging less pseudotumors are diagnosed and reported. There is, however, no consensus yet on the clinical relevance and consequences of pseudotumor formation.

To compare bone mineral density evolution after RHA and a 28-mm MoM THA

RHA is promoted as a femoral bone preserving implant. Protection of femoral and acetabular bone stock after RHA is important, especially for the relatively young population, since revision surgery is likely to occur. Bone loss prior to revision creates more complicated and complex revision surgery and a lower survival rate of the implants after revision. A potential pitfall of RHA might be gradual bone resorption at the femoral calcar and at the medial acetabular wall due to stress shielding. To determine femoral and acetabular bone mineral density changes after RHA compared with a 28-mm MoM THA a randomized controlled study with DEXA was performed and described in Chapter 8 and Chapter 9. DEXA measurements were made pre-operative, at 3, 6, 12 and 24 months with mean relative bone mineral density (BMD) calculated as a percentage of pre-operative (baseline) values.

In Chapter 8 the results of consecutive standardized DEXA scans up to 12 months after RHA (n=20) and THA (n=22) are presented. BMD was measured in the calcar region (Gruen zone 7) in both groups and four additional measurements of femoral regions of interest (ROI) in the RHA group. RHA did indeed preserve bone mass in the femoral neck. The mean relative BMD of the calcar significantly increased to 105.2% (p=0.012) for RHA versus a decrease to 82.1% (p<0.001) for THA, one year after implantation. The difference between groups was significant (p<0.001). In the four additional femoral ROI, an initial early non-significant decrease in bone density after RHA was followed by recovery to baseline levels after 12 months.

In Chapter 9 the results are presented of BMD measurements of the acetabulum up to 24 months after RHA press-fit cobalt-chromium cup (n=38) and THA threaded titanium cup with poly-ethylene-metal-inlay (Metasul) insert (n=33). The BMD in five separate acetabular periprosthetic ROI was prospectively quantified, which could be divided in two cranial, two medial and one caudal ROI. Our hypothesis was that periacetabular BMD would be better preserved after THA than after placement of a RHA. After an RHA both cranial ROI's remained stable around baseline levels (ROI 1 98.7%; ROI 5 101.9%) whereas after THA the cranial ROI 1 showed a significant BMD decrease (ROI 1 90.8% (p<0.001); ROI 5 93.8% (p=0.055)). As for the two medial ROI's, the BMD decreased significantly for RHA to 77.7% and 91.5% and THA to 67.3% and 97.0% (ROI 2 and 4 respectively) (p<0.05), in one of these ROI's this difference was in favor of the RHA group. BMD remained stable in the caudal ROI 3 for RHA at 99.8%, whereas a significant decrease was found for THA at 93.5% (p<0.001). Unlike the hypothesis, the acetabular bone was better preserved after the rigid press-fit cup RHA. The observed decrease in BMD medial to the cup (ROI 2 and 4) of 23% and 8.5% for RHA and 32% and 3% for THA at 24 months are in concordance with earlier literature on BMD changes after conventional THA with press-fit cups. An RHA press-fit cup does not lead to more decline in periprosthetic BMD as compared to an established conventional threaded titanium acetabular component. However, this is debatable if bigger acetabular cups are implanted with RHA (and therefore more acetabular bone is resected) in order to match the corresponding

diameter of the femoral component.[29-31] On the femoral side a more natural loading is proven after RHA, whereas bone diminution occurred after a conventional uncemented THA. In the short term in the femur and the acetabulum, RHA is more bone mineral density preserving compared to THA.

Discussion

As RHA is a (re-introduced) new concept and design for hip replacement it is important to compare its results with the gold standard, the THA. For this thesis, a randomized controlled trial was performed to provide an objective clinical comparison between RHA and THA, to increase the current level of evidence in literature, and to assess whether hip resurfacing would meet its expectations. Based on the results of this thesis it can be concluded that RHA does meet the expectations concerning bone mineral density, clinical outcome at short-term and stability. The RHA preserves the femoral head and conserves more femoral and acetabular bone mineral density compared to THA at clinical relevant locations, like cranial and medial to the acetabular cup and the femoral calcar. Clinical outcome scores and satisfaction prove to be good to excellent after RHA in our short-term study. OHS, UCLA Activity and VAS satisfaction scored significantly higher compared to THA at some time points. However, despite randomization the RHA patients also had a higher UCLA activity score at the pre-operative stage, thus one can argue whether this benefit is clinically significant. The difference in patient satisfaction and early clinical outcome between THA and RHA can, according to our preference study, not be attributed to the fact that patients might have received their preferred (RHA) implant. RHA proves to be the more stable implant, no dislocations were encountered compared to three dislocation in the THA group. With regard to metal ion levels, RHA initially produces higher cobalt and chromium levels than 28-mm MoM THA; at 24 months this difference was only significant for the chromium levels. Median metal ion levels remain, for the unilateral implants, below 2 µg/L.

Based on the current literature and registry studies the ideal candidate for RHA is male, less than 55 years of age, has a femoral head size greater than 50 mm, a BMI smaller than 35 kg/m^2 and osteoarthritis as primary diagnosis.[32-35] Male RHA patients with a femoral head size greater than 50mm have a ten year revision rate of 5.1%.[35] When comparing RHA and the conventional MoP THA (regarded as the gold standard) for a male patient, below 55 years of age, with osteoarthritis, the ten year revision rates are 6.1% for RHA and 9.3% for MoP THA. Based on the Australian registry the RHA meets the NICE criteria (joint replacement 10-year survival greater than or equal to 90%) easily when implanted in young, preferably male (or female with femoral head size over 50mm) patients with osteoarthritis.[35] It has to be noted that this successful 10 year follow-up is only available for two resurfacing brands (Conserve® Plus and Birmingham Hip Resurfacing (BHR)) and for a selected groups of ideal patients as described above.

Registry data apply to the merged results of different types of RHA and MoM THA implants and there is increasing evidence that results differ between different manufacturers. The initial release of the BHR on the market was tightly controlled, with selected surgeons and emphasis on the need for good surgical techniques and patient selection. The positive biomechanical, hip simulator and clinical (from designing surgeons) results of the BHR, drew the attention of other manufacturers keen to be part of the metal-on-metal revolution.[36] Manufacturers in Europe and the United States all developed their own MoM hip implant systems, and each available device has a different combination of modifications of the original design features.[6,37] Design features thought to influence wear are 1) the use of as cast versus forged material, 2) varying heat treatments of the components, 3) the radial clearance, 4) the arc of acetabular coverage, and 5) the angle of function of the femoral component.[6] Some designs, with low wear properties in vitro, proved to be extremely sensitive to sub-optimal acetabular positioning with high wear rates in a large number of patients as a consequence. Larger sizes of different designs seem more resistant to sub-optimal positioning.[6] In addition, large-diameter-head (LDH) MoM THA's show substantial higher and clinical concerning levels of metal ion levels compared to RHA and one should not lump the results of LDH MoM THA together with the RHA.

When the MoM devices were launched in Europe the regulatory parties placed these hip implants into a category of devices that required only hip simulator testing (an in vitro biomechanical cyclic loading process of the prosthesis) since the concept was considered only an extension of an earlier approved design. Several competing companies could thus quickly release their own MoM implant, since no clinical testing was mandatory to allow the release for commercial use. In the USA, the FDA considered the MoM THA components to be like other heads, cups, and stems already in use and declared they could be cleared through a 510(k) process. Therefore, again no clinical studies were required to show how LDH MoM heads worked when coupled with a modified stem.[36] Stimulated by the relative 'easy' approval and urged by receiving the return on their investment, the MoM implants were introduced rather quick onto the market by the manufacturers. The competition for market share resulted in an aggressive marketing campaign aiming at patients and surgeons. These circumstances resulted in a too fast global introduction of these new MoM implants, without data of long-term clinical results and identification of all possible complications.

At present, there are worldwide increasing concerns about these MoM implants. These concerns focus on relatively high revision rates, pseudotumor formation and potential metal ion toxicity. There is clear evidence that the risk for these problems varies between different types of MoM implants and this applies both for differences in type of MoM implant (LDH-THA versus RHA) and brand. On the other hand, no type or brand of these MoM implants is entirely free of these concerns. National guidelines from regulatory bodies and orthopedic societies differ throughout the world in their advice concerning MoM hip implants. These guidelines vary from attentiveness to restraints to prohibition, concerning specific designs or

all MoM prosthetic systems.[12,20,38] Despite the apparent need, a uniform international consensus is lacking. The problem of MoM hip replacement and the encountered adverse events are complicated, and research sometimes raises more questions than it answers. Another complicating factor is the number of involved parties consisting of patients, surgeons, manufacturers, researchers, regulatory bodies and notified bodies, each with their own interest, responsibility and involvement in the MoM hip implant problem. At a national level, encountered complications and concerns in literature, ask for a clear policy on MoM hip implants. In 2012, forced or not by the public opinion, it was decided to impose a time-out for all MoM hip replacements (including RHA and irrespective of implant brand) with a femoral head size greater than or equal to 36mm in the Netherlands.[12] With respect to the increasing revision rates and commonly encountered complications after LDH MoM THA, this seems a justified decision. However, considering RHA, it may be that we are 'throwing the baby out with the bath water' by banning all brands of the RHA for all patients as well. On the other hand, distinct clinically relevant benefits of RHA over THA could not be proven by this thesis and many uncertainties persist with respect to MoM related problems. Both warrant a time-out of its use. The Australian registry reports on revision and survival data according to implant design and category, which may gives the possibility of distinguishing between failing and surviving RHA and MoM THA designs in the future.[35] Already the differences between the well and non-functioning designs and MoM categories become increasingly clear. When RHA's are compared to LDH MoM THA's, the ten year revision rates are 9.1% and 20.3% respectively.[35] This might, in time, give the opportunity to allow certain RHA implants, which perform according to the NICE criteria in the national registries and do not show unacceptable adverse events in clinical trials. It may be reasonable to allow those RHA implants, in a controlled setting in a very specific group of patients; male under 55 years of age, with a femoral head size greater than 50 mm, a BMI smaller than 35kg/m^2 and osteoarthritis as primary diagnosis.

This thesis has concentrated on patients receiving a single brand of RHA (Conserve® Plus; Wright Medical) and all patients were operated by a limited number of experienced hip surgeons. There is clear evidence that the chance of a MoM related problem differ between different RHA brands, and that more concerns are related to the LDH MoM THA concept as compared to RHA. While reading the results of this thesis one has to realize that these two factors may very well be responsible for the relatively good results presented. These results may be applicable for the type of implant used in this study and are most likely not to be generalized to all MoM implants. In addition, the studies of this thesis present data from short-term follow-up and longer follow-up will be necessary to draw firm conclusions. In the meantime, patients will be followed with great care. Metal ions blood levels, DEXA analysis and functional outcome scores are included in the standard follow-up protocol; currently nearly all of the patients are beyond the 3 year follow-up and no clear shift in outcome or revision has been encountered yet. In accordance to the guidelines from the Dutch Orthopaedic Association the use of RHA in our clinic has been abandoned; whether this proclaimed time-

out is temporarily or permanent is not clear yet. For the near future cross-sectional imaging is planned with MARS-MRI on all the patients from the RCT and cohort of RHA as further clarification of the incidence of silent pseudotumors is important. To date, there is no consensus on the incidence of pseudotumors after different types of MoM implants and above all there is no consensus on whether these silent pseudotumors are clinically relevant or insignificant.

As the hype of MoM hip replacement has past and turned into a national professional allergy against MoM articulation, it is time to consolidate the successes and abandon the failures of MoM hip replacement in clinical practice. Therefore, research to further identify the causative factors behind these failures and successes remains of major importance. Prolonged follow-up of patients with MoM implants will help to determine to which extend there is a place for RHA and/or LDH MoM THA's in a selected group of patients using a selection of currently available implants.

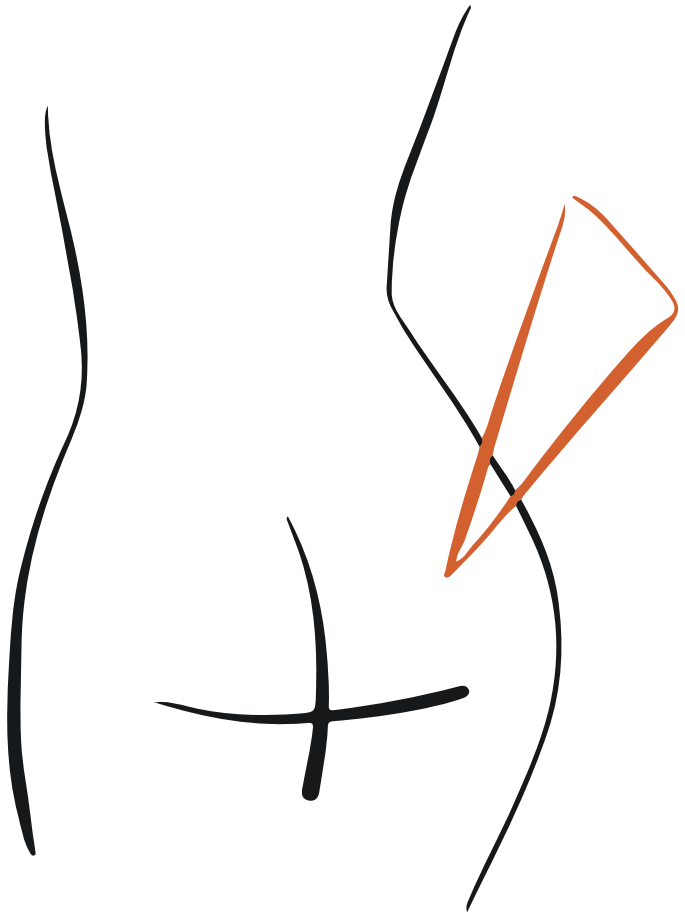
Future research should probably focus on elucidation of consequences of prolonged exposure to high metal ion levels, determination of triggering factors of an ARMD in the human body, the clinical significance of asymptomatic pseudotumors and clinical outcomes after RHA revisions. Intensified and prolonged follow-up of the patients with a MoM implant throughout the world will help clarify these issues and to establish whether the current debate on MoM bearing concerns will justify further use or not.

References

1. Otten R, van Roermund PM, Picavet HS. Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030 [Dutch article] *Ned Tijdschr Geneeskd.* 2010;154:A1534.
2. Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AVF. The effect of component size and orientation on the concentrations of metal ions after resurfacing arthroplasty of the hip. *J Bone Joint Surg Br.* 2008;90-B(9):1143-1151.
3. Amstutz HC, Le Duff MJ, Johnson AJ. Socket position determines hip resurfacing 10-year survivorship. *Clin Orthop Relat Res.* 2012;470(11):3127-3133.
4. Grammatopoulos G, Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, et al. Optimal acetabular orientation for hip resurfacing. *J Bone Joint Surg Br.* 2010;92(8):1072-1078.
5. Beaule PE, Lee JL, Le Duff MJ, Amstutz HC, Ebramzadeh E. Orientation of the femoral component in surface arthroplasty of the hip. A biomechanical and clinical analysis. *J Bone Joint Surg Am.* 2004;86-A(9):2015-2021.
6. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, et al. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. *J Bone Joint Surg Br.* 2011;93(2):164-171.
7. De Smet K, De Haan R, Calistri A, Campbell PA, Ebramzadeh E, Pattyn C, et al. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. *J Bone Joint Surg Am.* 2008;90 Suppl 4:202-208.
8. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br.* 2008;90-B(10):1291-1297.
9. Mabilleau G, Kwon YM, Pandit H, Murray DW, Sabokbar A. Metal-on-metal hip resurfacing arthroplasty: a review of periprosthetic biological reactions. *Acta Orthop.* 2008;79(6):734-747.
10. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AVF. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement. *J Bone Joint Surg Br.* 2010;92-B(1):38-46.
11. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br.* 2008;90(7):847-851.
12. Verhaar JA. The hard lesson of metal-on-metal hip implants. [Dutch article] *Ned Tijdschr Geneeskd.* 2012;156(42):A5564.
13. Murphy TP, Trousdale RT, Pagnano MW, Mabry TM, Sierra RJ. Patients' perceptions of hip resurfacing arthroplasty. *Orthopedics.* 2009;32(10).
14. Preference Collaborative Review Group. Patients' preferences within randomised trials: systematic review and patient level meta-analysis. *BMJ.* 2008;337:a1864.
15. Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin Orthop Relat Res.* 2005;438:177-181.
16. Daniel J, Ziaee H, Pynsent PB, McMinn DJ. The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. *J Bone Joint Surg Br.* 2007;89(6):736-741.
17. Garbuz D, Tanzer M, Greidanus N, Masri B, Duncan C. The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: A randomized clinical trial. *Clin Orthop Relat Res.* 2010;468(2):318-325.
18. Witzleb W-C, Ziegler J, Krummenauer F, Neumeister V, Guenther K-P. Exposure to chromium, cobalt and molybdenum from metal-on-metal total hip replacement and hip resurfacing arthroplasty. *Acta*

Orthop. 2006;77(5):697-705.
19. Hart AJ, Sabah SA, Bandi AS, Maggiore P, Tarassoli P, Sampson B, et al. Sensitivity and specificity of blood cobalt and chromium metal ions for predicting failure of metal-on-metal hip replacement. *J Bone Joint Surg Br.* 2011;93-B(10):1308-1313.
20. *MHRA*. Medical Device Alert: All metal-on-metal (MoM) hip replacements MDA/2012/008. 2012;28 february 2012.
21. Serum Cobalt (80084) and Serum Chromium (8638) [Web page] New England, Massachusetts: *Mayo Medical Laboratories.* 2010; Available from: http://www.mayomedicallaboratories.com/test-catalog/ alphabetical/C.
22. De Smet K, Campbell PA, Van Orsouw M, Backers K, Gill HS. Interpretation of metal ion levels after metal-on-metal resurfacing. *Proc AAOS.* 2010;Poster Presentation Number: P100.
23. Daniel J, Ziaee H, Kamali A, Pradhan C, McMinn D. What are the risks accompanying the reduced wear benefit of low-clearance hip resurfacing? *Clin Orthop Relat Res.* 2012;470(10):2800-2809.
24. Griffin WL, Fehring TK, Kudrna JC, Schmidt RH, Christie MJ, Odum SM, et al. Are metal ion levels a useful trigger for surgical intervention? *J Arthroplasty.* 2012;27(8 Suppl):32-36.
25. Heisel C, Silva M, Skipor AK, Jacobs JJ, Schmalzried TP. The relationship between activity and ions in patients with metal-on-metal bearing hip prostheses. *J Bone Joint Surg Am.* 2005;87(4):781-787.
26. Jacobs JJ, Skipor AK, Campbell PA, Hallab NJ, Urban RM, Amstutz HC. Can metal levels be used to monitor metal-on-metal hip arthroplasties? *J Arthroplasty.* 2004;19(8 Suppl 3):59-65.
27. Macnair RD, Wynn-Jones H, Wimhurst JA, Toms A, Cahir J. Metal Ion Levels Not Sufficient as a Screening Measure for Adverse Reactions in Metal-on-Metal Hip Arthroplasties. *J Arthroplasty.* 2013;28(1):78-83.
28. Kwon YM, Ostlere SJ, McLardy-Smith P, Athanasou NA, Gill HS, Murray DW. "Asymptomatic" pseudotumors after metal-on-metal hip resurfacing arthroplasty: prevalence and metal ion study. *J Arthroplasty.* 2011;26(4):511-518.
29. Vendittoli PA, Lavigne M, Girard J, Roy AG. A randomised study comparing resection of acetabular bone at resurfacing and total hip replacement. *J Bone Joint Surg Br.* 2006;88-B(8):997-1002.
30. Tanzer M, Tanzer D, Smith K. Surface replacement of the hip can result in decreased acetabular bone stock. *Clin Orthop Relat Res.* 2012;470(2):541-546.
31. Loughead JM, Starks I, Chesney D, Matthews JNS, McCaskie AW, Holland JP. Removal of acetabular bone in resurfacing arthroplasty of the hip: A comparison with hybrid total hip arthroplasty. *J Bone Joint Surg Br.* 2006;88-B(1):31-34.
32. McMinn DJ, Daniel J, Ziaee H, Pradhan C. Indications and results of hip resurfacing. *Int Orthop.* 2011;35(2):231-237.
33. Johnson AJ, Zywiel MG, Hooper H, Mont MA. Narrowed indications improve outcomes for hip resurfacing arthroplasty. *Bull NYU Hosp Jt Dis.* 2011;69 Suppl 1:S27-29.
34. McGrory B, Barrack R, Lachiewicz PF, Schmalzried TP, Yates AJ, Jr., Watters WC, 3rd, et al. Modern metal-on-metal hip resurfacing. *J Am Acad Orthop Surg.* 2010;18(5):306-314.
35. Annual report Hip and Knee Arthroplasty. University of Adelaide: *Australian Orthopaedic Association* 2012.
36. Cohen D. How safe are metal-on-metal hip implants? *BMJ.* 2012;344:e1410.
37. Heisel C, Kleinhans JA, Menge M, Kretzer JP. Ten different hip resurfacing systems: biomechanical analysis of design and material properties. *Int Orthop.* 2009;33(4):939-943.
38. Kmietowicz Z. British and Danish surgeons advise against using dangerous hips. *BMJ.* 2012;344:e1725.

Nederlandse samenvatting en discussie



Samenvatting

Nederland kent 238.00 mensen coxartrose (artrose van de heup). Jaarlijks komen hier 27.000 nieuwe gevallen bij. Coxartrose kan ernstige beperkingen in het dagelijks functioneren veroorzaken en de artrosepatiënt kan hierdoor van zijn omgeving en de gezondheidszorg afhankelijk worden. Indien pijnstilling en fysiotherapie niet effectief zijn in het reduceren van klachten bij invaliderende coxartrose kan een heupprothese worden overwogen. De totale heupprothese (THP) is een zeer succesvolle behandeling voor eindstadium coxartrose en werd door Learmonth zelfs 'de operatie van de eeuw' genoemd. Het is dus niet verwonderlijk dat in de loop der jaren het aantal heupvervangende operaties toegenomen is. Deze trend wordt niet alleen veroorzaakt door de vergrijzing en de daarbij behorende toenemende incidentie van coxartrose, ook worden de onderste leeftijdsgrenzen voor heupprothesiologie verruimd. De jongere patiënt (onder de 60 jaar) met eindstadium coxartrose wil graag dezelfde succesvolle behandeling als de oudere coxartrosepatiënt. Deze jongere patiënten hebben echter een grote kans om hun conventionele metaal-op-polyethyleen-heupprothese (MoP-THP) te overleven. De oorzaak hiervan is polyethyleenslijtage en de daaraan gerelateerde gevolgen zoals loslating van de prothese, pijn en/of instabiliteit. Dit is de achterliggende gedachte in de zoektocht naar alternatieve materialen voor de heuparticulatie, en de opleving van metaal-op-metaal-implantaten (MoM). Heupresurfacing (RHA) is reeds een oud concept, maar sinds de jaren 90 en 00 is het design en het metaalbewerkingsproces doorontwikkeld en verbeterd. De MoM-gewrichtsoppervlakten zouden hierdoor slijtvaster zijn en minder osteolyse en aseptische loslating veroorzaken. Het algemene doel van dit proefschrift is de RHA en THP objectief te vergelijken met betrekking tot klinische resultaten, samen met het beloop in de tijd van metaalionenconcentraties in bloed en botdichtheidsveranderingen.

Bepalen van de leercurve van een individuele chirurg voor de plaatsing RHA

Een RHA is een complexere ingreep dan een conventionele THP. De juiste acetabulaire cuppositie is bovendien een belangrijke factor voor de tienjaarsoverleving van een prothese en volledig afhankelijk van de kunde van de chirurg. Valkuilen in de positionering van een RHA zijn een steile cupplaatsing en plaatsing van de steel in de posterieure derde van het collum. Een slechte cuporiëntatie kan leiden tot *edge loading* (een fenomeen waarbij de femorale component in contact komt met de rand van de acetabulaire component), met als gevolg verhoogde slijtage en lokale ophoping van metaalpartikels. Volgens retrieval studies (studies waarbij gereviseerde componenten worden onderzocht) kan dit laatste leiden tot pseudotumorvorming. Als de cup niet juist gepositioneerd is, is deze kans viermaal groter.
Om het verloop van de leercurve te onderzoeken werden de radiologische resultaten van de eerste veertig RHA-patiënten (verdeeld over vier cohorten van tien patiënten) in het Ziekenhuis Rijnstate beoordeeld. De resultaten van dit onderzoek worden in Hoofdstuk 2 gepresenteerd. Zes vooraf vastgestelde radiologische parameters voor de implantaatpositie werden

op de preoperatieve planning (met daarop de optimale oriëntatie) gemeten. Deze parameters werden vergeleken met de uiteindelijke positie op de gestandaardiseerd genomen postoperatieve röntgenfoto. In de laatste cohort was gemiddeld tien minuten minder operatietijd nodig ten opzichte van de eerste cohort (p<0,013). De optimale röntgenologische plaatsing van een RHA is minder dan vijftig graden abductie van de cup en een femorale component centraal in het collum met lichte valgus. De opeenvolgende cohorten lieten per cohort een minder steile cupplaatsing, een progressieve valgus en een grote reproduceerbaarheid van de cup-kop-hoek zien. In de opeenvolgende cohorten nam het verschil tussen de positie op de preoperatieve planning en de definitieve postoperatieve positie af. Er was ook een duidelijke verbetering zichtbaar naar de optimale femorale positionering in de centrale derde van de femorale hals in twee radiologische vlakken. De optimale prothese-oriëntatie met een grote reproduceerbaarheid werd door een ervaren heupchirurg binnen veertig patiënten bereikt.

Vergelijken van RHA en 28-mm-MoM-THP met betrekking tot de kortetermijnresultaten van metaalionenverloop, functionele uitkomsten en complicaties

De kortetermijnresultaten van de gerandomiseerde klinische studie (RCT) naar de Conserve® Plus RHA (Wright Medical Technology, Arlington, Tennessee, USA) en Zweymüller® Classic Metasul® THP (Zimmer Orthopaedics, Warsaw, Indiana, USA) worden gepresenteerd in Hoofdstuk 3. Van juni 2007 tot januari 2010 werden 71 patiënten gerandomiseerd voor een van beide implantaten (38 RHA, 33 THP), veertig patiënten hadden ten tijde van publicatie van het artikel een follow-up van ten minste 24 maanden (19 RHA, 21 THP). Beide groepen waren vergelijkbaar met betrekking tot geslacht, leeftijd, body mass index (BMI) en bloedverlies tijdens de operatie. De operatietijd was echter langer voor de RHA-patiënten (p<0,001). Zoals verwacht verbeterden postoperatief de functionele uitkomstmaten significant in beide groepen. RHA-patiënten scoorden na 12 maanden significant beter op de *University of California Los Angeles*-activiteitsscore (UCLA; 8 versus 7) en *Visual Analogue Scale*-tevredenheid (VAS; 95 versus 85). Na 24 maanden werd er ook een verschil gezien in UCLA-activiteitsscore (8 versus 7) en Oxford Hip Score (OHS; 13 versus 16). De preoperatieve UCLA-activiteitsscores waren ondanks randomisatie echter ook beter voor de RHA-patiënten. De volbloedconcentraties van de unilateraal geïmplanteerde RHA-patiënten waren voor chroom significant hoger (p<0,001), terwijl de kobaltconcentraties vergelijkbaar waren met die van de THP-patiënten. Na 24 maanden was de mediane chroomconcentratie 1,2 µg/L (0,1-2,3) versus 0,5 µg/L (0,1-2,1) voor respectievelijk RHA en THP, voor kobalt was dit 1,2 µg/L (0,5-2,2) versus 0,9 µg/L (0,1-2,7). Ten aanzien van complicaties werden in de THP-groep drie patiënten met recidiverende heupluxaties gezien, twee van hen kregen een eenvoudige cupinsertwissel. Eén RHA-patiënt werd gereviseerd ten gevolge van een vroege aseptische loslating door een avasculaire necrose van de femurkop; voorafgaand aan de revisie was de kobaltconcentratie 2,3 µg/L.

Kobalt- en chroomconcentraties correleren met lineaire en volumetrische slijtage van

de femorale component. Hoge metaalionenconcentraties kunnen veroorzaakt worden door een continu verhoogde metaalionenafgifte door slijtage ten gevolge van edge loading. Dit ontstaat als gevolg van een steile acetabulaire cuporiëntatie of een resurfacingdesign met een kleinere overdekkingshoek. Extreme afgifte van kobalt- en chroompartikels kunnen leiden tot *aseptic lymphocytic vasculitis-associated lesions* (ALVAL), metalose en pseudotumorvorming. De verzamelnaam voor deze bevindingen is *adverse reaction to metal debris* (afweerreacties op metaalpartikels; ARMD), waarvoor revisiechirurgie noodzakelijk is. De gerapporteerde incidentie van pseudotumoren varieert en is afhankelijk van type diagnostiek, patiëntkarakteristieken en implantaatdesign. Dit wordt tevens in Hoofdstuk 7 besproken. Tijdens de recentste follow-up was er in geen van beide groepen een verdenking op pseudotumorvorming. Hierbij moet aangemerkt worden dat gestandaardiseerde cross-sectionele beeldvorming naar pseudotumorvorming geen deel uitmaakte van deze RCT. Na een run-in-periode van 12 maanden werden de metaalionenconcentraties van vier unilaterale (drie RHA, één THP) en één bilaterale (RHA) prothese aangemerkt als extreme uitbijters (een afwijking meer dan drie keer de interkwartielrange vanaf het hoogste kwartiel), Alle patiënten hadden goede klinische scores. De mediane metaalionenconcentraties waren hoger voor de RHA-patiënten, maar bleven wel onder de niet-afwijkende waarde van 2 µg/L voor unilaterale implantaten. OHS, VAS-tevredenheid en UCLA-activiteitsscore van de RHA-patiënten toonden op korte termijn een beter resultaat.

Vaststellen of een uitgesproken voorkeur voor RHA de postoperatieve uitkomsten en tevredenheid kan beïnvloeden

Patiëntentevredenheid speelt een belangrijke rol in postoperatieve uitkomstscores. Een stabiel, goed gepositioneerde prothese met geringe slijtage kan bijvoorbeeld worden aangemerkt als een mislukking wanneer de patiënt niet tevreden is. Postoperatieve tevredenheid van de patiënt wordt deels beïnvloed door de preoperatieve verwachtingen. Voorafgaand aan de inclusie en randomisatie voor de RCT werden de patiënten goed geïnformeerd over de reeds bekende voor- en nadelen van een RHA. Echter, randomisatie voor RHA dan wel THP in een periode waarin de heupresurfacing werd gepromoot als 'sportheup' en de ideale oplossing voor de jonge en/of actieve patiënt bleek zeer moeizaam. Patiënten baseren hun percepties en verwachtingen, die volledig in strijd kunnen zijn met resultaten uit de literatuur, op andere bronnen dan hun orthopedische chirurg. Bepaalde patiënten bleken zo'n sterke voorkeur voor RHA te hebben dat zij niet wilden deelnemen aan de RCT. Deze patiënten werden gevolgd in een separaat cohort van RHA-patiënten met identieke follow-up als de RCT. De differentiatie tussen de cohortpatiënten (voorkeursgroep) en RCT-patiënten (randomisatiegroep) was hun expliciete voorkeur voor RHA of niet. Hierdoor kon worden vastgesteld of de voorkeursbias van deze cohortpatiënten de postoperatieve tevredenheid en klinische resultaten positief beïnvloedt.

De resultaten van de vergelijking tussen 22 cohortpatiënten en 28 RCT-patiënten met een RHA worden gepresenteerd in Hoofdstuk 4. Beide groepen hadden twaalf maanden postoperatief een hoge VAS-tevredenheid: 97/100 voor de voorkeursgroep en 93/100 voor de randomisatiegroep. HHS, OHS en UCLA toonden voor beide groepen een vergelijkbare verbetering na twaalf maanden (p<0,001). Met betrekking tot de SF-12 scoorde de voorkeursgroep preoperatief lager op de mentale score (p=0,03) en in vergelijking met de randomisatiegroep verbeterde zij na twaalf maanden significant meer (p=0,03). De invloed van voorkeur op patiënttevredenheid en vroege klinische uitkomsten na RHA kon niet worden aangetoond. Dit spreekt een meta-analyse tegen die wel een invloed vond van voorkeur op het effect van de behandeling, hypothetisch op basis van meer therapietrouw en motivatie van de patiënten. De therapietrouw zou slechter kunnen zijn wanneer patiënten niet hun voorkeursbehandeling zouden krijgen en de behandelingsprotocollen verschillen met betrekking tot medicatiegebruik, rehabilitatie en bijwerkingen. Dit is niet van toepassing op heupvervanging waarbij alle patiënten een identieke postoperatieve behandeling krijgen.

Bepalen of de metaalionenconcentraties in serum en volbloed uitwisselbaar zijn en een omrekenformule opstellen

De evaluatie van metaalionenconcentraties na een MoM-heupprothese wordt steeds belangrijker en wordt gebruikt als indicator van het functioneren en de veiligheid van de prothese. Van de orthopedisch chirurg wordt verwacht dat hij/zij behoort te weten hoe de waarden geïnterpreteerd dienen te worden. Voor de beoordeling van metaalionenconcentraties bij patiënten kunnen verschillende matrices worden gebruikt, onder andere bloed en 24-uurs urine, waarbij analyse van bloed te voorkeur heeft. Er bestaat nog geen consensus welke meting in bloed het beste de metaalionenblootstelling in het lichaam weergeeft, zowel serum als volbloed kunnen worden gebruikt.

In Hoofdstuk 5 wordt de uitwisselbaarheid van serum- en volbloed-metaalionenmetingen geanalyseerd op basis van 343 specimens van 60 RHA en 32 MoM-THP-patiënten. Dit hoofdstuk bevat ook een richtlijn voor de interpretatie van een metaalionenanalyse in de klinische praktijk. De mediane metaalionenconcentraties lagen onder de 2 µg/L. Kobalt- en chroomconcentraties waren, in overeenstemming met Hoofdstuk 2, significant hoger voor RHA dan voor THP, hoewel de verschillen afnamen na de run-in-periode. Conform Daniel et al. is er geen directe uitwisselbaarheid tussen volbloed- en serumconcentraties gevonden. Het gemiddelde verschil van kobalt- en chroomconcentraties tussen volbloed en serum is respectievelijk +0.13 µg/L en -0.91 µg/L. De conversieformule voor serum- naar volbloedwaarden is: kobalt *volbloed = 0.34 + [0.88 * kobalt serum]* en chroom *volbloed = 0.14 + [0.58 * chroom serum]*, met een acceptabele foutmarge van ± 1.0 µg/L. Op basis van onze studie kan geen aanbeveling worden gegeven of volbloed boven serum geprefereerd kan worden, of vice versa. Vanwege praktische redenen zou volbloed volgens sommige studies de voorkeur hebben. Voor de interpretatie van metaalionenconcentraties is het belangrijk om op de hoogte te zijn van nierfunctiestoornissen, het design en (mal-)positie van de prothese,

contaminatie door voedingssupplementen, medicijnen of andere metalen implantaten. Met betrekking tot het implantaat is het belangrijk te bepalen welk merk en categorie MoM-implantaat het betreft: MoM-heupresurfacing, een large-diameter-head-MoM-THP (>36mm) of een small-diameter-head-MoM-THP (≤36mm) (LDH-MoM-THP). Deze verschillende implantaatontwerpen hebben een ander metaalionenafgiftepatroon en het succes en het falen van de verschillende categorieën kunnen niet worden gegeneraliseerd.

Vaststellen of er een verschil is in trend van metaalionenconcentraties tussen goed en slecht functionerende RHA-prothesen

Tot op heden bestaat er geen consensus over welk afkappunt gebruikt moet worden om onderscheid te maken tussen goed en slecht functionerende implantaten. Ondanks een overvloed aan studies zijn de bovengrenzen van metaalionenspiegels slecht gedefinieerd. Het Mayo Medical Laboratories-handboek geeft voor kobalt in volbloed als bovengrens 5 µg/L en 17 µg/L voor chroom in erytrocyten. Voor onze richtlijn is de waarde van De Smet et al. overgenomen als uiterst aanvaardbare bovengrens voor een goed functionerend MoM-implantaat; 4,4 µg/L voor kobalt (odds ratio van 6,0 voor revisie) en 5,1 µg/L voor chroom (odds ratio van 4,3 voor revisie). De MHRA adviseert kobalt en chroom ten minste eenmaal postoperatief in het bloed te bepalen en cross-sectionele beeldvorming (echo, CT, MRI) te verrichten indien deze waarden groter zijn dan 7ppb (ppb komt overeen met µg/L). De Nederlandse Orthopedische Vereniging (NOV) adviseert dat een waarde tussen de 2-5 µg/L moet leiden tot een poliklinische beoordeling, bij 5-10 µg/L is nader onderzoek met MRI, CT of echo geïndiceerd. Een waarde groter dan 10 µg/L is een alarmsignaal waarbij, in combinatie met de klachten en resultaten van het beeldvormende onderzoek, besloten kan worden tot een revisieoperatie. Ondanks deze richtlijnen heerst er onduidelijkheid wat de gevolgen zijn van langdurig verhoogde metaalionenspiegels bij patiënten en bij welke waarden nadelige effecten kunnen optreden. Bovendien is er uit literatuur bekend dat er goed functionerende implantaten met relatief hoge metaalionenspiegels zijn en slecht functionerende implantaten met lage spiegels, wat de onduidelijkheid voedt.

Op dit moment is de klinische betekenis en interpretatie van een enkele metaalionenmeting onduidelijk. De onderzochte hypothese was dat de evolutie van metaalionenconcentraties informatiever is dan de huidige vereiste enkelvoudige meting. Het doel van de studie, gepresenteerd in Hoofdstuk 6, was een prospectieve follow-up van kobalt- en chroomconcentraties in een cohort van 48 unilaterale RHA's te presenteren en de verschillen in metaalionentrend op de korte termijn tussen goed versus suboptimaal functionerende patiënten te identificeren. Op basis van de recentste postoperatieve functionele uitkomstmaat — HHS, waarbij 0 de slechtste en 100 de beste uitkomst is — werden de patiënten verdeeld in goed en suboptimaal functionerende groepen. Een HHS≥90 werd gedefinieerd als goed functionerend (n=42), een HHS<90 als sub-optimaal functionerend (n=6). De metaalionenspiegels en individuele trends werden geanalyseerd met een mediane follow-up van 24 maanden.

De mediane kobalt- en chroomconcentraties waren significant hoger voor de suboptimale groep op 24 maanden: 0,95 µg/L (0,1-9,3) versus 6,2 µg/L (2,0-29,3) voor kobalt en 1,70 µg/L (0,6-13,3) versus 4,70 µg/L (2,9-17,5) voor chroom. Het percentage goed functionerende patiënten met stijgende kobalt- en chroomconcentraties tussen twee opeenvolgende tijdsintervallen (stijgers) neemt geleidelijk af van 90/86% (0-3 maanden) naar 22/22% (24-36 maanden). De mediane absolute toename van de subgroep van stijgers was significant lager voor de goed functionerende groep dan voor de suboptimaal functionerende groep in de periode van 12 tot 24 maanden: 0,70 µg/L (0,1-4,6) versus 6,65 µg/L (2,9-23,7) voor kobalt en 0,80 µg/L (0,1-8,9) versus 11,6 µg/L (11,0-12,2) voor chroom. Concluderend; suboptimaal functionerende MoM-implantaten hebben een andere trend van metaalionenspiegels dan de goed functionerende implantaten, een hoger percentage stijgers en een grotere absolute toename per tijdsinterval.

Naar aanleiding van deze resultaten adviseren wij om laagdrempelig een metaalionenmeting te herhalen, in het bijzonder kobalt, aangezien dit het meest toxische van de twee is. In aanvulling op anamnese, lichamelijk en beeldvormend onderzoek kan een opeenvolgende meting duidelijkheid geven over het al dan niet falen van een implantaat. Het navolgende voorbeeld illustreert dit: een enkele kobaltmeting van 5 µg/L op 12 maanden kan als grenswaarde worden gezien. Bij een patiënt zonder klachten is een concentratie van 3 µg/L op 24 maanden geruststellend (aangezien het een daling betreft), terwijl een concentratie van 6 µg/L kan wijzen op een potentieel disfunctionerend implantaat. Bij de goed functionerende patiënten wordt twee jaar na implantatie zelden nog een stijging van de metaalionenconcentraties gezien. Indien metaalionenconcentraties na 12 maanden structureel stijgen kan dit een teken zijn van toenemende slijtage en een potentieel disfunctionerend implantaat. Opeenvolgende metingen na een jaar en een trendbeoordeling kunnen helpen in de besluitvorming rond revisieoperaties bij patiënten met milde symptomen en metaalionengrenswaarden (4-5 µg/L).

Beoordelen van het voorkomen van stille pseudotumoren in een cohort van heupresurfacing-patiënten

Lichamelijke klachten, een steile cuppositionering en/of hoge dan wel stijgende metaalionenconcentraties kunnen kenmerkend zijn voor een slecht functionerend MoM-implantaat en indicatief voor ARMD. Op dit moment wordt in richtlijnen onderzoek naar klinische symptomen, conventionele röntgenfoto's en metaalionenmetingen geadviseerd om patiënten met een slecht functionerend implantaat te identificeren. Als voorgenoemde kenmerken afwijkend zijn, moet cross-sectionele beeldvorming (zoals echo, CT of een *metal artefact reduction sequence*-MRI (MARS-MRI) verricht worden om een eventuele pseudotumor te detecteren. De sensitiviteit en specificiteit van de klinische kenmerken zijn echter nog niet vastgesteld. Er wordt tevens gesuggereerd dat cross-sectionele beeldvorming van alle patiënten met een MoM-heupprothese de enige mogelijkheid is om de volledige omvang van

pseudotumorvorming na een MoM-implantaat vast te stellen. Daarnaast zijn de klinische implicaties van de aanwezigheid van pseudotumoren ook nog onduidelijk.

Vooruitlopend op een mogelijke toekomstige screening van alle patiënten werd het screeningsprotocol voor de aanwezigheid van asymptomatische pseudotumoren in een cohort van 289 RHA's geïntensiveerd. Het doel van deze studie was om te bepalen of men alert dient te zijn op de aanwezigheid van stille pseudotumoren (pseudotumoren bij volledig asymptomatische patiënten) bij heupresurfacing-patiënten. Voordat het geïntensiveerde screeningsprotocol van start ging, was, gebaseerd op de beschikbare klinische scores en conventionele röntgenfoto's, geen van de 289 RHA's verdacht op de aanwezigheid van een pseudotumor. In Hoofdstuk 7 wordt de aanwezigheid van pseudotumorvorming op MARS-MRI in een hoogrisicogroep (n=11, 12 heupen), een laagrisicogroep (n=10, 10 heupen) en routine-follow-upgroep (n=19, 22 heupen) beschreven. De hoogrisicogroep bestond uit vrouwelijke patiënten met een acetabulaire inclinatie groter dan 45° en een femorale diameter kleiner dan 50 mm. De laagrisicogroep bestond uit asymptomatische mannelijke patiënten met een unilaterale RHA, acetabulaire inclinatie kleiner dan 45° en femorale diameter groter dan 50 mm. Het risico op pseudotumorvorming in de hoogrisico-, laagrisico- en controlegroep was respectievelijk 0,45, 0,33 en 0,30; hierbij werden geen significante verschillen tussen de groepen gezien.

Bij 15 heupen (34,1%) werd pseudotumorvorming vastgesteld, volgens de Anderson-classificatie werden er zes als licht, acht als matig en één als ernstige MoM-ziekte geclassificeerd. 27,3% van de pseudotumoren trad op bij asymptomatische patiënten en werd beschouwd als een stille pseudotumor, er was hierbij geen correlatie met de risicogroep. In 80% van de gescreende patiënten waren de metaalionenconcentraties normaal (kleiner dan 40 nmol/L). Evaluatie van alleen klinische resultaten, röntgenfoto's en metaalionenconcentraties onderschatten de aanwezigheid van pseudotumorvorming bij patiënten met een MoM-implantaat en zijn niet gevoelig genoeg om alle gevallen van ARMD detecteren. Concluderend: zonder cross-sectionele beeldvorming worden er minder pseudotumoren gediagnosticeerd en gerapporteerd. Er is echter geen consensus over de klinische relevantie en gevolgen van pseudotumorvorming.

Vergelijken van botdichtheidsveranderingen na RHA en 28-mm-MoM-THP

Een van de belangrijkste kenmerken van RHA is het femorale botbehoud door het ontwerp waarbij de eigen femurkop bedekt wordt met een metalen kap. Bescherming van de femorale en acetabulaire botmassa na een RHA is belangrijk, vooral voor de relatief jonge patiënt, aangezien er bij hen een grote kans is op toekomstige revisieoperaties. Bestaand botverlies kan leiden tot ingewikkelde en gecompliceerde reconstructies tijdens revisiechirurgie en een lagere overleving van de implantaten na revisie. Een potentiële valkuil van RHA kan geleidelijke botresorptie ter plaatse van de femorale calcar zijn en de mediale acetabulaire wand als gevolg van *stress-shielding* (afname in botdichtheid door afname van de normale belasting in het bot ten gevolge van een implantaat). Om de femorale en acetabulaire botdichtheidsveranderingen na RHA in vergelijking met een 28-mm-MoM-THP te beoordelen werd een RCT met *dual-energy Xray absorptiometry* (DEXA) uitgevoerd, beschreven in Hoofdstuk 8 en Hoofdstuk 9. De DEXA-metingen werden pre-operatief en na 3, 6, 12 en 24 maanden uitgevoerd, waarbij de gemiddelde relatieve botdichtheid berekend werd als een percentage van de preoperatieve waarde (die op 100% werd gesteld).

In Hoofdstuk 8 worden de resultaten van de opeenvolgende gestandaardiseerde DEXA-scan tot 12 maanden postoperatief na RHA (n=20) en THP (n=22) gepresenteerd. De botdichtheid werd bij beide groepen ter plaatse van de calcar (Gruen zone 7) gemeten en bij de RHA-patiënten werden vier extra femorale *regions of interest* (ROI) gemeten. Bij RHA kon de botdichtheid in de femurhals behouden worden. De gemiddelde relatieve botdichtheid ter plaatse van de calcar nam een jaar na RHA significant toe tot 105,2% (p=0,012) versus een daling tot 82,1% (p<0,001) voor de THP-groep. Het verschil tussen de groepen was significant (p<0,001). In de overige vier femorale metingen wordt initieel een niet-significante afname van de botdichtheid gezien, gevolgd door een herstel tot op preoperatief niveau na 12 maanden.

In Hoofdstuk 9 worden de resultaten van de botdichtheidsmetingen van het acetabulum tot 24 maanden na de RHA-press-fit-kobalt-chroom-cup (n=38) en THP-titanium-schroefcup met Metasul-insert (een metaal-inlay in een polyethyleen liner) (n=33) gepresenteerd. De botdichtheid in vijf acetabulaire periprothetische zones werd prospectief gestandaardiseerd geanalyseerd; deze zones konden onderverdeeld worden in twee craniale (ROI 1 en 5), twee mediale (ROI 2 en 4) en een caudale zone (ROI 3). In tegenstelling tot onze hypothese werd de periacetabulaire botdichtheid beter behouden na RHA dan na plaatsing van een conventionele THP. Na een RHA bleven beide craniale zones rond de uitgangswaarden stabiel (ROI 1 98,7%; ROI 5 101,9%), terwijl na THP de craniale zone 1 een significante afname in botdichtheid toonde (ROI 1 90,8% (p<0,001); ROI 5 93,8% (p=0,055)). Ten aanzien van de twee mediale zones was er een significante botdichtheidsafname in beide groepen: RHA tot 77,7% en 91,5% en THP tot 67,3% en 97,0% (ROI 2 en 4) (p<0,05), in zone 2 is het verschil in het voordeel van RHA. De botdichtheid bleef in de caudale zone 3 voor RHA stabiel op 99,8%, terwijl er een significante afname werd gevonden voor THP tot 93,5% (p<0,001). In tegenstelling tot de hypothese bleef het acetabulaire bot beter behouden ondanks de stijve press-fit RHA-cup. De waargenomen afnames van de botdichtheid mediaal van de cup (ROI 2 en 4) van 23% en 8,5% voor RHA en 32% en 3% voor THP na 24 maanden zijn in overeenstemming met eerdere literatuur over botdichtheidsveranderingen na conventionele THP met press-fit-cups. Een press-fit-RHA-cup leidt derhalve in deze studie niet tot een grotere afname van periprothetisch botdichtheid vergeleken met een gevestigde schroefcup. Dit resultaat is echter discutabel indien grotere acetabulaire cups moeten worden geïmplanteerd bij RHA (en dus meer acetabulair bot verwijderd wordt) om te passen bij de overeenkomstige femorale diameter. Aan de femorale zijde wordt na RHA een natuurlijkere belasting gezien, terwijl er botdichtheidsverlies optreedt na een conventionele ongecementeerde THP. Op de korte termijn is er in deze studies na RHA een groter behoud van botdichtheid gezien in

zowel het femur als het acetabulum, in vergelijking met THP.

Discussie

Heupresurfacing (RHA) is een (geherintroduceerd) nieuw concept en design voor heupprothesiologie en het is derhalve belangrijk om de resultaten te vergelijken met de gouden standaard, de totale heupprothese (THP). Voor dit proefschrift werd onder andere een gerandomiseerde studie tussen RHA en THP verricht voor een objectieve vergelijking van klinische uitkomsten, voor het vergroten van het niveau van bewijs in de huidige literatuur en om te onderzoeken of heupresurfacing voldoet aan de geopperde (hoge) verwachtingen. Gebaseerd op de resultaten van dit proefschrift kan geconcludeerd worden dat RHA voldoet aan de verwachtingen met betrekking tot botdichtheid, klinische uitkomsten en stabiliteit op de korte termijn. Een RHA behoudt de femurkop en conserveert meer botdichtheid rondom de prothese dan de THP in klinisch relevante zones van acetabulum, zoals craniaal en mediaal van de cup en de femorale calcarzone. Klinische uitkomstmaten en patiënttevredenheid zijn goed tot uitstekend na RHA in onze kortetermijnstudie. De scores van OHS, UCLA-activiteitsscore en VAS-tevredenheid waren significant hoger na RHA dan na THP op sommige tijdpunten. Ondanks randomisatie hadden de RHA-patiënten echter reeds preoperatief een hogere UCLA-activiteitsscore, dus is het de vraag of het postoperatieve voordeel klinische betekenis heeft. Het verschil in patiënttevredenheid en vroege klinische uitkomstmaten tussen RHA en THP kan, volgens onze voorkeursstudie, niet worden toegeschreven aan het feit dat patiënten mogelijk hun implantaat van voorkeur (RHA) kregen. De RHA blijkt ten slotte ook het stabielere implantaat te zijn. In de RHA-groep werden geen dislocaties gevonden, in de THP-groep drie. De metaalionenconcentraties kunnen bij metaal-op-metaalprothesen een reden van zorg zijn. In onze studies blijven de mediane metaalionenconcentraties echter laag, voor de unilaterale implantaten onder de 2 µg/L. In de RHA-groep is er initieel een significant hogere afgifte van kobalt en chroom dan in de 28-mm-MoM-THP-groep. Na 24 maanden is dit alleen nog significant verschillend voor de chroomwaarden.

Gebaseerd op de huidige literatuur en nationale implantaatregisters zijn de criteria voor een ideale kandidaat voor een RHA: mannelijk geslacht, jonger dan 55 jaar, een femorale diameter groter dan 50 mm, een BMI kleiner dan 35 kg/m^2 en primaire coxartrose. Mannelijke RHA-patiënten, ongeacht leeftijd, met een femorale diameter groter dan 50 mm hebben een tienjaars-revisiepercentage van 5,1%. Wanneer het revisiepercentage van RHA vergeleken wordt met de gouden standaard – de conventionele metaal-op-polyethyleen-THP voor een mannelijke patiënt, jonger dan 55 jaar met primaire coxartrose – is dit na tien jaar 6,1% voor de RHA en 9,3% voor de THP. Gebaseerd op het Australische implantaatregister voldoet RHA ruim aan de NICE-criteria (overlevingspercentage van een implantaat groter dan of gelijk aan 90% na tien jaar) wanneer het geplaatst wordt in jonge mannen (of vrouwen met een femorale diameter groter dan 50 mm) met primaire coxartrose. Er moet hierbij opgemerkt worden dat deze succesvolle tienjaars-follow-up alleen beschikbaar is voor twee resurfacingmerken (Conserve® Plus en de Birmingham Hip Resurfacing (BHR)) en voor een selecte groep van ideale patiënten zoals beschreven.

In de registers worden de resultaten van de verschillende soorten RHA- en MoM-THP-implantaten samengevoegd weergegeven. Er is echter steeds meer bewijs dat de resultaten variëren tussen de verschillende merken c.q. fabrikanten. De introductie van de BHR op de markt werd streng gecontroleerd, met geselecteerde chirurgen en de nadruk op de noodzaak van de juiste chirurgische techniek en selectie van patiënten. De succesvolle resultaten van de BHR in biomechanische, heupsimulator studies en klinische studies (van *designer surgeons*, chirurgen die bij de ontwikkeling van de prothese betrokken zijn) trok de aandacht van andere fabrikanten die graag deel uit wilden maken van de metaal-op-metaal-revolutie. Fabrikanten in Europa en de Verenigde Staten ontwikkelden hun eigen MoM-heupimplantaten, met in elk ontwerp een wisselende combinatie van aanpassingen aan de oorspronkelijke ontwerpkenmerken. Kenmerken van de RHA waarvan gedacht wordt dat ze de slijtage positief dan wel negatief beïnvloeden zijn: 1) het gebruik van gegoten (as cast) versus gesmeed materiaal, 2) verschillende hittebehandelingen van de componenten, 3) de afstand tussen de twee articulerende oppervlakten (*radial clearance*), 4) de mate van acetabulaire overdekking van de femorale component en 5) de functionele hoek van de femorale component. Sommige ontwerpen, met lage slijtage-eigenschappen in vitro, blijken zeer gevoelig te zijn voor suboptimale positionering in vivo, met extreem hoge slijtagewaarden tot gevolg bij grote aantallen patiënten. Grotere maten van bepaalde ontwerpen lijken juist weer ongevoelig voor suboptimale positionering. Daarnaast vertonen de grote diameter (groter dan 36 mm) LDH-MoM-THP aanzienlijk hogere en klinisch zorgelijke metaalionenwaarden in vergelijking met RHA en men moet de resultaten van deze LDH-MoM-THP niet samenvoegen met die van de RHA.

Toen de MoM-implantaten in Europa geïntroduceerd werden, werden ze door de reguleren-de partijen in de categorie prothesen geplaatst die alleen een heupsimulatortest (in vitro biomechanisch cyclisch belasten van de prothese) vereiste, aangezien het concept werd beschouwd als een uitbreiding van eerder goedgekeurde ontwerpen. Verschillende concurrerende ondernemingen konden snel hun eigen MoM-implantaat op de markt brengen, zonder dat klinische studies verplicht waren om commercieel gebruik toe te staan. In de Verenigde Staten beschouwde de Food and Drugs Administration (FDA) de componenten van de LDH-MoM-THP gelijk aan andere kopjes, cups en stelen die reeds in gebruik waren en verklaarde dat ze op basis hiervan goedgekeurd konden worden (een zogenaamd 510(k) proces). Derhalve waren er ook hier geen klinische studies nodig om te bewijzen hoe de LDH-MoM-koppen werkten wanneer ze gecombineerd werden met een gemodificeerde steel. Mede mogelijk gemaakt door de relatief 'gemakkelijke' goedkeuring en onder druk van hun investeringen introduceerden de fabrikanten de MoM-implantaten snel op de markt. De concurrentie om marktaandeel resulteerde in een agressieve marketingcampagne gericht

op patiënten en chirurgen. Dit resulteerde in een te snelle wereldwijde introductie van deze nieuwe MoM-implantaten zonder gegevens over langdurige klinische resultaten en identificatie van alle mogelijke complicaties.

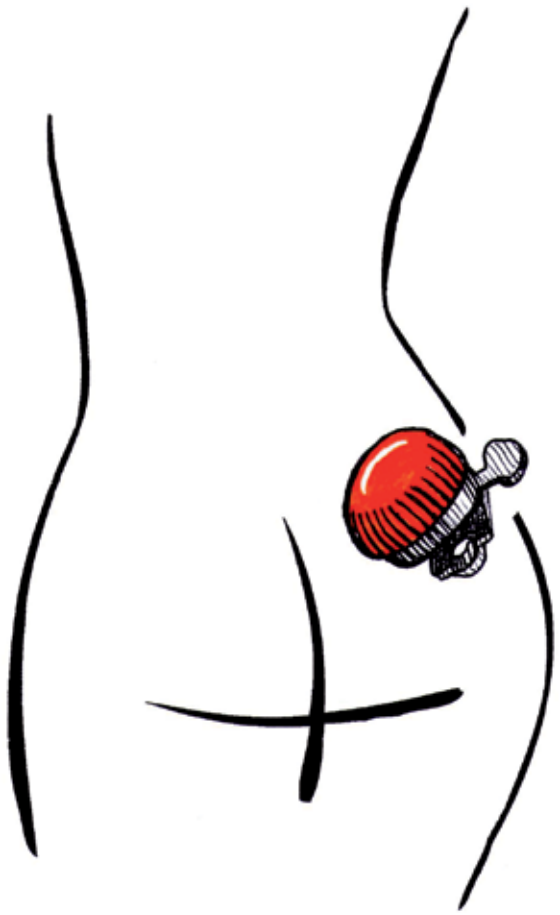
Op dit moment is er wereldwijd een toenemende bezorgdheid over de MoM-implantaten. De zorgen richten zich op relatief hoge revisiepercentages, pseudotumorvorming en mogelijke metaalionintoxicatie. Er zijn duidelijke aanwijzingen dat het risico op deze problemen tussen verschillende soorten MoM-implantaten verschilt. Dit geldt zowel voor verschillen in type implantaat (LDH-THP versus RHA) als voor de verschillende merken. Geen enkel type of merk MoM-prothese is geheel vrij van zorg. Nationale richtlijnen van de regelgevende instanties en orthopedische verenigingen verschillen in hun adviezen met betrekking tot MoM-heupimplantaten. Deze richtlijnen variëren van aandacht voor het probleem tot inperkingen in het gebruik tot aan een expliciet verbod, van bepaalde specifieke typen tot alle MoM-implantaten. Ondanks de duidelijke behoefte ontbreekt een uniforme internationale consensus. De problemen van de MoM-heupprothese en de gevonden bijwerkingen zijn ingewikkeld en onderzoek roept soms nog meer vragen op dan dat het beantwoordt. Een andere complicerende factor is het aantal betrokken partijen, bestaande uit patiënten, chirurgen, fabrikanten, onderzoekers, regelgevende instanties en keuringsinstanties, elk met hun eigen belangen, verantwoordelijkheden en betrokkenheid bij het MoM-implantaat-probleem. Op nationaal niveau vragen de complicaties en gesignaleerde problemen in de literatuur om een duidelijk beleid inzake de MoM-heupimplantaten. In 2012 werd in Nederland, al dan niet gedwongen door de publieke opinie, besloten om een time-out op te leggen voor alle MoM-heupimplantaten met een heupkop-diameter groter dan of gelijk aan 36 mm (inclusief RHA en merkonafhankelijk). Met betrekking tot de toenemende revisiepercentages en veelvoorkomende complicaties na LDH-MoM-THP lijkt dit een zeer terechte beslissing. Men kan zich, met het oog op RHA, echter afvragen of we nu de baby weggooien met het badwater door een verbod op álle merken van de RHA voor álle patiënten. Aan de andere kant kan in dit proefschrift geen uitgesproken klinisch relevante voordelen van RHA ten opzichte van THP bewezen worden en blijven er nog veel onzekerheden bestaan aangaande de MoM-gerelateerde problemen. Beide rechtvaardigen een time-out van het gebruik van MoM-implantaten. Met het oog op de toekomst geeft het Australische register de mogelijkheid revisie- en overlevingspercentages type- en merkspecifiek te beoordelen. Dit geeft de mogelijkheid om onderscheid te maken tussen falende en succesvolle RHA- en MoM-THP-ontwerpen. De verschillen tussen de goed en slecht functionerende ontwerpen en MoM-categorieën worden momenteel al steeds duidelijker. Wanneer RHA wordt vergeleken met LDH-MoM-THP is er een tienjaars-revisiepercentage van 9,1% versus 20,3%. Dit kan, mettertijd, de mogelijkheid geven om bepaalde RHA-implantaten toe te laten, als ze voldoen aan de NICE-criteria in de nationale registers en in klinische studies geen onaanvaardbare bijwerkingen hebben. Redelijkerwijs kunnen die RHA-implantaten in een gecontroleerde setting worden toegelaten, in een zeer specifieke groep patiënten: mannen jonger dan 55 jaar, met een heupkop-

diameter groter dan 50 mm, een BMI kleiner dan 35 kg/m^2 en primaire coxartrose.

Dit proefschrift heeft zich geconcentreerd op patiënten met een specifiek RHA-merk (Conserve® Plus; Wright Medical) en alle patiënten werden geopereerd door een beperkt aantal ervaren heupchirurgen. Er zijn duidelijke aanwijzingen dat de kans op een MoM-gerelateerd probleem verschilt tussen de verschillende merken van RHA en dat er meer problemen zijn die gerelateerd zijn aan het LDH-MoM-THP-concept dan aan het RHA-concept. Tijdens het lezen van de resultaten van dit proefschrift moet men zich realiseren dat deze factoren verantwoordelijk kunnen zijn voor de gepresenteerde, relatief goede resultaten. Deze resultaten kunnen waarschijnlijk niet worden gegeneraliseerd naar alle MoM-implantaten. Bovendien geven de studies in dit proefschrift de resultaten weer na kortetermijnfollow-up en zal een langere follow-up nodig zijn om harde conclusies te trekken. In de tussentijd zullen deze patiënten met grote zorg vervolgd worden. Metaalionen in het bloed, DEXA-analyse en functionele uitkomstscores zijn opgenomen in het standaard follow-up-protocol. Momenteel zijn bijna alle patiënten voorbij de driejaars-follow-up en worden er geen duidelijke verschuivingen in resultaten of revisiepercentages gezien. In overeenstemming met de richtlijnen van de Nederlandse Orthopaedische Vereniging is er afgestapt van het gebruik van RHA in onze kliniek. Of deze time-out tijdelijk of permanent is, is nog niet duidelijk. Voor de nabije toekomst staat beeldvorming met MARS-MRI bij alle RCT- en cohortpatiënten gepland, aangezien het concretiseren van de incidentie van stille pseudotumoren op dit moment belangrijk lijkt te zijn. Tot op heden is er geen overeenstemming over de incidentie van pseudotumoren na verschillende soorten MoM-implantaten. Ook de consensus over de vraag of deze stille pseudotumoren klinisch relevant zijn ontbreekt.

Nu de hype van de MoM-heupimplantaten overgegaan is in een nationale professionele afkeer van MoM-articulaties, is het tijd om de successen in de klinische praktijk te bestendigen en de mislukkingen af te wijzen. Daarom is onderzoek naar verdere identificatie van de oorzaken achter deze mislukkingen en successen van groot belang. Langdurige follow-up in een geselecteerde patiëntengroep met een kleine selectie van de momenteel beschikbare MoM-implantaten zal helpen om te bepalen in welke mate er plaats is voor RHA en/of LDH-MoM-THP.

Toekomstig onderzoek zou zich moeten richten op het scheppen van meer duidelijkheid over de gevolgen van langdurige blootstelling aan hoge metaalionenspiegels, bepaling van de provocerende factoren van ARMD in het menselijk lichaam, de klinische betekenis van asymptomatische pseudotumoren en klinische uitkomsten na revisieoperaties. Intensieve en langdurige follow-up wereldwijd van patiënten met een MoM-implantaat zal helpen deze kwesties te verhelderen en zal in het huidige debat over de zorgen rondom de MoM-articulatie verder gebruik wel of niet rechtvaardigen.



&

Dankwoord

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Curriculum vitae

José Smolders wordt op 27 juli 1982 in Lelystad geboren. Nadat het VWO-diploma op ISG Arcus is behaald gaat zij naar Nijmegen om Geneeskunde te studeren. Tijdens een wetenschappelijke stage in The Gambia bij de Medical Reseach Council gaat het onderzoekshart van José ondanks statusonderzoek met onleesbare handschriften harder kloppen en kan er met een portie levenservaring èn SPSS-kennis aan haar co-schappen worden begonnen. Tijdens het co-schap Orthopaedie bij prof. dr. R.P.H. Veth in het UMC St Radboud wordt direct duidelijk dat bij dit specialisme haar toekomst ligt en dit wordt bevestigd in een senior co-schap in het Rijnstate. Hier zorgt een onderzoek naar de inschatting van patiënten over het honorarium van de orthopaedisch chirurg voor onrust bij de onderzoekgroep en het ziekenhuis, maar ook voor de eerste publicatie.

Na het arts-examen wordt er eerst drie maanden onderzoek gedaan in het Orthopaedic Research Lab te Nijmegen en daarna is het tijd om als AGNIO Orthopaedie in Ziekenhuis Elkerliek te Helmond 'dokter te worden'. Na een succesvolle sollicitatie in regio Oost start in 2008 de vooropleiding algemene chirurgie in het Rijnstate (opleider dr. M.M.P.J. Reijnen) en wordt er gestart met eerste aanzet voor dit proefschrift bij de afdeling Orthopaedie onder supervisie van dr. J.L.C. van Susante. José begint in 2010 met de opleiding Orthopaedie in de Sint Maartenskliniek (opleider dr. A.B. Wymenga), UMC St Radboud (opleider dr. M.C. de Waal-Malefijt) en Rijnstate (opleider dr. W.J. Rijnberg), die zij eind 2014 zal afronden. José is getrouwd met Tijmen Moltmaker en samen hebben zij in 2011 dochter Koosje Jans gekregen.

Publicaties

JMH Smolders, A Hol, JLC van Susante. Metal ion trend may be more predictive *for* malfunctioning metal-on-metal implant than single metal ion measurement. Accepted for publication in *Hip Int.* April 2013.

JMH Smolders, DF Pakvis, B Hendrickx, NJJ Verdonschot, JLC van Susante. Periacetabular bone mineral density changes after resurfacing hip arthroplasty versus conventional total hip arthroplasty. A randomized controlled DEXA study. Accepted for publication in *J Arthroplasty.* December 2012.

W van der Weegen, **JMH Smolders**, T Sijbesma, HJ Hoekstra, K Brakel, JLC van Susante. High incidence of pseudotumors even in low risk Metal-on-Metal hip resurfacing patients; preliminary results from an intensified MRI based screening protocol in 44 ReCap hip resurfacing arthroplasties. Accepted for publication in *Hip Int.* December 2012.

JMH Smolders, A Hol, WJ Rijnberg, JLC van Susante. Metal ion levels and functional results after either resurfacing hip arthroplasty or conventional metal-on-metal hip arthroplasty Short-term outcome of a randomized controlled trial. *Acta Orthop.* 2011 Oct;82(5):559-66.

JMH Smolders, P Bisseling, A Hol, C van der Straeten, BW Schreurs, JLC van Susante. Metal ion interpretation in resurfacing versus conventional hip arthroplasty and in whole blood versus serum. How should we interpret metal ion data? *Hip Int.* 2011 Sep;21(5):587-95.

P Bisseling, **JMH Smolders**, A Hol, JLC van Susante. No clear influence of preference bias on satisfaction and early functional outcome in resurfacing hip arthroplasty. *Acta Orthop.* 2011 Apr;82(2):161-5.

JMH Smolders, A Hol, T Rijnders, JLC van Susante. Changes in bone mineral density in the proximal femur after hip resurfacing and uncemented total hip replacement: A prospective randomised controlled study. *J Bone Joint Surg Br.* 2010 Nov;92(11):1509-1514.

JMH Smolders, N Kock, S Koëter, JLC van Susante. Osteochondral autograft transplantation for osteochondritis dissecans of the knee. Preliminary results of a prospective case series. *Acta Orthop Belg.* 2010 Apr;76(2):208-18.

S Witjes, **JMH Smolders**, P Beaulé, P Pasker, JLC van Susante. Learning from the learning curve in total hip resurfacing: a radiographic analysis. *Arch Orthop Trauma Surg.* 2009 Oct;129(10):1293-1299.

N Kock, **JMH Smolders**, JLC van Susante, P Buma, A van Kampen, N Verdonschot. A cadaveric analysis of contact stress restoration after osteochondral transplantation of a cylindrical cartilage defect. *Knee Surg Sport Tr A.* 2008 May:16(5):461-468.

JMH Smolders, CJ van Loon, WJ Rijnberg, JLC van Susante. Patients poorly estimate the overall costs of a total knee arthroplasty and strongly overestimate the surgeon's fee. *Acta Orthop Belg.* 2007 Jun;73(3):339-344.