Unraveling the mystery of hip tissue in Metal on Metal Total Hip Arthroplasty
HEAVY READING IN HEAVY METAL

Unraveling the mystery of hip tissue in Metal on Metal Total Hip Arthroplasty
The research presented in this thesis was mainly conducted at Isala, Department of Radiology in Zwolle, The Netherlands.

Cover by Corrie Meiling, Zaandam, The Netherlands, February 2017. Aquarelle painting with permission based on a photograph by Tamara Oberholster, South-Africa.

About the cover “Kolmanskop Namibia: House with sand.”
The painting represents inevitable changes through time. Desert sand will in time erode the carefully erected house. What man has created will be replaced by nature if not properly taken care of. In this specific house you enter the main hall on the left side, and on the right side you can enter another room. The picture is a metaphor for the fact that we always come from one place, stay only temporarily in the current place and are always on our way to another temporary place. That relativizes.
One can also observe a door that is barricaded by the desert sand. It fuels our fantasy about what is behind that door. The urge comes up to dig out and open the door to go towards places that seemed unreachable before.

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HEAVY READING IN HEAVY METAL

Unraveling the mystery of hip tissue in Metal on Metal Total Hip Arthroplasty

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Chapter 1

Introduction
CONVENTIONAL TOTAL HIP ARTHROPLASTY AND ITS COMPLICATIONS

Osteoarthritis (OA) of the hip, also known as osteoarthritis, coxarthrosis or coxarthritis is one of the leading causes of global disability and common in the elderly population with an age-standardised prevalence of 0.85% (95% UI 0.74% to 1.02%). The terminology OA is generally used for non-inflammatory degenerative hip joint pathology that has resulted in cartilage loss. Patients are confronted with pain in weight-bearing situations and OA also results in a decreased range of motion of the hip. Overall, this leads to a lower quality of life. The prevalence of OA is predicted to grow as a result of an ageing population that is getting more obese.\textsuperscript{1,2}

In general, surgical replacement of the hip joint with an artificial prosthesis, known as total hip arthroplasty (THA) or total hip replacement (THR), is the solution in cases where the normal anatomy of the hip is affected by a certain stage of OA leading to clinical problems that cannot be resolved by non-operative treatment. In the Netherlands, this procedure was performed in 2005 in 20,715 patients and according to demographic projections this will increase up to 31,731 patients in 2030. If trend projection is incorporated, this could even rise up to 51,680 patients in 2030.\textsuperscript{3}

When a conventional THA is implanted, the femoral head and the collum are surgically resected and a metal stem is placed in the femur and a polyethylene cup or a polyethylene liner in a metal shell is placed in the acetabulum (Fig. 1).

\textbf{Fig. 1.} Anterior-posterior (AP) radiograph of a conventional total hip arthroplasty on the right side of the patient
Traditionally all components are cemented. Currently also uncemented (tight fit) components both acetabular and femoral are frequently used as well as (reversed) hybrid concepts.

A conventional THA has several distinctive components. The modular neck or taper is used to ensure that the specific size of the prosthetic head, which can be different in each patient due to the choice of the surgeon, can be placed on the stem. The various lengths, created by preferred head and taper of different lengths together, are used to mimic the initial natural situation in each individual patient. The prosthetic head articulates with the cup which inner diameter matches that of the head. This cup is always the first component that is placed and it is placed in the acetabulum of the patient.4

A conventional THA is characterized by a cemented all polyethylene cup. There are some common complications with the use of this type of THA. First of all, it is prone to wear, which can lead to an eccentric position of the head in the cup (Fig. 2).

A second complication is known as “particle disease”. Particle disease is a granulomatous inflammatory response to a foreign body. It can lead to bone loss which shows radiolucency’s on conventional radiographs. These lucencies are visible at the metal bone interface or bone cement interface in respectively uncemented and cemented prosthetic components (Fig. 3).5

Fig. 2. AP radiograph of an eccentric, non-symmetrical, position of the head in the cup and a metal-on metal THA on the left side of the patient. Arrow indicates upward placed position of the prosthetic head in the cup.

A second complication is known as “particle disease”. Particle disease is a granulomatous inflammatory response to a foreign body. It can lead to bone loss which shows radiolucency’s on conventional radiographs. These lucencies are visible at the metal bone interface or bone cement interface in respectively uncemented and cemented prosthetic components (Fig. 3).5
Infection, dislocations and component wear result in a limited life span of THAs.\textsuperscript{6}

The degenerative aetiology of OA leads to a peak age incidence in the 7\textsuperscript{th} decade of patients that have a sound indication for hip replacement.\textsuperscript{7,8} The combination of the increased life expectancy of patients and the limited life span of the conventional THA pose a problem for retaining mobility at older age. Moreover, younger patients with OA are also seen with increasing frequency.\textsuperscript{9} Young patients with higher activity levels experienced early failures with THA, whereas their longer life expectancy required that the THA lasts longer.

**MOM THA AND MOM HRA**

The bone resorption and component wear observed in conventional THA led 25 years ago to new concepts of hip replacements with longer survival rates. New materials and new components in THA were used such as metal-on-metal (MoM) THA and MoM hip resurfacing arthroplasties (HRA) with the assumption that these new arthroplasties could overcome the problems of limited life span in younger patients while being more suitable for the young and active patient with sufficient bone stock (Fig.4).\textsuperscript{10-13} The main difference between these THAs and conventional THAs is the articulation of the head and cup that is now by definition MoM instead of metal on polyethylene. The best indication for hip resurfacing seems to be the young and active patient with severe hip arthritis, good hip morphology and adequate bone quality.
The first person to use a MoM prosthesis on a regular basis was the English surgeon George McKee in 1953. It became unpopular in the 1970’s due to the observation of metal particles in cases of failure of the MoM THA that needed revision. With new designs, it gained some popularity in the beginning of the 21st century.14

However, already in 2008 alarming case reports on “pseudotumours” led to increased concerns about these MoM THA and MoM HRA. 15-17 In 2009 Malviya A et al. reported the incidence of pseudotumours after hip resurfacing by a single surgeon over a 10-year period and in 2012 the disappointing ten-year survival of the Birmingham hip resurfacing (BHR) was presented by Murray DW and colleagues.18,19 A pathological capsular reaction due to metal particles released in the hip joint was believed to be the underlying cause of the initially radiologically detected large pseudotumours. These pseudotumours were defined as semi-solid or cystic periprosthetic mass of 2 cm in diameter or larger semi-solid or cystic periprosthetic mass of 2 cm in diameter or larger. By assessing the hip capsule, a pathological reaction of the hip capsule could be confirmed by means of biopsy of the hip capsule and rule out malignancy.20

Additional case reports were published regarding metal ion deposits from the serum into the thyroid, heart and brain tissue anecdotally leading to cardiomyopathy and encephalopathy.21,22
Initial retrospective studies reported that the incidence of pseudotumours after MoM THA was about 1%. However, these incidences were derived from symptomatic and revision cases and therefore most likely underestimated the true incidence. A prospective cohort study in our hospital (Isala hospital, Zwolle, the Netherlands) showed a substantially higher incidence of pseudotumour formation (39%) and subsequent revisions (12% of the total research population of 116 patients; 31% of patients diagnosed with a pseudotumour) in patients with Biomet M2a-Magnum/ReCap MoM THAs.

Alerts were sent out by orthopaedic societies and the Dutch orthopaedic association was the first to advice to stop with all (both THA and HRA) MoM large head hip arthroplasties.

**IMAGING OF PSEUDOTUMOURS**

In order to detect a pseudotumour one needs to use radiological imaging to assess the hip capsule. Ultrasound (US), Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) are applied for the detection. All these modalities have their pro’s and con’s.

**US**

No radiation, easy accessibility and the low cost of US make it an attractive surveillance tool, and it demonstrated a high degree of sensitivity in detecting the presence of adverse tissue reactions after MoM hip prostheses.

Disadvantages of US include that it is not able to assess all tissue surrounding the MoM. Comparison in follow-up is more difficult and it is less suitable for research purposes in quantifying encountered pathology. Its ability to accurately report synovial thicknesses and its sensitivity in detecting smaller, deep tissue deposits have not been investigated yet.

**MRI**

MRI is also used without potentially harmful radiation. However, the cost and time associated with the use of MRI as a surveillance tool remains a concern. MRI is unique in its ability to predict the severity of tissue destruction found at revision and the degree of tissue necrosis found at histologic evaluation.

The presence of metal is a problem especially if only conventional MRI sequences are applied but the presence of metal is of course also a problem with the use of CT and US. The use of specific, metal artifact reduction sequences (MARS) such as MAVRIC (multiple acquisition variable-resonance image combination) and SEMAC (slice encoding for metal artifact correction) have increased the ability to both identify and characterize soft tissue lesions when compared with conventional MRI sequences.
Furthermore, in predictive models, the maximum synovial thickness and the presence of solid synovial deposits on MRI have greater sensitivity and specificity in detecting aseptic lymphocyte-dominant vasculitis-associated lesion (ALVAL) scores and quantifying intraoperative tissue damage than isolated serum ion levels.\textsuperscript{24}

In 2011 an MRI grading system was described which proved to be reliable for evaluating ALVAL in MoM prostheses using MRI but it was limited in differentiating mild disease from infection and it was not investigated whether this grading system correlated well with subsequent revision.\textsuperscript{26} In addition MRI does not detect acetabular osteolysis.\textsuperscript{27}

Overall, the main difficulty with MRI is that screening large cohorts of patients puts a lot of stress on already existing waiting lists for MRI in the radiology department and it is the most expensive modality.

**CT**

Until 2010 CT was not routinely used as the first-choice modality. This was probably mainly due to radiation burden and lack of visualization of the soft tissue around the hips. The main difficulty of CT in the MoM HA population was also the metal artefacts from the very large MoM implants that obscured the readability of acquired CT scans of the hips.\textsuperscript{28}

Relative low cost, the accessibility of CT, the possibility to assess different component orientations, evaluation of osteolysis in the acetabulum, all in combination with new dedicated CT metal artefact reduction techniques improving readability, paved the way for the use of CT as a primary tool for radiological evaluation of the MoM hip arthroplasty population.

**CT AND BONE MINERAL DENSITY MEASUREMENTS**

In cases where MoM THA has led to a significant pathological capsule reaction, the metal cup needs to be replaced by a conventional polyethylene cup, all polyethylene or as a polyethylene liner in a metal shell. Resection of the metal cup in the MoM-configuration often damages the native remnants of the acetabulum in such a way that before a new cup can be placed, additional hardware needs to be installed to keep the cup in the correct position (Fig. 5). If there is not enough surrounding bone or the surrounding bone present is not strong enough, additional hardware cannot be placed unless augmentation with bone graft is used routinely with homogeneous cancellous bone impacted in the deficient acetabulum. Thus, it is important for the orthopaedic surgeon to be aware of the bone status, more specific the bone mineral density (BMD), of the acetabulum before the start of the revision procedure.
Assessment of the BMD around the prosthesis components is not possible in the case of metal artefacts, due to disturbance of the radiation extinction defined by Hounsfield Units, but the acetabular bone at zone I according to De Lee and Charnley is free of metal artefacts. With the daily reality of a high amount of surgical revisions of MoM THA it could be useful if CT would be able to not only detect pseudotumours, evaluate component orientation, but in addition could also detect and quantify osteolysis in the acetabulum all in a single scan. With this approach, different causes for revision could be addressed in one scan.

**CT AND O-MAR**

Until the release of dedicated metal artefact reduction techniques, the pelvis in case of an inserted THA could be considered “no man’s land” due to severe metal artefacts. It was very difficult to read the soft tissues in the pelvis that were obscured by these metal artefacts. An experienced eye was capable of looking through, past, or behind the metal artefacts but with the introduction of orthopaedic metal artefact reduction software (O-MAR) this became much easier for every reader. Using O-MAR the reader is able to actually see the tissues in the pelvis between THA on both sides such as the posterior wall of the bladder, the pelvic floor muscles and delineation of the recto
sigmoid (Fig. 6). Although O-MAR was designed for large metal implants, there was actually no evaluation of O-MAR in patients with THA.30

The high incidence of pseudotumours after MoM THA and HRA and subsequent revisions warranted a screening program in our hospital (Isala hospital, Zwolle, the Netherlands) which was later adopted in the Netherlands. All patients involved were invited for intensive follow up consisting of an outpatient intake, quantification of serum metal ion levels and radiological evaluation by means of conventional radiographs and computed tomography (CT).

Because of the necessity to screen a large cohort of patients (>700) and to subsequently reduce pressure on the logistic capacity of the radiology department and associated costs, we decided to use CT as a primary screening tool. In addition, the advantage of CT is that it offers the possibility to measure the orientation of different components in THA and it can be used to assess BMD which is essential and meaningful in the indication procedure for revision surgery. During the follow up program an unusual amount of revisions had to be performed.

The large-scale use of CT put us in a special position since other investigators used ultrasound (US) and/or magnetic resonance imaging (MRI) for the evaluation of cohorts of these specific patients. Moreover, it gave us the opportunity to investigate dedicated MARS in CT.

![Fig. 6. Axial CT images of the pelvis in bilateral total hip arthroplasty with large head metal on metal without (a) and with O-MAR (b)](image-url)

(a) (b)
OUTLINE OF THE THESIS

In this thesis, we described 5 years of investigating the value of CT-imaging for the stratification and prevalence of pseudotumours in several screening cohorts that had been treated with a MoM THA or MoM HRA. In addition, the biological behaviour of acetabular bone, which is important when a revision is indicated, was investigated. Finally, the capacity of an orthopaedic metal artefact reduction (O-MAR) software tool to actually reduce metal artefacts in imaging was assessed.

Chapter 2
The use of CT for the pre-operative evaluation of the hip joint and planning of a hip resurfacing is reviewed. We describe a robust, easy-to-use five-point grading system (I to V) for morphology of the hip capsule based solely on morphological changes to the hip capsule observed in MoM THA.

Research question:
1. What is the spectrum of capsular disease in a screening population of patients with MoM THA?

Chapter 3
The description of the spectrum of pathology that can be seen by the radiologist in CT scans from MoM THA patients in a screening population, needs to be clear and meaningful for the orthopaedic surgeon.

A refined more comprehensive CT classification than described in chapter 2 is presented that shows clinical correlation with revision and is therefore of use for communication between radiologists and orthopaedic surgeons.

Research questions:
1. How reliable is the designed CT classification between observers?
2. How does the CT classification relate to surgical revision?

Chapter 4
We investigated the prevalence of pseudotumours and analysed whether we could identify risk factors for pseudotumour formation after MoM HRA with a BHR. The BHR is the result of a significant different prosthesis design of MoM THA that leaves the collum femoris relatively intact and only resurfaces the femoral head with metal that articulates with a metal cup. MoM orthopedic implants thus differ in design and therefore it is possible that patient populations differ in presented pathology. In this chapter, we discuss the prevalence of capsular reactions in MoM HRA with a BHR.
Chapter 1

Research question:
1. What is the prevalence of pathological capsular reactions in MoM HRA?

Chapter 5

Density measurements in CT depend on intrinsic patient variables. Therefore, we scanned a small cohort of patients with an external phantom during the first follow-up in order to be able to correlate Hounsfield Unit (HU) measurements with the external phantom. We compared both phantom based CT density measurements with Phantom Less Based Bone Mineral Density measurements (PLBMD) to investigate whether the use of an internal reference standard for fat and muscle could serve as a replacement for the external reference standard with a phantom.

Research question:
1. Can we measure BMD without the use of a phantom on non-iodine CT-scans of the pelvis?

Chapter 6

After the introduction of the PLBMD method in the pelvis we investigated whether MoM THA results in bone loss of the acetabulum over the course of time. In addition, we investigated whether the inflammatory environment in case of a pathological capsular reaction of the hip capsule leads to more bone loss of the acetabulum by using the contralateral hip in which no surgery was performed as internal reference.

Research questions:
1. Does the MoM THA result in bone loss of the acetabulum over the course of time?
2. Does the inflammatory environment in cases of pathological capsular reaction of the hip capsule lead to more bone loss of the acetabulum?

Chapter 7

In general, metal artefacts impede reading soft tissue and bone in CT-imaging. Post-processing tools may contribute to creating better images. Because of the large patient population in our hospital that received a metal implant, we used a special dedicated O-MAR add on for our 64-slice system. We aimed to optimize the CT image of the hips in our 64-slice scanner, by dealing with metal artefacts, to quantify the strength of this visually beneficial post processing software tool and to investigate whether the produced images also reflected in vivo or in vitro reality.
Research question:
1. Can we quantify the observed improved image quality in CT by use of the dedicated metal artefact reduction post-processing tool O-MAR?
REFERENCES


Chapter 2

The use of computerized tomography (CT) to evaluate hip resurfacing

M.F. Boomsma, H.B. Ettema, C. Van Der Straeten

ABSTRACT

Computerized tomography (CT) is a cross-sectional imaging technique suitable for measuring the position of hip resurfacing components and to evaluate the periprosthetic bone. Metal artifact reduction methods reduce the streak artifacts caused by the presence of metal components. This chapter reviews the use of CT for the pre-operative evaluation of the hip joint and the planning of a hip resurfacing. It further explains the measurement of acetabular component inclination and anteversion and of femoral anteversion. Peri-prosthetic bone and soft tissue lesions can be evaluated and accurately delineated in several planes.
THE SCIENCE OF COMPUTERIZED TOMOGRAPHY (CT)

The term computed axial tomography (CAT), more commonly called computerized tomography (CT) refers to an imaging method using radiographic cross-sectional (axial) tomography created by computer processing. A three-dimensional image of the inside of an object or body is constructed digitally from a large series of two-dimensional x-ray images around an axis of rotation. The images generated are usually in the axial or transverse plane, perpendicular to the long axis of the body or the part of the body being scanned. Modern scanners, however, also allow the reformatting of data in other planes or the construction of three-dimensional (3D) images of the scanned structures (so-called multi-slice CT). CT can be used together with other imaging techniques like single photon emission computed tomography (SPECT) on bone scan and positron emission tomography (PET). The CT imaging of metal devices is complicated by streak artifacts caused by the presence of metal corrupting projection data. As with magnetic resonance imaging, metal artefact reduction (MAR) algorithms have been developed. MAR methods are usually based on the attenuation of x-rays by metal implants partially impeding the projection of data. The 'missing' data are either avoided (in iterative reconstruction) or interpolated (in non-iterative, filtered back-projection with data completion; typically, with filling data 'gaps' via linear functions). A comparative study of four different algorithms demonstrated superiority of the iterative algorithm producing a considerable improvement of CT imaging in all uses. Recently, new MAR techniques have been developed to achieve more accurate image analysis and better image quality. A wavelet-based multi-resolution analysis method, in which information is extracted from corrupted projection data, was shown to be significantly more accurate for depiction of anatomical structures, especially in the immediate neighbourhood of metal devices like femoral stems. MAR is even more challenging in 3D-CT reconstruction, and further research is under way to improve the accuracy and quality of images in the presence of metal devices.

THE USE OF COMPUTERIZED TOMOGRAPHY (CT) SCANS FOR PRE-OPERATIVE EVALUATION AND PLANNING OF HIP RESURFACING

In order to avoid femoro-acetabular impingement (FAI) following hip resurfacing several authors have advocated the use of CT scanning for pre-operative evaluation of the femoral head and neck. Cam-type deformities of the femoral heads may complicate a hip resurfacing operation and require accurate pre-operative assessment of the anatomy in order to achieve correct implant positioning. Most hips with pre-operative painful FAI will require a greater correction of the femoral head/neck offset in order to minimize the risk of post-operative impingement leading to symptoms of pain,
increased wear and eventually to implant failure. CT scanning is a superior method compared to conventional x-rays with regard to correct pre-operative assessment of femoral head/neck deformities/abnormalities and the pre-operative measurement of acetabular anteversion (Fig. 1).

The use of navigation and robotics for accurate implant positioning in hip resurfacing is controversial. A number of studies have evaluated the post-operative femoral varus-valgus and combined femoro-acetabular anteversion position using image-free navigation based on measurements carried out with 3D CT scans and the reliability of the navigation software regarding the accuracy of the calculated implant position. Schnurr et al. showed an improved accuracy in varus-valgus angle positioning when using 3D CT measurements compared to biplanar radiographs. However, the software calculation of the acetabular position was often inaccurate needing manual adjustment. The precision achieved with robotics was assessed by Barrett et al. by comparing pre-operative CT-based plans with post-operative CT scans. A definite advantage of this method over visual planning could not be demonstrated. A study by Krüger et al. compared the post-operative result of freehand positioning of the femoral drill guide compared to navigated positioning using CT scan views for the computer-assisted operations. The post-operative position of implants was evaluated on plain radiographs showing no difference between both groups with regard to either femoral component position (p > 0.05) or femoral notching. A trend for a better cup anteversion was observed for the navigated hips, but there was no statistically significant difference. The authors concluded that navigation with hip resurfacing surgery may allow a better visualization but is probably only advantageous with mini-incision surgery (MIS).

![Fig. 1. Pre-operative assessment of acetabular anteversion](image)
THE USE OF COMPUTERIZED TOMOGRAPHY (CT) SCANS TO EVALUATE HIP RESURFACINGS

Evaluation of acetabular cup positioning

CT measurement of the inclination of the acetabular component is performed on an anterior pelvic image (as with plain x-rays) by drawing a line joining the ischial tuberosities and measuring the angle with the line drawn through the lateral and the medial edge of the acetabular rim (Fig. 2). For the measurement of the acetabular anteversion, a transischial line is drawn through the ischial tuberosities on an axial image. The line is then transposed to an axial image of the acetabular cup. A second line is drawn through the anterior and posterior edges of the cup rim. The version angle is the angle formed by the transischial line and the line through the cup (Fig. 3). Malpositioning of the acetabular component has been associated with higher wear and soft tissue reactions to metal debris.\textsuperscript{12,13} Optimal placement of the acetabular component is defined as an inclination of 45° and an anteversion of 20°.\textsuperscript{1} A ‘safe zone’ is defined as a zone of ±10° about the optimum orientation. Components placed outside the ‘safe zone’ are considered to be malpositioned.\textsuperscript{14}

![Fig. 2. Measurement of acetabular inclination](image-url)
Other authors\textsuperscript{15} still use Lewinnek’s safe zone definition\textsuperscript{16} of 30-50° inclination and 5-25° anteversion of the acetabular component to predict impingement and subluxation of hip resurfacing arthroplasties, although Lewinnek’s original diagram was referring to the risk of dislocation of conventional hip arthroplasty with a small diameter head (≤ 28 mm). Adequate measurement of cup position can be performed with EBRA\textsuperscript{1} and should be carried out on x-rays taken in standing position in order to take into account pelvic tilt which influences the orientation of the acetabulum and the forces exerted on the hip articulating surfaces. However, acetabular anteversion is sometimes difficult to assess on plain radiographs and therefore some authors have advocated the use of CT scans.\textsuperscript{15,17,18}

Three-dimensional (3D) CT scanning has been suggested as a better method of assessing component positioning compared to axial CT or plain radiographs because the acetabular cup is obscured by the large metal femoral head. Hart et al.\textsuperscript{15} (Imperial College London) use a validated 3D CT reconstruction software and base their measurements on an anatomical frame of reference to neutralize pelvic rotation. In the anterior pelvic plane points are set on the most anterior prominences of both anterior superior iliac spines and the most anterior point of one of the pubic tubercles. The anatomical inclination is measured as the angle to the transverse plane and the anatomical version as the angle to the parasagittal plane. Similarly the acetabular component inclination is measured as the angle to the transverse plane (Fig. 4) and the acetabular component version as the angle to the parasagittal plane (Fig. 5). The authors conclude 3D CT scans are useful for the confirmation of impingement and to identify cup malpositioning. However, as CT scans are currently taken in supine position, they are not the best method to accurately measure the acetabular angles in standing and sitting positions which represent heavier loading conditions and may be more hazardous with regard to subluxation. Lazannec and co-workers\textsuperscript{17,18} confirmed the bias of acetabular position measurements on CT scans.
However, they found a strong correlation ($r = 0.857$) between supine (mean 24.2°) and standing (mean 31.7°) measurements, whilst the correlation between the measurements in lying and sitting positions were very poor ($r = 0.484$) making supine CT measurements less adequate to predict subluxation or dislocation in sitting position.

For the identification of FAI as a cause of pain after hip resurfacing, CT scans are nevertheless the best current imaging method.


**Evaluation of femoral anteversion in total hip arthroplasty and hip resurfacing**

CT scanning can adequately measure femoral anteversion in total hip arthroplasty when the knee is included in the same sequence. A line is drawn parallel to the retrocondylar axis of the knee and then transposed to the hip. A second line is drawn along the taper (neck) of the total hip prosthesis or resurfacing component in order to measure anteversion (Fig. 6(a) and 6(b)). Measuring anteversion of the femoral stem is more relevant in total hip arthroplasty than in hip resurfacing. It can be used to detect malposition of the femoral stem or to do a pre-operative planning before an acetabular revision.

![Figure 6. Measuring femoral version on CT scan: (a) CT scan of the knee showing 5.7° of exorotation and 4° of anteversion relative to the horizontal plane; (b) transposition of this line to the femoral neck results in 1.7° retroversion (malposition of the stem). Note the anterior pseudotumour (arrows).](image)

**Evaluation of periprosthetic bone**

The presence and extent of osteolysis may be missed or underestimated on conventional plain radiographs by the overlapping of adjacent bone trabeculae. On a CT scan, lytic lesions are more easily recognized and delineated. The extent of the lesions can be measured in several planes, enabling the surgeon to calculate the volume of the lesion and plan bone grafting in case of a revision. However, MRI has been found to be the best imaging method to detect periacetabular osteolysis with a sensitivity of 95% compared to 75% with CT scans and 52% with plain oblique radiographs.19 The reduced sensitivity is probably related to artifacts generated by the large metal prosthesis obscuring an adequate evaluation of the medial wall when MAR is not used.

However, CT scans generate adequate imaging of the superior, anterior and posterior acetabulum. The evaluation of osteolytic lesions in the acetabulum can be helpful when
planning acetabular bone grafts or evaluating femoral bone stock in femoral revisions (Figs. 7 and 8). As metal debris can adversely affect bone behind the acetabular component without initially producing cystic lesions, the resulting bone defect following removal and debridement of the acetabular bone is often much larger than anticipated on plain x-rays. The extent and dimensions of the osteolytic lesion is better assessed on a CT scan (Fig. 9). In revision cases with bone grafting procedures, the incorporation of the bone graft can also be assessed adequately on a CT scan.

Fig. 7. (a) Acetabular bone defect, (b) acetabular defect detail

Fig. 8. (a) Anteromedial bone defect and partial deficiency of the posteriial acetabular wall. (b) Detail of anteromedial bone defect and deficient acetabular wall
Similarly, the onset and extent of heterotopic ossification is better visualized on CT scan than on plain x-rays. Whether phantom less based bone mineral density (PLBMD) can be reliably used for measuring the acetabular bone density in patients with metal-on-metal total hip arthropasty (MoM THA) or in patients with MoM hip resurfacing arthroplasty (MoM HRA) is still under investigation. Also the influence of a ‘pseudotumour’ on acetabular bone mineral density is being investigated. These post-processing techniques together with metal artefact reduction techniques will help the clinician to estimate the expected bone capacity of the acetabulum in revision surgery. Periprosthetic fractures behind hip resurfacing prosthetic components may not be readily visible on plain x-rays and have a greater chance to be discovered on CT scans, either at the level of the acetabulum (Fig. 10) or the greater trochanter (Fig. 11).
23.9 Extensive acetabular bone defects (arrows).

23.10 Fracture of the acetabulum wall and loosening of the cup.

Fig. 10. Fracture of the acetabulum wall and loosening of the cup

23.3.4 Evaluation of periprosthetic soft tissue

CT can also detect and delineate solid or cystic masses adjacent to a hip resurfacing arthroplasty, both on axial and coronal images reformatted for reduction of metal artifacts. (Bosker et al., 2011).

23.11 Fracture of the greater trochanter with callus formation and fracture of the pubic arch on the right side.

Fig. 11. Fracture of the greater trochanter with callus formation and fracture of the pubic arch on the right side
Evaluation of periprosthetic soft tissue

CT can also detect and delineate solid or cystic masses adjacent to a hip resurfacing arthroplasty, both on axial and coronal images reformatted for reduction of metal artifacts. Masses can be measured and aspirations or biopsies can be performed under CT guidance. However, MRI remains the gold standard for the identification and detailed description of soft tissue abnormalities. In one recent study, CT was used to screen for soft tissue masses surrounding a large femoral head metal-on-metal prosthesis and MRI was used to confirm the diagnosis. No additional information was gained when using MRI. Furthermore, in symptomatic cases where no soft tissue mass was detected using CT, MRI did not detect additional soft tissue masses.

The diagnosis of a soft tissue reaction to metal debris or so-called pseudotumour can initially be challenging, but in a non-infectious patient with a MoM HRA, screening in experienced hands by means of ultrasound is possible, although there is a greater inter-observer variability with this modality and follow-up can be more difficult. CT scanning, with or without metal artifact reduction algorithms, is also capable of establishing the diagnosis with good inter-observer agreement. Making use of window-level adjustment, such as a bone window on both axial and coronal reconstructions, enhances the accuracy and detection possibilities. MRI is useful because it is the most sensitive method to describe tissue abnormalities, but metal artifacts can make it hard to investigate the relation of the soft tissue lesion with the prosthesis. Moreover, metal artifact reduction sequences (MARS) are not always available on standard MR systems in all hospitals. Furthermore, MRI scanning is more time-consuming than CT, which is an issue with large cohorts that need to be screened. Nevertheless, MRI has the unique capacity to confidently distinguish solid from cystic components due to its superior soft tissue contrast capacity. However, in our experience, MRI has no higher sensitivity in comparison to CT in diagnosing pseudotumours and therefore is of no additional value to CT in the clinical setting of MoM THA or MoM HRA.

A reliable MR grading system for the severity of soft tissue changes associated with metal-on-metal hip replacement has been developed. This grading system describes the range of presentation from normal post-operative appearance through fluid-filled cavities and periprosthetic masses less and greater than 5 cm, up to severe disease where masses can extend through deep fascia, cause tendon avulsions and fracture. Analogous to this MRI grading, a practical CT grading system is under development. It consists of a grading system I-V that describes post-operative CT findings in MoM THA or MoM HRA with or without soft tissue reactions (Table 1). Type I represents normal post-operative changes of the capsule of the operated hip joint which consists of thickening of the capsule up to 4-6 mm (Fig. 12). Type II consists of a thickened capsule > 6 mm with or without bulging but not beyond the neck of the prosthesis and without eccentric enlargement of the capsule (Fig. 13).
Table 1. CT grading system I-V for post-operative CT findings in MoM THA or MoM HRA with or without soft tissue reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal thickening of the hip capsule up to 4-6 mm</td>
</tr>
<tr>
<td>II</td>
<td>Thickened capsule &gt;6 mm with or without bulging but not beyond the neck of the prosthesis</td>
</tr>
<tr>
<td>III</td>
<td>Bulging capsule both anteriorly and posteriorly</td>
</tr>
<tr>
<td>IV</td>
<td>Eccentric bulging or enlargement of the capsule</td>
</tr>
<tr>
<td>V</td>
<td>Bursitis mimicker, mostly located postero-laterally with extensive filling of the bursa subtrochanterica, or anteriorly with filling of the bursa iliopectinea</td>
</tr>
</tbody>
</table>

Fig. 12. Type I normal capsule on the left (right side of the image). Note: Transverse CT scan (and MRI) images look at the body from distally (feet) to proximally (head). Consequently, the right side of the body is on the left side of the image and vice versa.

Fig. 13. Type II thickened capsule on the right (left side of the image).
Fig. 14. Type III bulging capsule anterior and posterior on the right

Fig. 15. Type IV eccentric extension inferomedially bilaterally

Fig. 16. Type V bursitis mimicker anterior and posterolaterally on the right
Type III consists of a bulging capsule both anteriorly and posteriorly (Fig. 14). Type IV represents eccentric bulging or enlargement of the capsule (Fig. 15). This is often seen inferomedially to the prosthetic head. Type V is reserved for the so-called bursitis mimicker, often located postero-laterally with extensive filling of the bursa subtrochanterica, or anteriorly with filling of the bursa ilioplectinea, which can extend quite impressively into the abdominal compartment (Fig. 16). Although there are several other bursae in the hip joint, these two seem the most frequently involved and clinically relevant. In all CT grades (I-V), a thickened capsule is noted. Additionally, the soft tissue reaction further progresses from Type I to IV or V. Simultaneous to the progression of the disease, lesions tend to show more liquified content, although synovial hyperplasia is often present. There is actually considerable variation in the morphology of a ‘pseudotumour’ as described by Fang et al.22

If screening is carried out by an experienced team, pre-operative tissue sampling is not necessary because the characteristic appearance of morphological changes on CT scans in MoM HRA patients is diagnostic.20 In our opinion, if one feels a pre-operative biopsy is necessary, ultrasound-guided biopsies are less cumbersome and technically easier than CT-guided biopsies. After revision, the excised tissue can be examined microbiologically and histologically in order to look for signs of aseptic lymphocyte dominated vasculitis associated lesion (ALVAL) or infection.

CASE STUDIES FROM THE ISALA CLINIC, ZWOLLE, THE NETHERLANDS

Case 1
A 59-year-old female experienced a painless swelling in her right inguinal region for 4 months (Fig. 17(a)). Three years ago, she underwent bilateral metal-on-metal hip arthroplasty with large-size femoral heads (Fig. 17(b)) and experienced an unremarkable post-operative course. Additional CT scan (Fig. 17(c)) and MRI revealed a soft tissue mass of approximately 50 cm². Histological tests demonstrated extensive necrosis with granuloma-like collections of lymphocytes and viable macrophages with metal particles. Serum cobalt and chromium levels were raised (9.4 and 8.0 µg/L). Clinical presentation and CT/MRI findings suggested the presence of a soft tissue reaction to metal debris which was confirmed upon revision. The hip was revised using extensive bone impaction grafting on the acetabular side and a polyethylene cup.
**Case 2**

Six years after a MoM large femoral head THA, this 65-year-old patient presented with groin pain and clicking sensations (Fig. 18). Symptoms were progressive and had started 1 year after the operation. Her cobalt levels were 17.9 µg/l, chromium levels were 14.6 µg/l. CT scanning revealed a large anterior pseudotumour which involved the psoas muscle. The stem was found to be malpositioned, therefore the revision arthroplasty included revision of the femoral component.

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**Fig. 17.** (a) Case 1 swelling in the groin, (b) Case 1 x-ray, (c) CT scan showing soft tissue reaction
CONCLUSIONS

CT is a very accurate and reliable method for the pre-operative evaluation of femoral head and neck deformities, for the diagnosis of femoro-acetabular impingement either pre-operatively or post-resurfacing and for diagnosing post-operative soft tissue reactions. However, MRI is a better method than CT to distinguish solid from cystic components. CT scans are a better method than plain x-rays to detect and delineate osteolytic lesions but are probably not as sensitive as MRI, although this is currently still under investigation. Regarding the evaluation of component positioning, since current CT scans are taken in supine position, measurements of the inclination and version of the acetabular component do not take into account the pelvic tilt and cannot be simply extrapolated to the standing position or compared to measurements on standing radiographs. When the ipsilateral knee is included, adequate measurement of femoral anteverision relative to the retrocondylar axis of the knee can be performed.
REFERENCES


Chapter 3

Development and first validation of a simplified CT-based classification system of soft tissue changes in large-head metal-on-metal total hip replacement: intra- and interrater reliability and association with revision rates in a uniform cohort of 664 arthroplasties


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Validation of CT classification

ABSTRACT

Objective
After implantation of a metal-on-metal total hip arthroplasty (MoM THA), a large incidence of pseudotumor formation has been described recently. Several centers have invited patients for follow-up in order to screen for pseudotumor formation. The spectrum of abnormalities found by CT in MoM THA patients can be unfamiliar to radiologists and orthopedic surgeons. Previously, a CT five-point grading scale has been published. In this paper, a simplification into a three-point classification system gives insight in the morphological distinction of abnormalities of the postoperative hip capsule in MoM implants in relation to the decision for revision. The reliability of this simplified classification regarding intra- and interrater reliability and its association with revision rate is investigated and discussed.

Materials and methods
All patients who underwent MoM THA in our hospital were invited for screening. Various clinical measures and CT scan were obtained in a cross-sectional fashion. A decision on revision surgery was made shortly after screening. CT scans were read in 582 patients, of which 82 patients were treated bilaterally. CT scans were independently single read by two board-certified radiologists and classified into categories I-V. In a second meeting, consensus was obtained. Categories were subsequently rubricated in class A (categories I and II), B (category III), and C (categories IV and V). Intra- and inter-radiologist agreement on MoM pathology was assessed by means of the weighted Cohen’s kappa. Categorical data were presented as n (%), and tested by means of Fisher’s exact test. Continuous data were presented as median (min-max) and tested by means of Mann-Whitney U test (two group comparison) or Kruskal-Wallis test (three group comparison). Logistic regression analysis was performed in order to study independence of CT class for association with revision surgery. Univariate statistically significant variables were entered in a multiple model. All statistical analysis was performed two-tailed using alpha 5 % as the significance level.

Results
In total, 664 scores from 664 MoM hips obtained by two observers were available for analyses. Interobserver reliability for the non-simplified version (I-V) was $\kappa_w = 0.71$ (95 % CI: 0.62-0.79), which indicates good agreement between the two musculoskeletal radiologists. Intra- and interobserver reliability for the simplified version (A-C) were respectively $\kappa_w = 0.78$ (95 % CI: 0.68-0.87), and $\kappa_w = 0.71$ (95 % CI: 0.65-0.76). This indicates good agreement within and between the two observers. The simplified A-C version is significantly associated with revision exclusively due to MoM pathology, in
both patients with unilateral MoM THA (p < 0.001) and patients with bilateral MoM THA (p < 0.044). The simplified A-C version is associated with several clinical measures. In patients with unilateral MoM THA, with or without contralateral THA, in situ time (p < 0.008), cobalt and chromium (p < 0.001) were statistically significant. In patients with bilateral MoM, cobalt (p < 0.001) and chromium (p < 0.027) were statistically significant. Revision is significantly associated with cup size (p < 0.001), anteversion of the cup (p < 0.004), serum ion levels of cobalt and chromium (p < 0.001) and the adapted classification system (p < 0.001). In univariate logistic regression analysis on revision, cup, anteversion of the cup, cobalt-chromium ion serum levels, and the simplified (A-C) CT category system were statistically significant. The simplified (A-C) CT category system was an independent associate of revision, in several multiple logistic regression models.

**Conclusions**

The presented simplified CT grading system (A-C) in its first clinical validation on 48-and 64-multislice systems is reliable, showing good intra- and interrater reliability and is independently associated with revision surgery.
INTRODUCTION

Large-head metal-on-metal total hip arthroplasties (MoM THA) or metal-on-metal hip resurfacing arthroplasties (MoM HRA) were introduced because of their perceived advantages over the conventional metal-on-polyethylene articulations. However, there have been numerous alarming reports of the formation of peri-articular masses in patients with MoM arthroplasties, usually referred to as pseudotumors. Pseudotumors can be small or large, solid or fluid-filled masses with or without communication with the joint. The etiology is probably a capsular reaction to metal debris that eventually leads to pseudotumor formation. The reported incidence in different screening cohorts ranges from 28 to 39 % depending on the type of MoM prosthesis and the screening method used. Although often benign, pseudotumors can be destructive, causing soft tissue damage, osteolysis, fractures, and (sub)luxation with concomitant symptoms of pain and discomfort. With large pseudotumors, revision surgery is often warranted in symptomatic cases. Since 2010, MoM hip articulations have been under increased scrutiny from governmental regulatory agencies and national and international societies leading to alerts, advice, and post-marketing surveillance up to outright discontinuation of metal-on-metal devices. As of 2010, all patients in our hospital who received a MoM hip implant have been invited to a comprehensive screening protocol including CT imaging. Although there is no general consensus whether all different forms of capsular reactions found in screening populations are clinically relevant, adverse reactions to metal debris (ARMD) are prevalent in symptomatic as well as asymptomatic patients with MoM hip replacements.

Screening for capsular reactions by means of computed tomography (CT) is efficient and relatively quick. Availability of CT is much better than magnetic resonance (MR) and costs are estimated to be 2–4 times lower. In a previous study, we showed that CT correlates well with MR in detecting pseudotumors. CT has the additional advantage, however, that anteversion of the acetabular as well as femoral components can be calculated and is much better in detecting osteolysis. To use CT in a clinical setting, a robust, easy-to-use grading system for morphology of the hip capsule is mandatory. For this purpose, a five-point grading scale was developed in our hospital, based solely on morphological changes to the hip capsule. After we became more experienced with the grading system and applying it clinically in our first cohort of patients, it became apparent that the distinction between types I and II as well as between types IV and V did not seem to influence decisions regarding follow-up and revision of patients. Therefore, we decided to further modify the existing grading system I-V into classes A, B, and C, distinctive capsular changes. The primary aim of the present study was to develop a score for classification of absence or presence of MoM pathology and its association with revision by means of a cross-sectional design.
MATERIALS AND METHODS

All patients who underwent MoM THA in our hospital were invited for screening. Various clinical measures and CT scan were obtained in a cross-sectional fashion. A decision on revision surgery was made shortly after screening. We developed a score on capsular reactions and performed an intra- and interrater reliability study of capsular reactions in a cohort of a uniform MoM THA. This study consists of 582 patients, of which 82 patients are treated bilaterally who were all invited for follow-up. The implant consisted of a Bi-Metric porous coated uncemented stem with a metal-on-metal M2a-Magnum femoral head and ReCap acetabular component (Biomet, Warsaw, IN, USA). The modular head and acetabular component are high-carbon, as-cast (single heated) components. The first cohort of this group consisted of 108 patients that were part of a prospective single-center study for which approval of the medical ethical board was obtained.2 Subsequently, all treated patients in our clinic were contacted and invited for outpatient clinic screening again with approval of the institutional review board. Patients were scheduled for non-contrast CT scan analysis on a 48- and 64-slice scanner (Philips, Best, Netherlands) without iterative reconstruction protocols (iDose4) and without orthopedic metal artefact reduction post-processing protocol (O-MAR). CT parameters: kV 140, mAs 250, slice thickness 0.9, increment 0.45, collimation 48 or 64 × 0.625, pitch 0.675, rotation time 0.75. Reconstructions were made with D filter, 800/2000 WL/WW and A filter 50/350, WL/WW.

Reconstructions were processed axial, sagittal, and coronal from both D and A filters. Window width to window-level values were set at 2000:650. All examinations were reviewed on a workstation running Agfa IMPAX version 6.3.1.4537 with BARCO monitors type MDCC3120-DL, color, resolution 1536 × 2048, display orientation portrait, physical size 31.8 × 42.4 cm/12.52 × 16.69 inch. The Digital Imaging and Communications (DICOM) data of the CT examinations were anonymized using an available PACS anonimization tool for the second reader (MM). Both readers were board-certified musculoskeletal radiologists, had no previous experience in reporting metal-on-metal implants regarding capsular disease, and were blinded for patient’s further history. The first reader trained the second reader in mastering the newly designed CT classification system on morphological changes of the hip capsule as the second reader had not encountered MoM-related capsular pathology before. They obtained consensus in evaluating 20 cases before each observer scored all cases independently. The classification system incorporates five categories (I-V), covering the entire spectrum of post-operative CT findings of the hip capsule.6,11 All MoM THA implants were subsequently classified into categories I-V (Figs. 1, 2, 3, 4, and 5). After all CT scans were read and graded independently, consensus between observers was reached on observed differences in classifications. Based on this consensus experience we simplified our
Validation of CT classification

five-point classification system into a three-point classification system as distinction between I-II seemed not clinically relevant and IV-V were considered to be a different morphological expression of the same underlying disease. This adapted system distinguishes between categories A, B, and C capsular changes. In this adapted measure, the first two categories of capsular reactions (I and II) of the old system are merged into category A, category III coincides with category B, and categories IV and V correspond to category C (Table 1).

Fig. 1. Axial CT image, type I hip capsule reaction on the left, thickening of the hip capsule anteriorly not more than 4-6 mm

Table 1. Scoring method: simplified A-C classification system derived from traditional grade I-V grading system

<table>
<thead>
<tr>
<th>Class</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>I</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Reactive</td>
</tr>
<tr>
<td>B</td>
<td>III</td>
<td>MoM disease</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>MoM disease</td>
</tr>
<tr>
<td>V</td>
<td>MoM disease</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe</td>
</tr>
</tbody>
</table>

- Class A: Normal
- Class I: Thickening of the capsule up to 6 mm
- Class II: Reactive
- Class III: Capsule thickening over 6 mm without bulging posterior, not exceeding the neck of the prosthesis and without eccentric capsule enlargement
- Class IV: MoM disease
- Class Moderate: Eccentric capsular enlargement predominantly inferomedial of the prosthetic head
- Class V: MoM disease
- Class Severe: Bursitis mimicker with extensive filling of the subtrochanteric bursa posterior and/or with filling of the iliopectineal bursa anterior with potential extension in the abdominal compartment
regarding capsular disease, and were blinded for patient's further history. The first reader trained the second reader in mastering the newly designed CT classification system on changes [11] Fig. 2. Axial CT image, type II hip capsule reaction on the right, thickening of the hip capsule more than 6 mm

Fig. 3. Axial CT image, type III hip bulging capsule reaction both anterior and posterior on the right
Validation of CT classification

Fig. 4. Axial CT image, type IV hip capsule reaction bilaterally, inferomedial enlargement of the hip capsule

Fig. 5. Axial CT image, type V hip capsule reaction on the right, filling of the bursa iliopectinea and bursa subtrochanterica, both in connection with the hip capsule
The pre-clinical assumption is that only category C requires replacement surgery. Category A capsular reaction is not considered clinically relevant, as this reaction is present in patients with a conventional THA and consists of category I and II capsule reactions.\textsuperscript{12} Category B consists of category III capsular reaction and is rarely observed in both and therefore considered clinically relevant, as it shows some bulging mass effect anteriorly and posteriorly. Category B and C patients are considered candidates for revision if patients are either symptomatic or the peri-articular mass compromises the abductor apparatus or neurovascular bundle. A category C capsule is considered as either a category IV capsule or category V capsule under inflammatory pressure and subsequently developing in the direction of the least resistance. This can be eccentric, which is mostly seen inferomedial to the head of the THA or total hip replacement (THR) and in some cases above the neck of the prosthesis. In a category V lesion, pressure is reduced due to filling of the bursa ilio pectinea that may be non-communicating, communicating and/or septate (13\%) or by filling the bursa subtrochanterica. The subtrochanterica bursa is often damaged by approaching the hip joint in case of THA surgery. In case of an observed communicating fluid collection between the bursa and the hip joint, we believe this to be iatrogenic.\textsuperscript{13-15}

In the case that different types of CT findings in one THA were present, the highest score was applied.

Inter-radiologist agreement on MoM pathology was assessed by means of the weighted Cohen’s kappa for both classification systems (I-V, A-C). Intra-radiologist agreement for the simplified A-C classification system was studied by use of a random sample of 20\% of patients (n = 122). Categorical data were presented as n (%), and tested by means of Fisher’s exact test. Continuous data were presented as median (min-max) and tested by means of Mann-Whitney U test (two-group comparison) or Kruskal-Wallis test (three-group comparison). The decision for screening took place immediately after the screening, which also consisted of serum ion levels and taking the clinical situation of the patient into the decision process.\textsuperscript{16}

To assess whether the classification system correlated well with the decision for revision surgery, logistic regression analysis was performed. For this analysis, we excluded patients revised for reasons other than adverse local tissue reaction such as instability, infection, and aseptic loosing. Several variables were included, such as age, in situ time of the prosthesis, contralateral THA, acetabular version, cup size, cup inclination and anteversion, serum ion levels of cobalt and chromium and the simplified (A-C) classification system. Univariate statistically significant variables were entered in multiple models, in order to study independence of variables. All statistical analysis was performed two-tailed using alpha 5\% as significance level. (SPSS version 22.0).
RESULTS

In total, 664 scores from 664 MoM hips in 582 patients obtained by two observers were available for analysis. CT was performed an average of 37 months after surgery. Interobserver reliability for the non-simplified version (I-V) was \( \kappa_w = 0.71 \) (95% CI: 0.62-0.79), which indicates good agreement between the two musculoskeletal radiologists. Interobserver reliability for the simplified version (A-C) was \( \kappa_w = 0.71 \) (95% CI: 0.65-0.76), which again indicates good agreement between the two observers.

Intra-observer reliability for the simplified version (A-C) was \( \kappa_w 0.78 \) (95% CI: 0.68-0.87). As expected, the intra-observer reliability is higher than the interobserver reliability. Outcomes were also tested for differences between non-simplified and simplified scales. As to be expected, outcomes for interobserver reliability did not differ between versions (\( p < 0.87 \)).

Table 2 shows MoM-related patient characteristics and revision decision for all patients and patients with unilateral or bilateral MoM THA. Figure 6 shows that the adapted CT category system is associated with revision exclusively due to MoM pathology, in both patients with unilateral MoM THA (\( p < 0.001 \)) and patients with bilateral MoM THA (\( p < 0.044 \)).

Table 3 shows that the adapted CT category system is associated with several clinical measures. Table 4 shows the association of revision status with several clinical measures in patients with a unilateral MoM THA. Table 5 shows logistic regression analysis regarding associates of revision surgery in patients with unilateral MoM THA with or without contralateral conventional THA. In univariate logistic regression analysis on revision, cup, anteversion of the cup, cobalt-chromium ion serum levels, and the simplified A-C classification system were statistically significant. Nagelkerke R square of the simplified A-C classification system was 0.211.
Table 2. Characteristics of the patients and revision decision

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 578 patients, n = 655 hips)</th>
<th>Unilateral MoM (n = 501)</th>
<th>Bilateral MoM (n = 77 patients, n = 154 hips)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>64.1 (21.4-88.8) PL</td>
<td>63.9 (21.4-88.8)</td>
<td>65.5 (48.9-74.6) PL</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Metal-on-metal total hip arthroplasty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cup (mm)</td>
<td>46 (36-58) n = 653 HL</td>
<td>46 (36-56) n = 499</td>
<td>46 (38-58) n = 148</td>
<td>0.821</td>
</tr>
<tr>
<td>Inccup (degrees)</td>
<td>48 (18-72) n = 653 HL</td>
<td>48 (22-68) n = 499</td>
<td>49 (18-72) n = 148</td>
<td>0.917</td>
</tr>
<tr>
<td>Avcup (degrees)</td>
<td>+12 (-17 to +45) n = 624 HL</td>
<td>+12.5 (-17 to +45) n = 484</td>
<td>+11 (-15 to +40) n = 140</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>In situ time</td>
<td></td>
<td></td>
<td></td>
<td>0.525</td>
</tr>
<tr>
<td>In situ time (month)</td>
<td>37 (1.2-78) n = 653 HE</td>
<td>36.2 (1.2-78)</td>
<td>37.3 (9-67.9) n = 148</td>
<td></td>
</tr>
<tr>
<td><strong>Blood levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt (µg/l)</td>
<td>2.8 (0.4-176.5) n = 576 PL</td>
<td>2.6 (0.4-176.5) n = 499</td>
<td>5.4 (1.2-81.1) n = 140</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Chromium (µg/l)</td>
<td>2.9 (0.3-94.7) n = 576 PL</td>
<td>2.7 (0.3-94.7) n = 499</td>
<td>7.4 (0.8-90.7) n = 140</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td><strong>Revision decision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revision (yes)</td>
<td>63 (9.6 %) n = 653 HL</td>
<td>43 (8.6 %)</td>
<td>20 (13 %) n = 148</td>
<td>0.118</td>
</tr>
<tr>
<td>Revision (yes), excluding those due to other than MoM pathology</td>
<td>49 (7.7 %) n = 640 HL</td>
<td>33 (6.7 %) n = 490</td>
<td>16 (10.7 %) n = 140</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Significance levels are indicated in bold

**With or without contralateral conventional THA**

HL hip level; PL patient level; MoM metal-on-metal; THA total hip arthroplasty
Table 3. Association of CT category with patient characteristics, in patients with an unilateral MoM** and patients with a bilateral MoM

<table>
<thead>
<tr>
<th>Category A</th>
<th>Category B</th>
<th>Category C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilateral (n=262)</td>
<td>Bilateral (n=51 patients, n=102 hips)</td>
</tr>
<tr>
<td>Metal-on-Metal Total Hip Arthroplasty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cup size (mm)</td>
<td>46 (36 – 56) $^{n=261}$</td>
<td>46 (38 – 56) $^{HL}$</td>
</tr>
<tr>
<td>Incucp (degrees)</td>
<td>49 (27 – 68) $^{n=261}$</td>
<td>48 (18 – 66) $^{HL}$</td>
</tr>
<tr>
<td>Avucup degrees)</td>
<td>+12 (-17 to +45) $^{n=261}$</td>
<td>+10 (-9 to +40) $^{HL}$</td>
</tr>
<tr>
<td>Follow-up until CT (months)</td>
<td>5.1 (6 – 73.8) $^{n=262}$</td>
<td>35.1 (10.3 – 76.8) $^{HL}$</td>
</tr>
<tr>
<td>Cobalt (µg/L)</td>
<td>2.1 (0.4 – 18.8) $^{n=261}$</td>
<td>4.6 (1.2 – 81.1) $^{HL}$</td>
</tr>
<tr>
<td>Chromium (µg/L)</td>
<td>2 (0.5 – 16.3) $^{n=261}$</td>
<td>6.8 (0.8 – 90.7) $^{HL}$</td>
</tr>
</tbody>
</table>

**,** with or without contralateral conventional THA; MoM, Metal on Metal; THA, Total Hip Arthroplasty; HL, hip level; PL, patient level; **, patient level
Significance levels are indicated in bold
(a) All patients (n = 655 hips). Revision due to any reason (white bars): p < 0.001 Revision for adverse local tissue reactions (grey bars): p < 0.001

(b) Unilateral MoM, with or without contralateral conventional THA (n = 501). Revision due to any reason (white bars): p < 0.001 Revision excluding those due to reasons other than MoM pathology (grey bars): p < 0.001

c) Bilateral MoM (154 hips). Revision due to any reason (white bars): p = 0.092 Revision excluding those due to reasons other than MoM pathology (grey bars): p = 0.044

Fig. 6. Percentage revision surgery by CT category: MoM metal-on-metal; THA total hip arthroplasty

When all univariate statistically significant variables were entered in a multiple logistic regression model, Nagelkerke R square was 0.445. Cobalt and chromium lost statistical significance, however. Cobalt and chromium appeared to be highly correlated with r = 0.931, p < 0.001. In a model including cup, anteversion of the cup, chromium, and the simplified A-C classification system, all variables were statistically significant, and Nagelkerke R square was 0.444. In an even smaller model including cup, chromium, and the simplified A-C classification system, all variables were statistically significant, and Nagelkerke R square was 0.433.
Table 4. Association of revision status\textsuperscript{a} with several clinical measures, in patients with a unilateral MoM THA\textsuperscript{b,c}

<table>
<thead>
<tr>
<th></th>
<th>No revision (n = 457)</th>
<th>Revision (n = 33)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.9 (21.4-88.8)</td>
<td>63.2 (42.5-71.9)</td>
<td>0.534</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient category</td>
<td>90 (19.8 %)</td>
<td>11 (33.3 %)</td>
<td>0.075</td>
</tr>
<tr>
<td>Contralateral THA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prosthesis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cup (mm)</td>
<td>48 (36-56)\textsuperscript{+}\textsuperscript{455}</td>
<td>44 (40-54)</td>
<td>0.001</td>
</tr>
<tr>
<td>IncCuP (degrees)</td>
<td>48 (22-68)\textsuperscript{+}\textsuperscript{455}</td>
<td>50 (32-64)</td>
<td>0.608</td>
</tr>
<tr>
<td>AcuP (degrees)</td>
<td>+13 (-17 to +45)\textsuperscript{+}\textsuperscript{443}</td>
<td>+8.5 (-8 to +22)\textsuperscript{+}\textsuperscript{50}</td>
<td>0.004</td>
</tr>
<tr>
<td>Follow-up to CT (months)</td>
<td>36 (1.2-78)</td>
<td>42.1 (6.7-62)</td>
<td>0.115</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT category</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>- A</td>
<td>256 (56 %)</td>
<td>2 (6.1 %)</td>
<td></td>
</tr>
<tr>
<td>- B</td>
<td>58 (12.7 %)</td>
<td>3 (9.1 %)</td>
<td></td>
</tr>
<tr>
<td>- C</td>
<td>143 (31.3 %)</td>
<td>28 (84.8 %)</td>
<td></td>
</tr>
<tr>
<td>Blood levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt (μg/l)</td>
<td>2.4 (0.4-27.7)\textsuperscript{+}\textsuperscript{455}</td>
<td>9.5 (0.9-111.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Chromium (μg/l)</td>
<td>2.5 (0.3-27.8)\textsuperscript{+}\textsuperscript{455}</td>
<td>8.6 (0.5-90.4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Significance levels are indicated in bold
\textsuperscript{a}Excluding revision surgery due to reasons other than metal on metal pathology
\textsuperscript{b,c}With or without contralateral conventional THA
MoM metal-on-metal; THA total hip arthroplasty; HL, hip level; PL, patient level

DISCUSSION

In this study, we show good intra- and interobserver reliability with a simplified classification system for classifying swelling around large-head MoM hip arthroplasties. No practical CT grading system with good intra- and interrater reliability has been previously described. The interrater agreement was good for the more extensive as well as the simplified version. Intra-observer agreement was slightly higher (κ\textsubscript{w} 0.78) than inter-observer agreement (κ\textsubscript{w} 0.71).

Extensive analysis shows that the classification shows association with other MoM-related parameters in distinctive patient categories. Perhaps unsurprisingly the simplified A-C classification system showed to be an independent associate of revision in several multiple logistic regression models. It is the independent associate of revision that is most unlikely to be attributed to chance (p < 0.001).

The possibility in CT scans of measuring femoral and acetabular anteversion was of great added value to surgeons, especially in planning revision surgery. The CT scan gave us the opportunity to assess the position (ante/retroversion) of acetabular component and stem (supplementary knee scan), which is of great interest to the clinician, as it is one of the parameters that influence the indication and execution of revision surgery.
### Table 5. Logistic regression analysis for associates of revision*, in patients with a unilateral MoM THA** (n = 490)

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β p(SE)</td>
<td>value</td>
</tr>
<tr>
<td>Personal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.003 (0.022)</td>
<td>0.897</td>
</tr>
<tr>
<td>Patient category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral THA a vs. no contralateral THA</td>
<td>0.707 (0.388)</td>
<td>0.068</td>
</tr>
<tr>
<td>Metal-on-metal total hip arthroplasty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cup (mm) b vs. A</td>
<td>-0.174 (0.059)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Inccup (degrees) b vs. A</td>
<td>0.009 (0.023)</td>
<td>0.704</td>
</tr>
<tr>
<td>Avcup (degrees) b vs. A</td>
<td>-0.062 (0.021)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Insitu time</td>
<td>0.017 (0.011)</td>
<td>0.127</td>
</tr>
<tr>
<td>Blood levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobalt (μg/l)</td>
<td>0.189 (0.029)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Chromium (μg/l)</td>
<td>0.219 (0.036)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Radiological score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT category B a vs. A</td>
<td>1.890 (0.924)</td>
<td><strong>0.041</strong></td>
</tr>
<tr>
<td>CT category C a vs. A</td>
<td>3.221 (0.739)</td>
<td><strong>0.001</strong></td>
</tr>
</tbody>
</table>

Significance levels are indicated in bold

*Excluding revision surgery due to other than metal on metal pathology

**With or without contralateral conventional THA; MoM metal-on-metal; THA total hip arthroplasty
We have shown here that in a multiple logistic regression model, anteversion of the cup is indeed an independent associate of revision, notably a negatively association.

Consensus meetings for clinical purposes showed that it is often difficult to assess the thickness of the capsule because of the presence of streak artefacts. The best location to assess the thickness in our opinion is the insertion on the trochanter anteriorly.

The demand for imaging studies has dramatically increased in patients with MoM THA and THR. Firstly, as a consequence of the issued recommendations. Secondly, because of the media attention that these recommendations attracted, and thirdly because of the large amount of patients that are invited for follow-up in order to screen for capsular reactions. This situation subsequently puts a demand on a hospital’s financial resources.

Furthermore, it calls for an efficient means to screen for significant pathology to identify those patients that could be a candidate for revision. The diagnostic techniques used to assess MoM THR patients include ultrasound (US), CT, and MRI. Especially, MRI with metal artefact reduction sequences (MARS) is an excellent tool to detect pseudotumors, and recently three reliable MR classifications of soft tissue changes found in MoM THA have been published.\textsuperscript{17-20} Many centers do not have access to MARS, however. Moreover, the lengthy MRI scans, absence of MARS software, costs, and large numbers to screen preclude the widespread application of MR for this purpose. In contrast to MRI, screening by means of computed tomography is efficient and relatively quick. Generally, availability of CT is much better, and costs are estimated to be 2-4 times lower in the Netherlands. It has the essential additional advantage of calculating the orientation of the individual prosthesis components as malposition is vital in the decision-making process prior to potential revision surgery.

Radiation exposure is nevertheless a reason for concern. By careful planning, the dose length product can be reduced to a minimum. An upgrade from a 48- to a 64-slice system with iDose reduced the computed tomography dose index (CTDI) by approximately 30\%. Data from the literature suggest that the administrated radiation dose can be decreased over 50\%.\textsuperscript{21-23} Furthermore, new hybrid iterative and full-iterative protocols are available from various manufacturers. This development will almost certainly further reduce the dose exposure to the patient. New metal artefact suppression post-processing software is also available, generating better visibility of the immediate soft tissues around metal implants.\textsuperscript{24-26} Recent research suggests that reducing the streak artefacts can be further improved.\textsuperscript{27-31} Due to these on-going technical developments, image quality can potentially be improved in the areas affected by metal artifacts. The derived benefit can be twofold: either from information on the morphology that was not visible without these correcting methods, or where poorer photon statistics, by introducing dose-saving protocols, are balanced by these methods to achieve similar image quality. The present capacity of full-iterative reconstruction techniques will re-
duce the radiation dose substantially. This study shows that there is a reliable, feasible, and easy-to-use classification system for CT in capsular MoM-related disease. With ongoing dose reduction developments in the future and the added benefit of measuring component position and osteolysis, we believe CT is an attractive alternative to MR. One concern with CT imaging is that it is often difficult to assess the thickness of the capsule because of the presence of streak artefacts. Post-processing techniques such as metal artifact reduction in combination with full iterative reconstructions and in time possibly spectral CT will reduce the presence of streak artefacts.

The best location, however, to assess the thickness of the capsule in our opinion is the insertion on the trochanter anteriorly.

This investigation adds clinical validity to a tool that in our hospital significantly helped in the communication between radiologists and orthopedic surgeons with regard to management of the MoM patients.

Although the classification suggests a linear progression in capsular reaction, this study was not designed to evaluate progression of capsular reaction from grade A to C. Patients who did not need, or did not want, revision surgery, are currently followed up by CT scanning in our institution at 1-, 5-, and 10- year intervals to evaluate if such a progression will eventually occur. Asymptomatic pseudotumors, however, seem to show little change within 1 year. The classification in this study is now part of a comprehensive screening protocol together with physical symptoms and serum ion levels.

**CONCLUSIONS**

The presented simplified CT grading system (A-C) in its first clinical validation on 48- and 64-multislice systems is reliable, showing good intra- and interrater reliability and is independently associated with revision surgery. In a multiple logistic regression prediction model together with other unilateral significant MoM-related variables of interest when considering revision, the simplified A-C version shows to be an independent predictor for revision that is the most unlikely to be attributed to chance. Further clinical validation could consist of multinational multireader validation preferentially in latest CT techniques with higher multislice systems with partial or even full iterative reconstruction techniques with dedicated metal artifact reduction protocols.
REFERENCES


Chapter 4

High prevalence of pseudotumors in patients with a Birmingham Hip Resurfacing prosthesis: a prospective cohort study of one hundred and twenty-nine patients


*R. Bisschop and M.F. Boomsma contributed equally to the preparation of this article

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ABSTRACT

Background
Recently, concern has emerged about pseudotumors (lesions that are neither malignant nor infective in the soft tissues surrounding total hip arthroplasty components) after hip arthroplasties with metal-on-metal bearings. Patients treated in our hospital for degenerative arthritis of the hip with a Birmingham Hip Resurfacing (BHR) prosthesis were invited to return for follow-up evaluation. The prevalence and clinical relevance of pseudotumors were investigated. Risk factors for pseudotumor formation were sought.

Methods
A single-center cross-sectional prospective cohort study was conducted and included all patients who received a BHR from 2005 to 2010 in Martini Hospital, Groningen, The Netherlands. Data were collected on patient and surgical characteristics, clinical hip outcome scores (Harris hip score and Oxford score), serum metal ion levels (cobalt and chromium), and radiographs. A computed tomographic scan (without metal suppression) was made. In patients who had a revision, tissue samples were histologically examined.

Results
Originally, there were 129 patients with 149 BHRs. Four patients (six hips; 4 %) were lost to follow-up. Our final cohort consisted of 125 patients (143 hips). From this final cohort, eleven patients (twelve hips) had a revision, and three of them (three hips) had the revision before the present study was conducted. Seven patients (eight hips; 5.6 %) had a revision because of a symptomatic pseudotumor. Survival analysis showed an implant survival rate of 87.5 % at five years (failure was defined as a revision for any reason). A pseudotumor was found on computed tomography in thirty-nine patients (forty hips; 28 %). Of those patients, ten (eleven hips; 28 %) had complaints involving groin pain and discomfort, a noticeable mass, or paresthesia. Symptomatic pseudotumors were significantly larger than asymptomatic pseudotumors (a mean volume of 53.3 cm³ compared with 16.3 cm³; p = 0.05). A serum cobalt level of >85 nmol/L was a predictor for pseudotumor formation (odds ratio, 4.9).

Conclusions
Pseudotumor formation occurred in 28 % of hips after an average follow-up of forty-one months. Most pseudotumors (72.5 %) were asymptomatic. Larger pseudotumors were associated with more complaints. Survival analysis showed an implant survival of 87.5 % at five years. Failure occurred in 5.6 % (eight) of 143 hips because of a symptomatic pseudotumor.
INTRODUCTION

In the mid-1970s, metal-on-polyethylene total hip arthroplasty components were used instead of the first-generation metal-on-metal total hip arthroplasty components. Because of good clinical results, the indication for hip replacement was widened and younger patients with end-stage degenerative arthritis were treated. Because of increased risk of polyethylene wear and subsequent prosthetic loosening, metal-on-metal total hip arthroplasty and metal-on-metal hip resurfacing arthroplasty were reintroduced. Hip resurfacing arthroplasty offers more hip stability, preserves the femoral neck and a portion of the femoral head, and optimizes stress transfer to the proximal part of the femur.1

We believe that the best indication for metal-on-metal hip resurfacing arthroplasty is a young active man with end-stage degenerative arthritis and good bone quality. In such patients, survivorship of the components has been reported to be 99% at ten years and 98% at thirteen years of follow-up.2 A recent systematic review of the metal-on-metal hip resurfacing arthroplasty devices has shown survival rates of 84% to 100%, with a mean duration of follow-up ranging from 0.6 to 10.5 years.3 The most frequent mode of failure was aseptic loosening in 3.5% of hips.

Recently, concern has emerged about soft-tissue reactions after metal-on-metal hip resurfacing arthroplasties.4 One reaction is pseudotumor formation, which may be due to an adverse immunological reaction to metal particles, but the exact mechanism remains unclear. These nanometer-sized metal particles can corrode in synovial fluid, forming cobalt and chromium ions. Uptake from the synovial fluid results in raised serum levels of cobalt and chromium ions. Cardiac and neurologic toxicity of cobalt has been described, although reports are scarce.5,6 Pseudotumors can be asymptomatic or have a wide variation in presentation, with pain and discomfort in the groin but also with spontaneous hip dislocation, a noticeable mass in the groin, a rash, or nerve palsy.7 Because of a high failure rate, the Articular Surface Replacement (ASR; DePuy, United Kingdom) has been withdrawn from the market.8

Because of the concerns of pseudotumor formation and possible systemic effects of elevated metal ions, all patients who had had a metal-on-metal hip resurfacing arthroplasty (Birmingham Hip Resurfacing [BHR]; Smith & Nephew, Birmingham, United Kingdom) were invited to return for follow-up evaluation. The purpose of this study was to investigate the prevalence of pseudotumors. We also analyzed whether we could find a risk factor for pseudotumor formation after metal-on-metal hip resurfacing arthroplasty.
MATERIALS AND METHODS

Study design
From January 2005 to November 2010, in the Martini Hospital, Groningen, The Netherlands, a BHR prosthesis was implanted in young patients with end-stage osteoarthritis of the hip. Exclusion criteria were previous surgery of the ipsilateral hip, known metal sensitivity, or osteoporosis (as determined on a dual x-ray absorptiometry scan). All procedures were performed with a metal-on-metal BHR femoral head and acetabular shell. Three different orthopaedic surgeons (including one of us [C.L.E.G.]) performed the surgery.

A single-center cross-sectional prospective cohort study was conducted following approval of our institutional medical ethics committee. All patients with a BHR were recruited. Informed consent was obtained. Patient characteristics (sex, age, body mass index, cup size, and duration of follow-up) were determined, as well as the Harris hip and Oxford scores. An anteroposterior radiograph was made, with special interest in the inclination of the acetabular component. Serum ion cobalt and chromium levels were determined, and a computed tomographic (CT) scan of the periprosthetic region was made. Indications for revision as well as the findings during the revision procedure were documented. Finally, retrieved tissue specimens in the revised hips were analyzed by a pathologist with expertise in pseudotumor characterization.

Metal ions
Blood samples were obtained via Venflon (Becton Dickinson, Helsingborg, Sweden), discarding the first 5 mL. All samples were frozen and sent to the same laboratory (Humicon, Maastricht, The Netherlands) for blinded analysis of whole blood and serum chromium and cobalt levels, using inductively coupled plasma mass spectrometry. To analyze the predictive value of metal ion levels for the prevalence of pseudotumors, all bilateral BHRs were removed from the analysis. The ion levels of 107 patients were evaluated.

CT scans
CT scans were performed on a sixteen-slice CT scanner (Philips; Best, The Netherlands). CT scans were viewed in a bone window to minimize artifacts resulting from metal implants. Window width to window-level values were set at 2000:650. The CT scans were performed without a metal suppression protocol. A CT grading system was used to describe the amount of synovial reaction postoperatively (see Supplement). In our study, grade IV or V findings, which consist of a solid, semisolid, or cystic eccentric extension of the capsule, resulting in an increase in the volume of the capsule that could not be attributed to an infection, malignancy, bursa, or scar tissue, were classified as a pseudotumor. There was no minimum size of the pseudotumors.
Thickened capsule with or without bulging (grade II or III) was recorded but was not considered to be a pseudotumor. The volume (V) of the pseudotumor was calculated by using the formula for elliptical volume\(^1\): \(V = 0.52 \times \text{height} \times \text{width} \times \text{depth}\).

**Histological analysis**

All specimens were fixed in neutral buffered formalin (10%). Tissue samples were embedded in paraffin and processed. Sections that were 3 mm thick were stained with hematoxylin and eosin and evaluated histologically. Tissue responses were classified by a surgical pathologist (A.T.M.G.T.) using the aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) score described by Campbell et al.\(^1\)

**Statistical analysis**

To assess differences in several variables between patients with and without a pseudotumor, t tests were used for continuous variables or the Mann-Whitney U test was used when the variables were not normally distributed. The chi-square test and the Fisher exact test were used for categorical variables. The prevalence of peri-articular masses in our patients was expressed in percentages. On the basis of logistic regression analyses, the potential risk factors, including age, sex, cup size, inclination, Harris hip score, Oxford score, and elevated metal ion levels, were initially studied in a univariate analysis. Only variables that demonstrated an association of \(p < 0.20\) in univariate analysis were fitted in a multivariate logistic regression model. A best subset stepwise forward procedure was followed to develop a prediction model for peri-articular mass. Only significant factors in the final regression model were considered predictors. For all tests, a two-tailed significance level of \(p < 0.05\) was used.

**Source of funding**

There was funding from Smith & Nephew for the CT imaging and measurement of serum cobalt and chromium levels. Only the contributors had full access to the study data.

**RESULTS**

From 2005 to 2010, 149 BHR prostheses were implanted in 129 patients. The mean duration of follow-up (and standard deviation) was 41 ± 16.2 months (range, ten to eighty-two months). Four patients (six hips; 4%) were not available for follow-up. Before this study was conducted, three BHR prostheses (in three patients) were revised; two were revised because of impingement and one was revised because of a pseudotumor. These prostheses had already been analyzed with serum ion levels and CT and were therefore included in the study population, although one of these patients
did not have a clinical prerevision score available. Therefore, the final cohort consisted of 125 patients (143 hips).

The patients had an average age (and standard deviation) of 53.5 ± 6.8 years (range, twenty-one to seventy-three years) at the time of the index surgery. Seventy BHR prostheses (47 %) were in female patients. Eighteen patients had a bilateral hip resurfacing. In thirty-nine patients (forty hips; 28 %) the CT scan revealed a pseudotumor (Fig. 1). Twenty-seven (67.5 %) of the hips with a pseudotumor had a grade-IV lesion, and thirteen hips (32.5 %) a grade-V lesion.

Of the multiple variables analyzed, age, sex, body mass index, cup size, inclination, and follow-up time did not differ significantly between the patients with and without a tumor (Table 1). Both cobalt and chromium levels were elevated in patients with a pseudotumor.

The chance of having a pseudotumor was significantly higher (odds ratio, 4.9) in patients with an elevated serum cobalt level of > 85 nmol/L. An increase in cobalt or chromium ions of 1 nmol/L increased the chance of a pseudotumor by 1.3 %. A serum cobalt level of > 85 nmol/L was found in eighteen patients (twenty-three [21.1 %] of 109 hips) with a BHR acetabular cup inclination of ≥ 45° (range, 45° to 67°) and in two patients (two [5 %] of forty hips) with a cup inclination of < 45° (range, 30° to 44°); the difference was significant (p = 0.024).
Chapter 4

Table 1. Associations of Variables with Pseudotumor Formation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group with Pseudotumor*</th>
<th>Group without Pseudotumor*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age† (yr)</td>
<td>54.6 (40-65)</td>
<td>53.2 (21-73)</td>
<td>0.26</td>
</tr>
<tr>
<td>Females (%)</td>
<td>49</td>
<td>46</td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass index† (kg/m²)</td>
<td>27.7 (20.5-37.6)</td>
<td>26.5 (19.8-37.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cup size† (mm)</td>
<td>56.8 (50-64)</td>
<td>56.4 (50-66)</td>
<td>0.56</td>
</tr>
<tr>
<td>Inclination† (deg)</td>
<td>50.5 (37-65)</td>
<td>49.6 (30-67)</td>
<td>0.54</td>
</tr>
<tr>
<td>Follow-up time† (yr)</td>
<td>2.57 (0.6-5.6)</td>
<td>2.45 (0.8-6.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Serum cobalt† (nmol/L)</td>
<td>94.4 (17-930)</td>
<td>47.5 (14-311)</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum chromium† (nmol/L)</td>
<td>106.8 (13-918)</td>
<td>56.2 (10-202)</td>
<td>0.10</td>
</tr>
<tr>
<td>Median Oxford score (range)</td>
<td>16 (14-42)</td>
<td>16 (14-61)</td>
<td>0.56</td>
</tr>
<tr>
<td>Median Harris hip score (range)</td>
<td>97 (51-100)</td>
<td>98.5 (36-100)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*There were thirty-nine patients (forty hips) with a pseudotumor and eighty-six patients (103 hips) without a pseudotumor. †The values are given as the mean, with the range in parentheses.

Of the thirty-nine patients (forty hips) that had a pseudotumor on CT, ten (eleven hips; 28%) had complaints. All ten patients (eleven hips) had pain and discomfort in the groin. Three patients (four hips) had a noticeable mass, and one of these patients had neurologic complaints (paresthesias in the distribution of the lateral femoral cutaneous nerve). These patients had an average Harris hip score of 70 points. Twenty-nine patients (twenty-nine hips; 73%) had an asymptomatic pseudotumor (average Harris hip score of 97.8 points; range, 91 to 100 points). Eight patients (nine hips; 9%) without a pseudotumor on CT had complaints; these patients had an average Harris hip score of 69.5 points (range, 36 to 84 points). Symptomatic pseudotumors (mean volume, 53.3 cm³) were significantly larger than asymptomatic pseudotumors (mean volume, 16.3 cm³) (p = 0.05). Of the eighteen patients who had bilateral hip resurfacing with BHR implants, one had a pseudotumor bilaterally and three had a pseudotumor unilaterally, one of which was symptomatic. The mean serum level (and standard deviation) of cobalt was 86.8 ± 70.4 nmol/ L (range, 33.9 to 310.6 nmol/L) in the eighteen patients with BHR implants bilaterally compared with 54.6 ± 97.2 nmol/L (range, 13.6 to 930.0 nmol/L) in the patients with BHR implants unilaterally.

Three patients (three hips) had a revision before this study was conducted, and an additional eight patients (nine hips) had a revision at the time of the final follow-up (Table 2). The average time to revision was thirty-six months (range, nine to seventy-two months). Eight patients had a pseudo-tumor. Specimens of these eight pseudotumors were analyzed. Macroscopically, five patients had a solid or cystic soft-tissue mass with white or yellowish or brown discoloration (Fig. 2). Three patients had a gray soft-tissue mass, mostly anteriorly to the hip.
Table 2. Characteristics of Patients with a Revised BHR Prosthesis

<table>
<thead>
<tr>
<th>Case</th>
<th>Harris Hip Score*</th>
<th>Serum Cobalt (nmol/L)</th>
<th>Grade of Pseudotumor on CT†</th>
<th>Indication For Revision</th>
<th>Timing Revision of (mo)</th>
<th>Histopathological Findings (ALVAL Score)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1§</td>
<td>NA</td>
<td>57.7</td>
<td>V</td>
<td>Pseudotumor</td>
<td>40</td>
<td>7</td>
</tr>
<tr>
<td>2§</td>
<td>82</td>
<td>55.7</td>
<td>IV</td>
<td>Impingement</td>
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<td>3§</td>
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<td>Impingement</td>
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<td>64</td>
<td>156.1</td>
<td>IV</td>
<td>Pseudotumor</td>
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<td>73</td>
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<td>Loosening cup</td>
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<td>1109</td>
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<td>Pseudotumor</td>
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<tr>
<td>12**</td>
<td>64</td>
<td>156.1</td>
<td>II</td>
<td>Pseudotumor</td>
<td>49</td>
<td>4</td>
</tr>
</tbody>
</table>

*NA = not available. †CT = computed tomography. ‡ALVAL = aseptic lymphocyte-dominated vasculitis-associated lesion score. §Revision was done before patient was invited back to participate in the current study. #The hips were in a patient with bilateral involvement. **The hip was revised because of progressive pain without a pseudotumor on CT. On revision, the hip showed excessive metallosis.

**Histological findings in the pseudotumors showed two reaction patterns**

In four of the eight hips, pseudotumors had a thick acellular area of eosinophilic fibrinoid material lining the pseudocysts. Deeper in the tissue, often sharply demarcated, were thick dense aggregates of lymphocytes. Acute inflammation was not observed. Only focally, macrophages filled with metal particles were seen. These pseudotumors were classified as high ALVAL scores (7, 8, 8, and 9, respectively). The patient with the bilateral pseudotumors had ALVAL scores of 8 and 9. The histological findings in patients with high ALVAL scores were thought to represent a metal hypersensitivity reaction (Fig. 3). In the other four patients, pseudotumors were histologically dominated by macrophages with intracytoplasmic phagocytosed metal particles. The aforementioned organization of acellular eosinophilic areas with lymphocyte aggregates was not observed. These pseudotumors were classified as low ALVAL scores (1, 3, 4, and 4, respectively). The patient with BHR implants bilaterally with a unilateral symptomatic pseudotumor had an ALVAL score of 4. The histological findings in patients with low ALVAL scores are thought to represent a high wear reaction (Fig. 4).
Fig. 2. Intraoperative image of a pseudotumor. After the femoral head was resected, yellow-grayish villous tissue appeared at the anterior side of the acetabulum. The pound sign indicates the pseudotumor, and the asterisk indicates the acetabular cup of the BHR implant.

Fig. 3. Low-power photomicrographic image of ARMD (adverse reactions to metal debris), demonstrating the dense, deep eosinophilic (pink) fibrinoid material lining the pseudocyst (upper and lower area), with the thick dens (blue) lymphoid aggregates, composed of lymphocytes and plasma cells, between the fibrinoid material. The white arrow indicates lymphocytic aggregates, and the black arrow indicates fibrinoid necrosis and tissue organization (hematoxylin and eosin stain, original magnification, x25).
Survival analysis shows a survival rate of 87.5% at five years (Fig. 5). Failure was defined as revision for any reason. A BHR was revised because of a symptomatic pseudotumor in 5.6% (eight) of 143 hips.

**Fig. 4.** High-power photomicrographic image of ARMD (adverse reactions to metal debris), showing the lymphoid aggregates in the cases of ARMD. The lymphoid aggregates are predominantly composed of lymphocytes and plasma cells (hematoxylin and eosin stain; original magnification, x400)

**Fig. 5.** Kaplan-Meier survivorship curve for the BHR prosthesis. Failure was defined as revision for any reason
DISCUSSION

A pseudotumor is a lesion in the soft tissues surrounding a total hip arthroplasty implant that is neither malignant nor infectious in nature. The diagnosis is made on the basis of clinical and radiographic criteria. Histologically, the terms ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesions) or ARMD (adverse reactions to metal debris) are given. ALVAL is commonly thought to represent an immune reaction to metal particles. This reaction can develop even with low wear.

In our study population, the prevalence of pseudotumors was high (28%). Most of the pseudotumors (72.5%) were asymptomatic. Recently Williams et al. found a 25% prevalence of pseudotumors detected by ultrasound in twenty asymptomatic hips after a resurfacing arthroplasty. To our knowledge, our study is the first to investigate the prevalence of pseudotumors in a cohort of asymptomatic patients who had a metal-on-metal hip resurfacing arthroplasty. Different researchers, however, have described revision rates because of symptomatic pseudotumors after metal-on-metal hip resurfacing arthroplasty. The Canadian Hip Resurfacing Study Group described a prevalence of 0.1% of hips that required revision because of a pseudotumor. Carrothers et al. described a 0.3% revision rate. Ollivere et al. described a revision rate of 3.1% after five years. Kwon et al. described a revision rate of 6.5%. Results from registries in Australia, England, Wales, and New Zealand have also demonstrated an increased rate of revision for any reason after metal-on-metal total hip arthroplasty and metal-on-metal hip resurfacing arthroplasty. In our series, which had an overall revision rate of 8.4%, most revisions (eight hips; 5.6%) were performed because of a symptomatic pseudotumor.

Pseudotumor formation has been described mainly in studies involving metal-on-metal hip arthroplasties, although case reports of patients with metal-on-polyethylene bearings have also described such lesions.

Glyn-Jones et al. found female sex and young age to be significant risk factors for pseudotumor formation. Carrothers et al. also found a significantly higher prevalence of revision in women (5.7%) than in men (2.6%) (p < 0.001). In our study, sex and cup size were not predictors of pseudotumors. Because of the concerns with regard to pseudotumor formation and possible systemic effects of elevated metal ions, all patients (including patients with a recently placed BHR implants) were invited to return for a follow-up evaluation. This accounts for the wide range of follow-up time (mean, 41 ± 16.2; range, ten to eighty-two months). The duration of follow-up did not prove to be a predictor. Six pseudotumors developed between 1.5 and two years postoperatively, suggesting patient susceptibility is an important etiological factor.

Some studies have suggested that edge-loading, resulting from adverse cup orientation, leads to more wear. A recent study by Matthies et al. showed a rate of pseudo-
tumor formation in hips with well-positioned metal-on-metal hip replacements to be similar to that in hips with replacements positioned outside the safe zone. Inclination angle did not prove to be a predictor in our study. An important limitation of our study is the lack of measurement of the acetabular anteversion. Conventional postoperative images could not all be retrieved because of a switch from analogue to digital imaging. Furthermore, many axial images were of poor quality and without enough penetration to quantify acetabular anteversion. CT reconstructions to address the anteversion are not possible because of the fact that the thin slices that were initially produced were not stored, to save space on the server. Reformatting the thick slices was not possible.

We chose CT for follow-up evaluation because a previous study showed no higher sensitivity for magnetic resonance imaging than for CT, and the use of ultrasound is, in our opinion, less suitable for double reading. The CT classification used for describing the synovial reaction is currently under investigation for its reliability regarding interobserver variation.

High serum levels of cobalt and chromium alone are not necessarily an indication for revision, although cardiac and neurological toxicity of cobalt has been described. Patients in our study with very high serum ion levels, however, were at risk of having a pseudotumor on CT scan. Serum ion levels can therefore be used as a screening tool.

Several groups have reported good clinical results after metal-on-metal hip resurfacing arthroplasty. Follow-up evaluation of these patients was by means of clinical examination and radiographs. We investigated our study population by means of CT scan, so we were able to see more abnormalities. Further follow-up will determine whether these abnormalities are of clinical importance. The survival rate of 87.5 % at five years in our study population is based on 125 patients (143 hips) and can be considered low according to the NICE (National Institute for Health and Clinical Excellence) guidelines (≥ 90 % survival after ten years). The survival rate decreases aggressively after five years, but only twenty-three hips had a follow-up period of more than five years.

In conclusion, our results show that pseudotumor formation occurs in 28 % of patients as seen on CT scan after an average follow-up interval of forty-one months. Most pseudotumors (72.5 %) are asymptomatic. Symptoms are pain and discomfort in the groin, a noticeable mass in the groin, and paresthesia. Larger pseudotumors are associated with more symptoms. Failure of the BHR implant occurred in 8.4 % of the patients (5.6 % due to a symptomatic pseudotumor) after an average follow-up of forty-one months. No risk factor for pseudotumor formation was identified. In our opinion, patients with a symptomatic pseudotumor should have a revision, and patients with a BHR with complaints need to be screened for a pseudotumor. Serum cobalt and chromium ion levels may be used for screening, but we find CT to be the best technique for diagnosing pseudotumors. Further follow-up of our patients with asym-
tomatoic pseudotumors will provide more information on whether these pseudotumors progress over time and become symptomatic.
REFERENCES


SUPPLEMENT

Table showing the grading system for postoperative findings on computed tomographic scans of patients with metal-on-metal hip arthroplasty components

**Table. CT Grading System for Postoperative Findings in Patients with Metal-on-Metal Hip Arthroplasty Components**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal or acceptable</td>
<td>Thickening of capsule up to 4-6 mm</td>
</tr>
<tr>
<td>II</td>
<td>Reactive</td>
<td>Thickening of capsule of &gt;6 mm, but not more than the neck of the prosthesis, with or without bulging and without eccentric enlargement with respect to the capsule</td>
</tr>
<tr>
<td>III</td>
<td>Mild metal-on-metal disease</td>
<td>Consists of a bulging capsule both anteriorly and posteriorly</td>
</tr>
<tr>
<td>IV†</td>
<td>Moderate metal-on-metal disease</td>
<td>Represents eccentric bulging or enlargement of the capsule, which is often seen inferomedially to the prosthetic head</td>
</tr>
<tr>
<td>V†</td>
<td>Severe metal-on-metal disease</td>
<td>Represents the so-called bursitis mimicker, often extending posterolaterally with extensive filling of the subtrochanteric bursa, or anteriorly by filling of the iliopineal bursa, which can extend into the abdominal compartment</td>
</tr>
</tbody>
</table>

*The grading system is from the study by Boomsma et al.*

†In the present study, hips with grade-IV or V findings were considered to have a pseudotumor.

DISCLOSURE

One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work.
Chapter 5

Use of internal references for assessing CT density measurements of the pelvis as replacement for use of an external phantom


* M.F. Boomsma and I. Slouwerhof contributed equally to this work

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ABSTRACT

Purpose
The purpose of this research is to study the use of an internal reference standard for fat- and muscle as a replacement for an external reference standard with a phantom. By using a phantomless internal reference standard, Hounsfield unit (HU) measurements of various tissues can potentially be assessed in patients with a CT scan of the pelvis without an added phantom at time of CT acquisition. This paves the way for development of a tool for quantification of the change in tissue density in one patient over time and between patients. This could make every CT scan made without contrast available for research purposes.

Materials and methods
Fifty patients with unilateral metal-on-metal total hip replacements, scanned together with a calibration reference phantom used in bone mineral density measurements, were included in this study. On computed tomography scans of the pelvis without the use of intravenous iodine contrast, reference values for fat and muscle were measured in the phantom as well as within the patient’s body. The conformity between the references was examined with the intra-class correlation coefficient.

Results
The mean HU (± SD) of reference values for fat for the internal- and phantom references were -91.5 (± 7.0) and -90.9 (± 7.8), respectively. For muscle, the mean HU (± SD) for the internal- and phantom references were 59.2 (± 6.2) and 60.0 (± 7.2), respectively. The intra-class correlation coefficients for fat and muscle were 0.90 and 0.84 respectively and show excellent agreement between the phantom and internal references.

Conclusion
Internal references can be used with similar accuracy as references from an external phantom. There is no need to use an external phantom to assess CT density measurements of body tissue.
INTRODUCTION

Failure of total hip replacement is caused in part by loosening of the cup due to osteolysis. This complication also plays a role in the biological behavior of metal-on-metal (MoM) total hip replacements. Acetabular bone stock is an important factor in revision surgery of THA: the preoperative assessment of acetabular bone stock before revision surgery is critical because the amount and location of pelvic osteolysis can determine the type and success of revision surgery. To examine the bone stock in the acetabulum, bone mineral density (BMD) measurements could be performed. The bone density in the acetabulum could serve as a predictor in the behavior of the MoM hip replacements. Furthermore, adverse soft tissue reactions are observed in THA MoM such as inflammatory capsular reactions resulting in solid, cystic or mixed so-called pseudotumours. At this moment MR seems to be the gold standard as MR is superior in determining soft tissue characteristics. Recently a CT classification of the hip capsule has been described with good association with revision. CT has the added benefit of being able to measure the position of the different components such as anteversion and inclination of cup and stem. CT has the disadvantage of dealing with metal artefacts such as photon starvation, scatter and beam hardening that makes it difficult to assess the hip capsule and its composition. Fatty atrophy of muscle and edema of the soft tissue is not easily assessed at all by means of CT. Metal artefact reduction in CT shows promising results but density measurements in the plane of metal do not seem to be feasible on a 64-slice CT scan; however, various CT innovations such as multi-slice systems, use of software algorithms to deal with photon starvation and spectral CT for dealing with beam hardening seem to make peri-prosthetic measurements of soft tissue and bone in the future possible.

BMD measurements conducted with dual-energy x-ray absorptiometry (DEXA) are the gold standard in the diagnosis of osteoporosis. Another method of measuring the BMD is the use of volumetric CT image. Recent studies have shown the possibility to assess bone density with the use of CT images. The direct measured Hounsfield numbers can be used to review bone density because the Hounsfield unit is an index of x-ray attenuation and is, therefore, directly correlated to tissue density. CT for BMD measurements offers some advantages over DEXA: the measurements are volumetric and differentiation between trabecular bone and cortical bone is possible. BMD measurements using CT can be achieved in two different ways: phantom-based and phantomless. In the phantom-based method, calibration is based on an extracorporeal phantom placed under the patient during the CT acquisition. Phantomless BMD (PLBMD) is based on internal patient references obtained from measurements in fat and muscle without the use of a calibration phantom. The calibrations based on internal patient references are needed to account for differences between scans and
The purpose of this study is to examine whether internal references from CT data are consistent with references obtained from a calibration phantom in patients with a metal-on-metal total hip replacement.

**MATERIALS AND METHODS**

**Patient population and image acquisition**

The pelvic CT scans of 50 patients (21 male, 29 female) from a larger cohort study were prospectively randomly enrolled in this study. Informed consent was obtained. Approval was given by the Medical Ethical Committee under METC number 14.11161. Mean age (± SD) of the reviewed patients was 61.8 years (± 6.4). The minimum and maximum ages were 40 and 72 years respectively.

All patients underwent a unilateral MoM total hip replacement. The replacements were composed of a Bi-Metric porous coated uncemented stem with a metal-on-metal M2a- Magnum femoral head and ReCap acetabular component (Biomet, Warsaw, Indiana, USA). The modular head and acetabular component are high-carbon, as-cast (single heated) components. All CT datasets were obtained with the Philips Brilliance 40-slice CT scanner or the Philips Brilliance 64-slice CT scanner and one patient on 128-slice CT scan. The CT parameters included a slice thickness of 0.9 mm, a tube voltage of 140 kVp, a mean current of 171 mA (range: 97-331) and a matrix size of 512 × 512 for all reviewed CT datasets. CT images were reconstructed with filtered back projection (FBP). During all image acquisitions, a solid phantom was placed underneath the patient at the pelvic level. The phantom consists of five different rods representing the density of, among others, bone and fat.

**HU analysis**

HU analysis was performed in the Philips Extended Brilliance Workspace. Regions-of-interests (ROI) were manually placed with the use of the CT viewer. A slice 1 cm above the metal implant was selected for HU analysis. At this level in the acetabulum, metal artefacts from the MoM prosthesis are not present, which has been researched before (Supplement: part of the manuscript still in preparation). For each patient, one researcher placed four circular ROIs. In the phantom, the ROIs were placed in the rods with a density comparable with muscle and fat. The internal reference for muscle was placed in the musculus iliopsoas, anterior from the anterior superior iliac spine. The ROI for the internal reference for fat was placed in the dorsal subcutaneous fat, whereas all internal references were placed on the side opposite to the MoM implant. An example is illustrated in Fig. 1. For each ROI, the average HU value was recorded.
Fig. 1. Illustration of ROI placement. Axial view: Four ROIs are placed 1 cm above the metal implant. The average HU values were calculated.

**Statistical analysis**

All statistical analyses were performed with IBM SPSS Statistics, version 22. Association was visualized by scatterplots; explained variance $r^2$ was calculated. Agreement between the phantom and internal references was visualized using Bland Altman plots, and quantified using the intra-class correlation coefficient (ICC). All statistical analyses were performed separately for fat and muscle references.

**RESULTS**

All patients scored a grade 0 or 1 for the Goutallier classification for fatty infiltration of the musculus iliopsoas.$^{16,17}$ The mean ± SD for the average HU values of the internal fat reference is -91.5 ± 7.0 (range: -114.2 to -76.5) and -90.9 ± 7.8 (range: -113.3 to -71.6) for the extracorporal fat reference. For muscle, the mean ± SD or the internal reference is 59.2 ± 6.2 (range: 40.0 - 71.8) and for the extracorporal muscle reference 60.0 ±
7.2 (range: 35.7 - 70.5). Figure 2 shows scatterplots, revealing positive associations between internal references and phantom reference. The explained variance $r^2$ is 0.82 for fat and 0.73 for muscle.

In Fig. 3, the Bland Altman plots are shown for both fat and muscle. A mean bias of -0.59 is found for fat references. The limits of agreement for HU difference range from -7.19 to 6.00. For the muscle references, a mean bias is found of -0.76, while the limits of agreement range from -8.23 to 6.72. The ICC for the fat references is 0.90 and the 95 % confidence interval is (0.74, 0.91). For muscle, the ICC is 0.84 with a 95 % confidence interval of (0.85, 0.95). Both can be classified as excellent agreement between phantom references and internal references.

![Fig. 2](image)

**Fig. 2.** Scatterplots from the phantom and internal references for fat (a) and muscle (b). The HU values for the phantom are plotted against the HU values of the internal references. $R^2$ is the explained variance.

![Fig. 3](image)

**Fig. 3.** Bland Altman plots for both fat (a) and muscle (b) references. The difference between phantom and internal references is plotted against the mean of the two references.
DISCUSSION

We have shown that internal soft tissue references have similar accuracy as references obtained from an external phantom in the acetabular roof region in patients with MoM. The ICCs of 0.90 and 0.84 indicate excellent agreement. The mean bias between the two different references for fat and muscle are −0.59 and −0.76. These findings show that internal references can be used with a similar accuracy as phantom references. We have proven these findings in the acetabular roof region in patients with a metal-on-metal total hip replacement. These results may also be valid in other bone locations in a certain CT scan or in CT scans obtained because of other non-skeletal pathologies.

Thus, without additional radiation more information from every CT scan made in the radiology department can potentially be extracted. This study is part of a larger research in our institute to study the biological behavior of MoM total hip replacements. An extensive database was set up with patients who underwent MoM total hip replacement; therefore, a relatively large patient group could be used in this study. All patients were reviewed for muscle inhomogeneities and all patients met criteria for Goutallier 0 and occasionally 1 for muscle fatty degeneration.

In the literature, acetabular bone-density measurements have been previously describe. Zijlstra et al. conducted DEXA measurements in all four regions according to Wilkinson. In this study, acetabular bone density was not significantly decreased in any of the regions. In this study, DEXA measurements in combination with metal exclusion software were used. These results were compared with MoP (metal-on-polyethylene) bearings, which showed decreased bone density in three-quarters of the regions. This study shows the clinical utility of BMD measurements in THA follow-up. When standard follow-up CT scans can be used to measure BMD, additional DEXA measurements will be redundant. PLBMD measurements in the thoracic and lumbar vertebrae, using internal references for calibration, have already been described. These studies appear to show a patient-friendly method of measuring bone density with a lower dose, a better resolution and less artefacts. There are multiple advantages when using PLBMD compared to phantom-based BMD measurements: the internal references are close to the bone of interest, which makes the measurement less prone to imaging artefacts. Besides, every CT scan can be used for PLBMD measurements. There may also be some disadvantages to the use of PLBMD: inhomogeneities in the internal muscle or fat references as well as variation in vasculature can influence the accuracy of the internal calibration measure. Use of BMD values has multiple advantages over the use of Hounsfield units, whose values are dependent on a number of factors, including radiation dose, patient constitution and artefacts. For this reason, for example in CT PLBMD measurements, the internal HU references are used to correct the bone density. Because the BMD is a corrected, calibrated measure, tissue density measurements
can be compared in a patient over time or between patients regardless of the afore-mentioned factors and without a phantom and without an extra scan, thus without extra radiation.

However, some conditions have to be met for the implementation of PLBMD measurements of the periprosthetic hip in current practice, such as dealing sufficiently with metal artefacts in affected regions of interest and the need of a clinical reference list regarding attenuation of bone in an age- and sex-adjusted score, analogue to the T- and Z-score in DEXA. The PLBMD method applied in bone stock measurements of the acetabular roof could potentially be used in cross-sectional studies as well as follow-up studies for patient who undergo total hip replacements if certain conditions are met. Pre-operative CT scans and follow-up CT scans can thus potentially be used without adjustments in scan protocol to study the progress of the acetabular roof bone density without an additional DEXA scan. A weakness of our study is that these measurements can only be done in region 1, according to Wilkinson et al.\textsuperscript{6} due to the metal artefacts present in the other regions. Investigations using metal artefact reduction for orthopedic implants (O-MAR) show only the region above the metal implant is unaffected by metal artefacts (Supplement: part of the manuscript still in preparation).

Currently in 9.6 % of patients with a MoM THA, revision is needed.\textsuperscript{8} Clinical relevance for being able to measure BMD, in addition to subjective visual interpretation, of the acetabular roof might be of interest for the orthopedic surgeon in charge of revision who likes to be informed beforehand whether or not he needs to harvest bone in the case of cup revision. Secondly, it could be of interest to have a simple tool that is able to study the bone density reaction when future newly developed implants are being placed in patients when particle disease and bone loss is associated with failure of the implant.\textsuperscript{23} The results from this study give a basis to investigate the use of PLBMD measurements in the acetabular roof in patients with a metal-on-metal total hip replacement. This phantomless method has the potential to increase the applicability in today’s clinical practice. Ultimately all CT scans could be used to measure and follow-up bone density.

**CONCLUSION**

This study shows that internal references of fat and muscle are of similar accuracy as compared to references obtained from an extra-corporal phantom at the level of the acetabular roof in patients with a one-sided MoM THA. The intra-class correlation coefficient shows excellent agreement between the two different references. Thus, there is no need to use an external phantom to quantify CT density measurements of body tissue.
REFERENCES


CONFLICTS OF INTEREST

Dirk Mueller and Julien Milles are employees of Philips Healthcare.
Chapter 6

CT-based quantification of bone stock in large head metal-on-metal unilateral total hip replacements


* Both authors contributed equally

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ABSTRACT

Purpose
To explore ipsilateral and contralateral acetabular roof bone stock density in unilateral large head MoM THA whether there is a significant lower acetabular bone stock in the hip with a metal-on-metal (MoM) total hip replacement compared to the contralateral side. Second part of this study is to examine if there are any associates with regard to potential bone stock density difference.

Materials & methods
A database of 317 patients with unilateral metal-on-metal (MoM) total hip replacements was set up retrospectively for this study. On computed tomography scans, conducted after a relative short in situ time period averaging 2.8 years, regions-of-interests were drawn in the trabecular bone of the acetabulum to measure average Hounsfield Units (HU). HU differences were calculated and tested by Wilcoxon signed-rank test. Univariate analysis was conducted to examine associates of potential bone loss.

Results
In a population of 317 patients (156 male, 161 female) with an average age of 61.9 ± 7.8, the median HU on the side of the MoM replacement was 123.3 (7.6 - 375.4). On the contralateral side, median HU was 144.7 (-0.4 to 332.8). The median HU difference was 21.4 after a mean post-operative in situ time of 2.8 years. The Wilcoxon signed-rank test proved a significant difference (p < 0.001). Univariate analyses show that the in situ time of the MoM THA has a significant correlation with the bone density difference.

Conclusion
Results show a significant lower bone density at the acetabular roof at the side of the prosthesis compared with the contralateral side after short in situ time of the MoM THA in patients with unilateral MoM total hip replacements. In our patient population, the in situ time showed a significant association with the acetabular bone density difference. As acetabular roof bone stock measurements are feasible and show temporal decline this could become an important parameter to be used in orthopedic decision making for revision surgery.
INTRODUCTION

Metal-on-metal (MoM) total hip replacement was introduced to reduce the complication of wear, increase stability and increase of range of motion as observed in conventional total hip replacement. However, concerns about the MoM prostheses increased over time. The MoM prostheses show tissue reactions, including bone loss and formation of pseudotumors in surrounding soft tissues. An inflammatory environment as seen in MoM total hip arthroplasty (MoM THA) may predispose to acetabular bone loss. Insufficient acetabular bone stock in general may lead to aseptic loosening of the cup and therefore revision surgery. More importantly, current MoM screening populations have been associated with high revision rates. Pre-operative assessment of bone stock is of interest when considering and planning revision surgery in MoM patients. Furthermore the quantification of the bone density in the acetabulum might contribute to a better understanding of the biological behavior and failure of total hip replacements in general.

The conventional method to quantify bone mineral density (BMD) is with the use of dual-energy X-ray absorptiometry (DEXA). The BMD is the amount of bone matter per square centimeter (mg/cm²). It is the most common predictor and indicator of osteoporosis. Recent research however shows that assessment of bone stock by quantification of Hounsfield Units (HU) from the trabecular area obtained with diagnostic computed tomography (CT) scans have a strong, positive correlation with the DEXA determined BMD. This indicates that HU values can be used to examine bone density from diagnostic non iodine contrast CT scans. In general, CT assessment needs calibration for inter-patient analysis. Inter-patient analysis is not yet feasible due to lack of a clinical reference list regarding attenuation of bone in an age and sex adjusted score analog to the T- and Z-score in DEXA. However, it should be possible to detect a bone stock difference between the ipsilateral side of the prosthesis and the contralateral side as differences are not influenced by inter patient CT related differences. A well-known phenomenon is that MoM hip prostheses cause metal streak-artifacts on the CT scan. However, the area superior to the prosthesis is not affected by metal artifacts. For this reason the acetabular roof is the region of interest in this study.

The purpose of this study is twofold. First, to explore ipsilateral and contralateral acetabular roof bone stock density in unilateral large head MoM THA. Second, to examine if there are any associates with regard to potential bone stock density difference.
MATERIALS AND METHODS

Patients & database design
A database with unilateral MoM hip prostheses was extracted from a larger database of 506 THA MoM patients in the period 2010 and 2011 for this study, consisting of all patients with MoM hip prostheses in our institute.12 189 patients were excluded due to contralateral THA or patients of which the CT dataset did not match the image criteria (CT datasets had to encompass one centimeter cranial to the top of the MoM prosthesis). All included unilateral MoM THA patients underwent CT scans after implantation. This finally resulted in a study database of 317 patients (156 male, 161 female). All hip replacements were composed of a Bi-Metric porous coated uncemented stem with a metal-on-metal M2a-Magnum femoral head and ReCap acetabular component (Biomet, Warsaw, Indiana, USA). To determine MoM associated hip capsule reaction, patients were graded according to the simplified classification of Boomsma et al.7 and included in the database.

Image acquisition
All CT datasets were obtained with the Philips Brilliance 40CT scanner or the Philips Brilliance 64CT scanner. (Philips Medical Systems, Best, The Netherlands) CT parameters included a slice thickness of 0.9 mm, a tube voltage of 140 kVp, mean current of 175 mA (min. 97, max. 347) and a matrix size of 512 × 512 for all reviewed CT datasets. The field-of-view (FOV) of the CT datasets had to encompass one centimeter cranial to the top of the MoM prosthesis. An example is shown in Fig. 1.

HU measurements
HU analysis was performed in the Philips Extended Brilliance Workspace. CT datasets were analyzed in the CT viewer review module. The slice one centimeter above the metal acetabular implant (cup) was selected for HU measurements. At this level, as expected from literature, metal artifacts from the prosthesis are not present in the longitudinal axis. Therefore, we expect that measured HU values in this region are not influenced by these artifacts. To be sure that one cm is far enough, we have shown in a previous publication that metal artifacts are not present in this region.11 In the axial plane, regions-of-interest were always placed in the trabecular bone of the acetabular roof, one centimeter above the acetabular roof. The exact placement was determined by coronal assessment and balancing the image in order to be sure that on both sides one centimeter space was left between the acetabular roof and the measurement plane as shown in Fig. 1. Because of the high metabolism in trabecular bone, it is more prone to bone degeneration. For this reason, the cortical bone is not included in the region-of-interest (ROI). For all measurements, the largest possible ROI was drawn,
excluding the cortical bone. For both ROIs, the average HU value was calculated. The HU difference was defined as the average HU value at the contralateral side minus the average HU value at the side of the prosthesis. Thus, when bone stock density in the acetabular roof is lower at the ipsilateral side, the HU difference will obtain a positive value.

**Fig. 1.** Example of a HU measurement. ROIs are placed in the trabecular bone at both sides in the acetabular roof region one centimeter above the metal implant. Average HU values are calculated.

**Reproducibility**

Intra-observer reproducibility of the HU measurements was performed on 50 randomly selected patients from the total patient cohort. Measurements as described above were repeated by the same observer. Slice selection and previous results were not visible to the observer.

**Statistical analysis**

All statistical analyses were performed in IBM SPSS Statistics, version 22. To test whether the HU difference for all patients is normally distributed, skewness and kurtosis were
quantification of bone stock in MoM THA calculated. Wilcoxon signed-rank test was used to test HU values at the side of the prosthesis and the contralateral side.

Reproducibility was tested with the intra-class correlation coefficient (ICC) to determine the conformity between the two measurements. The ICC was reported as a score between 0 (no correlation) and 1 (total correlation).

To study the influence of pseudotumor formation on the acetabular bone stock, mean HU differences were calculated for each pseudotumor gradation group. To test if there is a significant difference between group A, B and C capsular reactions the Mann-Whitney test was performed. Associations with bone stock difference were studied by means of correlation analysis. Only when linearity between the bone stock difference and the potential predictor was observed, univariate linear regression was performed. In this study, patient age, gender, in situ time, pseudotumor gradation, cobalt and chromium levels, inclination, cup size and anteversion were examined. These factors are mainly thought to associate with THA failure in MoM related capsular disease.

RESULTS

The database of 317 patients (156 male, 161 female) with an average age of 61.9 ± 7.8 was analyzed. The in situ time period between the hip replacement and CT scan (follow-up time) varied from 6 months to 5.4 years. Mean in situ time of the prosthesis is 2.8 years. Mean age of the reviewed patients at time of the CT image acquisition was 61.9 years ± 7.8 (29 - 76).

Ipsilateral and contralateral HU values

Median HU at the side of the prosthesis was 123.3 with a minimum of 7.6 and a maximal value of 375.4. At the contralateral side, median HU was 144.7 with a minimum of -0.4 and a maximal value of 332.8. The intra-class correlation coefficient of the reproducibility is 0.921 with a 95 % confidence interval of [0.866 - 0.955].

HU difference

Of all patients, 248 patients have a lower HU value at the side of the prosthesis, 68 patients have a higher HU value and for 1 patient the average HU values were equal both sides. The median of the HU difference was 21.4 HU with a minimum of -190.3 and a maximum of 189.80. Skewness and kurtosis were -0.96 and 5.07 respectively. The normality tests showed a skewed distribution (Shapiro-Wilk showed p < 0.001). The Wilcoxon signed-rank test showed that there is a significant difference between the average HU value at the side of the prosthesis and the contralateral side (Z = -9.142, p < 0.001). Medians for the HU values for the individual pseudotumor gradation groups
are listed in Table 1. The Mann-Whitney test showed no significant difference between group A and group C.

Table 1. HU difference values for the different pseudotumor gradation groups.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>170</td>
<td>31</td>
<td>116</td>
</tr>
<tr>
<td>Median of HU difference</td>
<td>19.1</td>
<td>2.0</td>
<td>24.9</td>
</tr>
<tr>
<td>Std. deviation</td>
<td>37.8</td>
<td>63.8</td>
<td>32.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>-190.3</td>
<td>-154.7</td>
<td>-82.7</td>
</tr>
<tr>
<td>Maximum</td>
<td>189.8</td>
<td>91.4</td>
<td>87.3</td>
</tr>
</tbody>
</table>

Fig. 2. Histogram of the average HU difference between the acetabular roof at the side of the MoM prosthesis and the contralateral side

Associates of HU difference

The results of the linearity between potential bone loss predictors and the bone stock difference are shown in Table 2. Except for the in situ time, none of the potential predictors showed a significant correlation with the bone density difference. The scatterplot of the in situ time versus the bone density difference is shown in Fig. 3.

Because the in situ time shows a significant correlation with the bone density difference, a linear regression analysis with this variable was performed. The regression
coefficient B was 0.011 with a confidence interval of \([0.002 - 0.020]\). The p-value was 0.013.

**Table 2.** Linearity analyses

<table>
<thead>
<tr>
<th></th>
<th>Pearson’s correlation coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>-0.083</td>
<td>0.143</td>
</tr>
<tr>
<td>Gender</td>
<td>0.034</td>
<td>0.544</td>
</tr>
<tr>
<td>In situ time</td>
<td>0.125</td>
<td>0.013</td>
</tr>
<tr>
<td>Pseudotumor gradation</td>
<td>0.024</td>
<td>0.666</td>
</tr>
<tr>
<td>Cobalt level</td>
<td>-0.065</td>
<td>0.248</td>
</tr>
<tr>
<td>Chromium level</td>
<td>-0.067</td>
<td>0.238</td>
</tr>
<tr>
<td>Inclination</td>
<td>-0.074</td>
<td>0.188</td>
</tr>
<tr>
<td>Cup size</td>
<td>-0.001</td>
<td>0.991</td>
</tr>
<tr>
<td>Anteversion</td>
<td>0.024</td>
<td>0.674</td>
</tr>
</tbody>
</table>

**Fig. 3.** Scatterplot of in situ time and bone density difference to evaluate linearity.
DISCUSSION

In this study we performed CT-based HU measurements in a large homogeneous cohort of large head MoM THA patients with short in situ time (mean 2.8 years). The results show a relative small but, due to the large number of patients, significant bone density difference of 21.4 HU (range -190.3 to 189.8) between the acetabulum at the side of the prosthesis and the contralateral. The in situ time appeared to be the only linear predicting factor for the bone stock difference. To the best of our knowledge, the use of CT-based HU measurements in the acetabular roof in patients with total hip replacements has not been previously published.

The results replicate findings in which DEXA was used to estimate bone stock in conventional THA.\textsuperscript{13,14} Being able to use this non-invasive method offers new possibilities in assessing bone stock in a MoM screening population without additional examinations as is the case with DEXA scans and can be used in follow-up. If screening of MoM patients for capsular disease with CT is performed, BMD measurements can be obtained together with measurements of rotation and anteverision of the femoral stem and measurements of anteverision and inclination of the cup.\textsuperscript{15} These measurements add information for the orthopedic surgeon who considers and plans potential revision. Measurements as performed in this study can be implemented on all non-iodine contrast CT scans. In this study, the average HU is used to represent acetabular bone density. Recent research shows a significant correlation between the HU measured by CT and the BMD measured by DEXA \textsuperscript{[10]. Schreiber et al. and Lee et al. \textsuperscript{[9,10] correlated Hounsfield Units in the vertebrae with T-scores. Respectively, they found a T-score of ≥-1 (normal) correlated to a HU of 133 and 121, a T-score between -1.0 and -2.5 (osteopenic) correlated to a HU of 101 and 79 and T ≤-2.5 (osteoporotic) correlated to a HU of 79 and 55.}

The use of the average HU also has its limitations. Hounsfield Units depend on a number of factors, including patient constitution, radiation dose and scanning artifacts. Consequently, comparison between patients is not possible at this moment. In order to make bone-density comparisons between patients and relate it to BMD measurements from DEXA scans, the bone mineral density should be calculated. This could be done in a phantom-less method in which internal references from fat and muscle are used. Because no phantom-less BMD analysis software suitable for measurements in the hip is yet available, at this point in time average HU were used.\textsuperscript{11}

An important limitation in this study is the absence of a baseline CT measurement before implementation of the total hip replacement as primary pre-operative planning consists of conventional radiographs and therefore no CT data are available. In the future new full iterative reconstruction techniques will decrease dose dramatically and CT scans might be more routinely performed pre-operatively as more information can
be obtained by means of CT than with conventional radiography. Due to the lack of baseline measurement pre-operatively we cannot state that the absolute bone loss is only due to the intrinsic characteristics of the MoM prosthesis.

Inflammatory conditions in a joint is known for bone loss in general. Therefore it could be expected that the inflammatory environment as seen in a large percentage of MoM THA patients might attribute to bone loss. As we did not find a correlation between the grade of the capsular reaction as can be observed in MoM screening populations this seems not to be the case.

The variations in measurements, visible in the histogram in Fig. 2, shows a relatively wide range of HU differences [-190.3 to 189.8] with a mean of 18.1 HU. This mean is significantly different from zero, however a well-grounded explanation for the wide range cannot be provided with the knowledge obtained from this study.

CONCLUSION

In this study a statistically significant bone density difference with respect to the contralateral side by means of CT analysis between the acetabulum at the side of the prosthesis and the contralateral side after 2.8 years postoperative follow-up in patients with unilateral MoM total hip replacements is shown. Only the in situ time of the MoM THA showed a significant correlation with the bone density difference. Pseudotumor formation did not correlate with bone density differences. As acetabular roof bone stock measurements are feasible and show temporal decline this could become an important parameter to be used in orthopedic decision making for revision surgery.
REFERENCES


Chapter 7

Quantitative analysis of orthopedic metal artifact reduction (O-MAR) in 64-slice computed tomography scans caused by large head metal-on-metal total hip replacement, a phantom study


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ABSTRACT

Purpose
Quantification of the effect of O-MAR on decreasing metal artefacts caused by large head metal on metal total hip arthroplasty (MoM THA) in a dedicated phantom setup of the hip.

Background
Pathological reactions of the hip capsule on Computed tomography (CT) can be difficult to diagnose due to different metal artefacts. The O-MAR algorithm deploys an iterative loop where the metal sinogram is identified, extracted, and subsequently serves as a mask to correct the measured sinogram. Main goal of this study is to quantify the ability of the O-MAR technique to correct deviation in medullary bone attenuation caused by streak artefacts from the large-head MoM THA embedded in a phantom. Secondary goal is to evaluate the influence of O-MAR on contrast-to-noise ratio (CNR).

Methods
The phantom was designed as a Perspex box (PMMA) containing water and a supplementary MOM THA surrounded by Perspex columns comprising calibrated calcium pellets. Each column contains 200 mg of hydroxyapatite/calcium carbonate to simulate healthy bone tissue. Scans were obtained with and without a MoM THA at different dose levels. Different reconstructions were made with filter A, iDose4 level 5 and with and without O-MAR. The scans without the prosthesis were used as the baseline. Information about the attenuation in Hounsfield units, image noise in standard deviation within the ROI’s were extracted and the CNR was calculated.

Results
Pellet L0 and R0 (proximal of the MoM THA) were defined as reference, lacking any disturbance by metal artefacts; L5, L6 and L8 were respectively visually categorized as “light” “medium” and “heavy disturbance”. Significant improvements in attenuation deviation caused by metal artefact were 43, 68 and 32 %, for respectively pellet L5, L6 and L8 (p < 0.001). Significant CNR improvements were present for L5 and L6 and were respectively 72 and 52 % (p < 0.001). O-MAR showed no improvement on CNR for L8.

Conclusion
This phantom study significantly increases image quality by the use of O-MAR in the presence of metal artefacts by significantly reducing metal artefacts subsequently and increasing CNR on a 64 slice CT system in light and medium disturbance of the image.
BACKGROUND

Metal-on-metal total hip arthroplasties (MoM THA) were introduced because of their purported advantages above the conventional metal-on-polyethylene articulations. Favorable patient satisfaction, lower rates of dislocation, wear and good survival have been reported at medium-term follow-up. However, there have been reports of the formation of symptomatic peri-articular masses in some patients, referred to as pseudotumours. The exact incidence of these pseudotumours is unknown, seems to differ between type of MoM prosthesis. These so-called pseudotumours or pathological capsular reactions of the hip after MoM THA are seen in different frequencies depending on prosthesis type and population. It is generally accepted that revision surgery is warranted to halt the process of pseudotumour formation. Radiological imaging studies are used in screening protocols in symptomatic patients to identify those patients that are candidates for revision surgery. This has led to a dramatic increase in the demand for imaging studies.

Various imaging studies are described for diagnosing pseudotumours. Computed tomography (CT) is relatively inexpensive, readily available and very sensitive in illustrating bone defects and has the important advantage that orientation of components can be measured. It exposes patients however to a certain amount of radiation. Pathological capsular reactions can be difficult to diagnose with MR or CT due to different metal artefacts caused by the high atom number of these MoM-prostheses and therefore hide underlying pathological capsular reactions.

Previously a reliable classification system has been established for reporting CT appearances of the hip capsule and pseudo tumours in MoM disease that shows significant association with revision. We investigated several clinical populations in two different hospitals during follow up. By analyzing CT scans made in follow up from these different hospitals we encountered marked quality differences in visual acuity in the various used Philips CT systems (16, 48, 64, 128 and 256 in different generations). We found diagnostic improvement in imaging quality by use of the latest multi-slice systems together with Orthopedic Metal Artifact Reduction (O-MAR, Philips Healthcare, Cleveland, OH, USA) post processing software in our current clinical daily practice.

The O-MAR algorithm deploys an iterative loop where the metal sinogram is identified, extracted, and subsequently serves as a mask to correct the measured sinogram. For more detailed description of O-MAR we refer to “Supplement”.

For the subsequent interpretation of the results from the use of O-MAR it is important to reflect here shortly on the different contributions for image noise and artefacts in CT. Noise comprises random and structural components. Random noise can be attributed to purely statistical variations inherent in all physical phenomena. More specific for CT: quantum noise and electronic noise e.g. in the A/D conversion. It is possible to
characterize the average behavior of the noise by a variety of statistical methods (e.g. histogram analysis and SD). Pronounced high density variations in the scanned object lead to structural noise, i.e. artefacts, caused beam hardening and photon starvation. As the X-ray beam passes through a dense object such as a metal implant, more low-energy photons are absorbed as compared to high-energy photons, leading to a shift of the X-ray spectrum. Secondly, dense structures, such as metal, attenuate photons to a degree where the photon flux is so low, that the detectors are ‘starved’ for photons. Filtered back-projection (FBP) has been the industry standard for CT image reconstruction for decades. While it is a very fast and fairly robust method, FBP is sub-optimal for under-sampled data or for noisy data. When these very high levels of noise are propagated through the reconstruction algorithm, the result is an image with significant artefacts and high degrees of random noise. The resulting artefacts can be seen as streak artefacts, which after rescanning remain at very similar angles throughout the image. These artefacts remain with the use of combination protocols consisting of iterative reconstruction techniques and FBP.

O-MAR has previously shown to be effective in reducing metal artefacts in dental implants, planning radiotherapy with implants and in a phantom. This and our personal observation of a positive effect regarding metal artefact reduction have not yet been extensively quantified for MoM THA in a phantom. We decided to quantify the effect of O-MAR on metal artefacts in a phantom setup that resembles the imaging situation of our local clinical population of large head MoM THA. In this way we tried to correlate our aforementioned subjective visual observations with objective quantitative image quality estimates in a phantom study.

The main goal of this study is to quantify metal artefact reduction by O-MAR, caused by streak artefacts from the large head MoM THA in a phantom. The secondary goal is to evaluate the influence of O-MAR on CNR.

METHODS

Phantom design

The phantom walls were made of a polymethyl-methacrylate (Perspex) to form a watertight box open at the top. Inner dimensions of width, length and height were 42 × 29.5 × 13 cm. To simulate heavy patients the box dimensions in the x, y, z plane were designed to correspond to a Water-Equivalent Diameter (WED) of 39.7 cm. The box held 18 columns as shown in Fig. 1. The columns with calibrated calcium pellets were placed at standard Gruen zones and DeLee and Charnley regions that are used for bone analysis near the stem and at other critical locations such as the assumed acetabulum. Each column contained 200 mg of hydroxyapatite/calcium carbonate (HA/CC, from company
QRM, Möhrendorf, Germany) to simulate healthy bone tissue. The pellets were embedded within a polymethyl-methacrylate (Perspex) and were not suspended. Within a tolerance of 0.05 and 0.1 mm in the X, Y and Z-axis the center of the pellets were situated within one plane. The pellets had a height of 1 cm and a diameter of 1 cm. On the left side of the phantom the supplementary placed large head MoM THA prosthesis could be attached by fitting into Perspex holders in the phantom with its main axis falling into the plane defined by the pellets. No additional fixation was needed. The Perspex box was always, with or without the MoM THA completely and equally filled with tap water. The air bubbles that arose around the columns were removed carefully to create a homogenous density. A silicon foil was placed on top of the box before the cover was placed, ensuring that any residual air on the sides was removed (Fig. 1). Prior to scanning on a Philips Brilliance 64 CT-scanner (Philips Healthcare, Cleveland, OH, USA), an air calibration was performed. Additionally a scan was made by which randomly the Hounsfield unit (HU) values across the Field of View (FOV) were checked to lie within the tolerance of HU and SD defined by the CT manufacturer in the product specifications. Because of the small amount of scans that were necessary for the study [two X-ray tube voltage (kVp) settings, three current-time product (mAs) values and with and without MoM THA prosthesis, leading to 12 scans] the variations in tube temperature were negligible. Scans were repeated by duplicating the static scan settings (Table 1), apart from the variables under investigation. The phantom was placed on the table of the CT scanner and it’s position was checked for displacement after each scan performed. This enabled to create consistent DICOM image data sets, with as little uncontrolled variation as possible.

Fig. 1. Schematic drawing of the phantom used in this study. Measurements are performed on the calcium pellets embedded in Perspex columns
Table 1. Applied scan parameters

<table>
<thead>
<tr>
<th>Scan parameters</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOV (reconstructed)</td>
<td>455 mm</td>
</tr>
<tr>
<td>Resolution</td>
<td>High resolution</td>
</tr>
<tr>
<td>Pitch</td>
<td>0.49</td>
</tr>
<tr>
<td>CTDI (120/140 kVp)</td>
<td></td>
</tr>
<tr>
<td>101/150 mAs</td>
<td>9.8 mGy</td>
</tr>
<tr>
<td>202/300 mAs</td>
<td>19.6 mGy</td>
</tr>
<tr>
<td>405/600 mAs</td>
<td>39.3 mGy</td>
</tr>
<tr>
<td>Collimation</td>
<td>64 x 0.625 mm</td>
</tr>
<tr>
<td>Collimation speed</td>
<td>0.75 s/rotation</td>
</tr>
<tr>
<td>Pixel size</td>
<td>0.44 mm</td>
</tr>
<tr>
<td>Matrix</td>
<td>1024 x 1024</td>
</tr>
<tr>
<td>Scan length</td>
<td>303 mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>0.90 mm</td>
</tr>
<tr>
<td>Increment</td>
<td>0.45 mm</td>
</tr>
<tr>
<td>Dose modulation</td>
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<tr>
<td>Zoom factor</td>
<td>1</td>
</tr>
<tr>
<td>SP filter</td>
<td>On</td>
</tr>
<tr>
<td>Adaptive filter</td>
<td>On</td>
</tr>
</tbody>
</table>

Image acquisitions

The phantom was scanned with and without the MoM-hip prosthesis using different scan parameters. The scans were reconstructed with Filter A and O-MAR. Filter A was used in order for later research purposes and for clinical resemblance in reading soft tissues around the hip. With ImageJ, Region of Interest (ROIs) were placed in the calibrated calcium pellets and in the surrounding water at standard Gruen zones and at other particularly critical locations. Information about the attenuation in HU and image noise in standard deviation (SD) within the ROIs were extracted and the CNR was calculated. The scans without the prosthesis were used as the baseline. Effects of O-MAR in conjunction with different scan parameters were investigated based on the different combinations in helical scan mode.

The current-time product mAs with a X-ray tube voltage setting of 140 kVp was lowered to create an equal Computed Tomography Dose Index (CTDI) as with the setting of 120 kVp (Table 1). Scans were made with CTDI’s of respectively 9.8, 19.6 and 39.6.

All scans were reconstructed with level 5 of the iterative reconstruction method iDose4 (Philips Medical Systems, Cleveland, OH, USA). This was the strongest combination of iterative reconstruction with FBP.
All the used parameters in this phantom study were based on patient protocols to mimic the clinical environment as much as possible, with adequate dose (as low as reasonably achievable - ALARA).

**Quantitative measurements**

The circular regions-of-interest (ROI's) were placed over the 10 mm circular pellets, slice thickness was 1 mm. The histogram showed normal Gaussian behavior (Fig. 2). The diameter of the circle was 8 mm (c.f. 10 mm pellet size), thereby avoiding partial volume effects. The ROI’s were centrally placed on all calcium pellets together with a reference ROI in the water next to it. The used field of view of 455 mm and a matrix of 1024 × 1024 gives a pixel size of 455/1024 = 0.44 mm in the x-y plane. A circular ROI with a diameter of 8 mm this corresponds to 8/0.44 mm = 18 pixels for the diameter. Therefore in the ROI there are \( \pi(8/2)^2 \) = 255 pixels, sufficient for a reliable statistical analysis, because of the high homogeneity of the pellet material. This was checked and found to be correct.

Measurements of HU values and CNRs were performed in a coronal reconstruction by using the open source software program ‘ImageJ V1.46r’ (National Institutes of Health, Bethesda, Maryland, USA). ImageJ gave the opportunity to organize the ROI placements in a template, which could be copied exactly to the same position in all the 216 acquisitions. By using this method both the phantom setup and the ROI placements were exactly the same for each acquisition. In addition, there was no change in the caudal or cranial direction, which could be the case because of the helical acquisition. ImageJ proved to accurately reproduce the ROI set on different scans and no adjustments were needed.

Four different pellets with different expected amounts of metal artifact influence in abovementioned positions were chosen for final analysis. Attenuation deviation reflects the difference in HU values with and without the insertion of a prosthesis. Pellet L5 was categorized as ‘light disturbance’, L6 as ‘medium disturbance’ and pellet L8 as ‘heavy disturbance’ based on visual assessment (Fig. 3).

No disturbance is expected in pellet R0 and L0 due to its location in the phantom. The HU values of the pellets after prosthesis placement were compared to the corresponding pellets from the scan of the phantom without prosthesis. The effectivity of O-MAR in artefact reduction was analyzed for each of abovementioned categories of disturbance.

The HU values and SD values from the calcium pellets were used to calculate the difference between measurement and baseline. The HU values and SD values were used to calculate the CNR.
Measurements of HU values and CNRs were performed in a coronal reconstruction by using the open source software program ‘ImageJ V1.46r’ (National Institutes of Health, Bethesda, Maryland, USA). ImageJ gave the opportunity to organize the ROI placements in a template, which could be copied exactly to the same position in all the 216 acquisitions. By using this method both the phantom setup and the ROI placements were exactly the same for each acquisition. In addition, there was no change in the caudal or cranial direction, which could be the case because of the helical acquisition. ImageJ proved to accurately reproduce the ROI set on different scans and no adjustments were needed.

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The HU values and SD values from the calcium pellets were used to calculate the difference between measurement and baseline. The HU values and SD values were

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**Fig. 2.** Number of pixels in ROI

**Fig. 3.** HU deviations compared to baseline for all pellets with large head MoM THA prosthesis in ascending order by 120 kVp, 600mAs, iDose level 5, Filter A, O-MAR on and off. The red circled pellets L0, R0, L5, L6 and L8 were visually chosen for degree of metal artifacts: no, light, medium and heavily disturbed.
Statistical analysis

Statistical analysis was performed by means of repeated measure ANOVA (full factorial, type III), utilizing two within-subject factors for pellets (‘L0’, ‘L5’, ‘L6’, ‘L8’, ‘R0’) and O-MAR (‘off’, ‘on’), generalizing to scan protocol.

RESULTS

The selection of pellets for which data regarding HU values are presented in Fig. 3. It shows the deviation of the HU value for the pellets after inserting the THA in ascending order. Pellets were categorized for analysis based on the visual assessment of the degree of metal artefacts: light, medium and heavily disturbed, as can be observed in the actual scan in Fig. 3. This selection resulted in analysis of pellet L5, L6 and L8. We also analyzed L0 and R0 in order to confirm that these pellets are not disturbed by metal artefacts as could be theoretically expected, because these pellets are not in the same plane as the prosthesis. However, scatter could theoretically disturb these pellets if they were located too close to the THA.

Tables 2 and 3 show the absolute and relative HU deviation, respectively, and absolute CNR values in the scan with large head MoM THA prosthesis scans with and without O-MAR. These are compared to baseline for pellets L0, L5, L6 and L8 and absolute CNR values for pellets L0, L5, L6 and L8, with and without O-MAR. Figure 4 shows the scans with and without O-MAR. It can be clearly observed that the metal artefacts are reduced and subjective contrast seems improved, by looking at the better delineation of the different pellets. Figure 5 shows the relative HU and CNR deviations between prosthesis scans with and without O-MAR, with regard to the baseline for pellets L0, L5, L6 and L8. With Δ the relative improvement on HU and CNR deviation is denoted.

To test the results for significance we used the 6 different scan protocols varying kVp and mAs, with Filter A, suitable for soft tissue, and iDose® level 5, used in our current clinical practice in order to try to optimize CNR. Finally, two scans with reconstructed slice thickness of 0.9 mm are shown in Fig. 6a and b in a patient with bilateral THA, namely MoM THA on the right and conventional THA on the left, with and without O-MAR. With the use of O-MAR it is possible to view the pelvic region that was not visualized at all due to the bilateral metal artefacts. Repeated measures ANOVA for both HU and CNR resulted in statistical significant beneficial results for pellet L5, L6 and L8 (p < 0.001) and O-MAR (p < 0.001). The interaction term for pellet and O-MAR was statistically significant as well (p < 0.001) (Fig. 7). No changes for L0 and R0 were, as expected, not found.
Table 2. Absolute and relative HU deviation in the scan with large head MoM THA prosthesis scans with and without O-MAR with filter A and iDose⁴ level 5 compared to baseline for pellets L0, L5, L6 and L8

<table>
<thead>
<tr>
<th>Scan protocol</th>
<th>Pellet</th>
<th>Δ</th>
<th>HU</th>
<th>O-MAR off</th>
<th>Δ HU</th>
<th>O-MAR off (%)</th>
<th>Δ</th>
<th>HU</th>
<th>O-MAR on</th>
<th>Δ HU</th>
<th>O-MAR on (%)</th>
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<td>120 kVp,</td>
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<tr>
<td>L8</td>
<td>795</td>
<td>306</td>
<td>538</td>
<td>207</td>
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<tr>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>L5</td>
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</tbody>
</table>

Significant positive effect of O-MAR (p < 0.001) for pellet L5, L6 and L6 regarding absolute and percentage of change in HU values caused by metal artefacts
Table 3. Absolute CNR values without and with large head MoM THA prosthesis scans with and without O-MAR for pellets L0, L5, L6 and L8

<table>
<thead>
<tr>
<th>Pellet</th>
<th>kVp</th>
<th>mAs</th>
<th>Filter</th>
<th>IDose level</th>
<th>No MoM THA baseline CNR</th>
<th>MoM THA O-MAR off CNR</th>
<th>MoM THA O-MAR on CNR</th>
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<tr>
<td>L0</td>
<td>120</td>
<td>150</td>
<td>A</td>
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<td>5</td>
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<td>40.34</td>
<td>8.51</td>
<td>6.13</td>
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Significant positive effect of O-MAR (p < 0.001) for pellet L5 and L6 regarding absolute change in CNR values caused by metal artefacts

Fig. 4. Visual observed difference of Metal artifacts caused by large head MoM THA with and without use of O-MAR, with 120 kVp, 600 mAs, filter A and iDose level 5 with a WW/WL of 360/60
imaging of structures which were not visible without O-MAR. The researchers concluded images corrected by O-MAR have a supplementary role in oral diagnosis. All of the above study outcomes show an overall image improvement, represented by a better CT number accuracy and significant noise reduction. These findings are in

Fig. 5. Relative HU and CNR deviation between prosthesis scans with and without O-MAR with regard to the baseline for pellets L0, L5, L6 and L8. With Δ as relative improvement on HU deviation. Using 120 kVp, 600 mAs, filter A and iDose⁴ level 5

Fig. 6. 0.9 mm scans of a patient with bilateral THA; MoM THA on the right and conventional THA on the left. a without and b with the use O-MAR
Fig. 7. a HU value for each investigated pellet is shown for different scan protocols with and without O-MAR. b CNR value for each investigated pellet is shown for different scan protocols with and without O-MAR. Average beneficial significant effect for HU and CNR by use of O-MAR for each position (L0, R0, L5, L6 and L8), by six different scan settings (p < 0.001). Protocol pairs: 5 and 6, 120 kVp; 150 mAs; Filter A; iDose® level 5; 23 and 24, 120 kVp; 300 mAs; Filter A; iDose® level 5; 41 and 42, 120 kVp; 600 mAs; Filter A; iDose® level 5; 59 and 60, 140 kVp; 101 mAs; Filter A; iDose® level 5; 77 and 78, 140 kVp; 202 mAs; Filter A; iDose® level 5; 95 and 96, 140 kVp; 405 mAs; Filter A; iDose® level 5.
DISCUSSION

We have shown on a 64-slice CT system that the reduction of metal artefacts by O-MAR is dependent upon the disturbance caused by the metal artefact. Relative improvement in HU deviation varies between 32 and 68%. O-MAR showed a significant improvement on CNR as well. The decrease in CNR is dependent upon the disturbance caused by the metal artifact and improvement varies from 52 and 72%. To our knowledge, these quantitative results have not been published before with regard to large head metal-on-metal THA.

Based on literature, other researchers have investigated the effect of O-MAR in a variety of applications. Huang et al. used anthropomorphic phantoms from which they conclude O-MAR can be used in the head, thorax and is especially well suited in the pelvic area with unilateral hip prostheses. Hilgers et al. studied the CT number accuracy in large orthopedic implants in a phantom-based setting, which showed significantly better CT number accuracy in O-MAR reconstructions compared to non-O-MAR reconstructions. Li et al. evaluated O-MAR for the use of CT simulations in radiation therapy. The results indicate an improvement of the CT HU accuracy and noise, from which the authors suggest that images corrected by O-MAR are more suitable for treatment planning in radiation therapy than without. The added value of O-MAR for metal artifact reduction in CT dental applications was studied by Kidoh et al. Image noise in soft tissue corrected by O-MAR was significantly lower and O-MAR enabled imaging of structures which were not visible without O-MAR. The researchers concluded images corrected by O-MAR have a supplementary role in oral diagnosis.

All of the above study outcomes show an overall image improvement, represented by a better CT number accuracy and significant noise reduction. These findings are in line with those in this study.

Despite O-MAR and showing excellent results in the reduction of metal artefacts on a 64 slice CT system, we observed that O-MAR combined with iDose level 5 was incapable of increasing CNR in heavily distorted regions (L8). We believe this is caused by photon-starvation, with associated poor photon statistics creating a spurious decrease of CNR for this particular region. The poor photon statistics in the affected region presumably lead to an inefficiency of iDose level 5 to reconstruct images with higher CNR than without O-MAR, as can be observed in low and medium affected regions. The large amount of disturbances is probably the result of a combination of both photon starvation and scatter from the large MoM THA.

The “net” effects of metal artefacts on a CT scan is a result of photon starvation, scatter and iterative reconstruction level. Model-based iterative protocols in general have shown the potential to scan with even lower dose than previous generations of iterative reconstruction. It could also give the opportunity to create better images.
in regions with less information due to photon starvation, since the modelling might resemble the realistic situation of lowered photon statistics. Whether this can be done in combination with lower dose needs additional investigation. The effectivity of O-MAR with more novel multi-slice systems, in combination with model-based iterative reconstruction might reveal the full potential of O-MAR.\textsuperscript{19}

Our phantom design was slightly oversized with a WED of 39.7 cm where a WED of 29.5 cm is representative in patients with a body-mass-index of 25. Subsequently, an elliptical phantom design instead of this rectangular phantom design could minimalize boarder artefacts. Furthermore, the use of additional pellets with different densities could give information about the depiction of soft tissue such as pseudotumours.

Follow-up patient studies must appreciate the clinical value of O-MAR in various THA populations. Improving image quality by compensating for metal artifacts by O-MAR with CT systems of a higher slice number, in combination with full iterative reconstruction will potentially enable further image quality improvements. The radiation dose regarding CT scans resulting in metal artefacts due to large metal implants such as THA, might possibly also be lowered if O-MAR is applied in combination with full iterative protocols such as IMR.

\textbf{CONCLUSION}

This phantom study shows a significant reduction of metal artefacts by O-MAR caused by MoM THA. The reduction is dependent on the amount of disturbance in attenuation caused by the metal artefact and relatively improved between 32 and 68 %. O-MAR showed a significant improvement in CNR as well. The decrease in CNR decrement is also dependent on the attenuation disturbance caused by the metal artefact, and varies between 52 and 72 %.
REFERENCES


SUPPLEMENT

The O-MAR algorithm deploys an iterative loop where the metal sinogram is identified extracted and subsequently serves as a mask to correct the measured sinogram. The output correction image is then subtracted from the original input image. The resultant image then becomes the new input image and the process can be repeated. The first step is to establish a threshold in the input image to create a metal-only image. The metal-only image consists of all pixels set to zero except for those pixels categorized as metal. The metal data points in the sinogram are replaced with interpolated values, which will simulate tissue in place of the metal. This sinogram is back projected and the resultant image is used to segment tissue and create the tissue-classified image. For subsequent iterations, this step is not performed. After one or several rounds, if no large clusters of metal pixels are present in the image, no further processing is performed and the final, corrected images are calculated.

COMPETING INTERESTS

Dirk Mueller is an employee of Philips Healthcare.
Chapter 8

General discussion
The Orthopaedic Department of Isala hospital, Zwolle, the Netherlands implanted many large head metal-on-metal (MoM) prostheses from January 2005 till 2010. This resulted in 2012 in a publication in which we reported a high incidence of pseudotumour formation after large diameter MoM total hip replacement in our prospective cohort study.\textsuperscript{1} This publication added knowledge regarding classification and presentation of pseudotumour formation and showed that magnetic resonance imaging (MRI) was not favourable over computed tomography (CT) in detecting clinical significant capsular reactions.

The usability of CT and the observations regarding morphological reactive capsular changes laid the foundation for this thesis in which we described the role of CT in total hip arthroplasty (THA) in general and in the detection, stratification and incidence of pseudotumours, investigated the bone mineral density of the acetabular roof and quantified the positive effect of orthopedic metal artefact reduction post-processing protocol (O-MAR) on metal artefacts.

**THE ROLE OF CT IN THE DETECTION OF PSEUDOTUMOURS**

Hitherto, surveillance of MoM THA and MoM hip resurfacing arthroplasties (HRA) patients is not evidence based.\textsuperscript{2} Factors that make it difficult to make guidelines concern different prosthetic devices, symptomatic versus non-symptomatic cases and above all there is a variety of imaging tools used. The imaging tools ultrasound (US), MRI, and CT all have been used to diagnose wear-related corrosion problems after hip arthroplasty. The relative advantages and disadvantages of these modalities remain a source of controversy.

**CT**

The use of CT in Isala hospital, Zwolle, The Netherlands and Martini hospital, Groningen, the Netherlands to detect pseudotumours proved to be efficient and sufficient. Our results contributed to the debate on what screening modality could be used for detecting capsular pathological reactions (chapters 3 and 4).\textsuperscript{1,3-5} CT is a reliable method for the pre-operative evaluation of femoral head and neck deformities, for the diagnosis of femoro-acetabular impingement (FAI) either pre-operatively or post-resurfacing, and for diagnosing post-operative soft tissue reactions (chapter 2).\textsuperscript{6} When the ipsilateral knee is included, adequate measurement of femoral anteverision relative to the retrocondylar axis of the knee can be performed.\textsuperscript{7} CT can also be used for evaluation of the distinctive components and their underlying geometrical relations after the performed surgical procedure (chapters 2 and 3).\textsuperscript{1,4,6,8-13}
A disadvantage of a CT scan that is caused by the design of the scanner, is the finding that, in case of a CT scan made in supine position, measurements of the inclination and version of the acetabular component do not take into account the natural pelvic tilt. These measurements cannot be simply extrapolated to the standing position or compared to measurements on standing radiographs. Cone beam CT in standing weight-bearing position is available but only for foot, ankle and knees. The limited field of view in cone beam CT will obstruct the availability of cone beam CT for imaging of the hips.14-18

In this thesis, we presented a CT classification of the hip capsule in capsular reactions detected after MoM THA which shows good intra- and interobserver reliability and is independently associated with revision surgery. In a multiple logistic regression prediction model including revision and several other unilateral significant MoM-related variables of interest, the simplified A-C classification showed to be the independent predictor for revision that is most likely not attributed to chance (chapter 3).6 Our CT classification can improve communication between the radiologist and the orthopedic surgeon in screening or follow-up populations and shows the importance of cross sectional imaging in detecting pathological capsular reactions that are possibly in need for revision.

**CT versus US and MARS-MRI**

CT provides several potential advantages over US. CT is less operator-dependent and it also provides information regarding component positioning.19 However, CT scans are limited in their ability to provide enhanced soft tissue contrast, they require ionizing radiation, and they have not yet been proven to predict the severity of tissue destruction intra-operatively as is the case for the use of MR.

Nam et al. stated in their review on the advantages and disadvantages of the different imaging modalities to diagnose MoM hip arthroplasty (HA) wear-related corrosion problems, that studies assessing the use of CT in the detection of adverse tissue reactions have been limited to cohort studies on consecutive patients, and that its sensitivity and specificity have not been directly compared with other imaging modalities.19 However, in 2012 Bosker et al. investigated the additional value of CT. In an initial screening of all patients with pseudotumours identified on CT and all patients with high serum ion levels, many complaints and no positive findings on CT underwent an additional MRI. No additional pseudotumours were identified with MRI. Therefore screening by means of MRI showed in this study no advantage over CT with regard to identification of those patients that were a candidate for revision.1

In 2014 Robinson et al. investigated 50 MoM HA patients (30 female) with unexplained painful prostheses and these patients underwent metal artefact reduction sequences (MARS) MRI and CT imaging. CT was found to be superior to MRI for detection of
osteolysis adjacent to MoM HA, and should be incorporated into diagnostic algorithms. However, CT was unable to classify and failed to detect many pseudotumours, and it was unreliable for assessment of muscle atrophy. They concluded that where MARS MRI is contraindicated or unavailable, CT would be an unsuitable substitute and other modalities such as US should be considered. However, in this study old CT techniques were used without hybrid iterative reconstruction techniques and without dedicated CT metal artefact reduction (MAR) protocols making it in our opinion hard to properly compare these two modalities. Over the last five years we have invested in improving CT image quality using younger generation 256-multislice detector CT scanners, hybrid iterative techniques and MAR software. This has strengthened us in our idea that CT is an excellent, more cost effective alternative for MARS-MRI.

US, CT and MR

In summary, all three imaging modalities may have a role in the assessment of adverse local tissue reactions after THA. US may serve as a screening technique for the detection of larger periprosthetic collections and follow-up by US seems reliable enough in experienced hands. Only MRI has been shown to predict the severity of tissue destruction found at revision and correlate to the degree of tissue necrosis at histologic evaluation. CT has gained territory over the last two years due to improved imaging techniques, MAR protocols and our finding that the CT grading system showed highest correlation with revision surgery over other clinical parameters in one of the largest investigated homogeneous cohorts (chapter 3).

DISTINCTIVE MOM BEARINGS AND INCIDENCE OF PSEUDOTUMOURS

There are several distinctive MoM bearings available for the treatment of patients with osteoarthritis. Depending on the MoM implant used, more or less pseudotumour formation can be expected. In this thesis we investigated the Birmingham hip resurfacing (BHR) MoM HRA. We compared our findings with the Biomet M2a-Magnum/ReCap MoM because both cohorts were screened by means of CT and read with the use of the same CT classification. Pseudotumours were detected on CT scans of 28 % of the patients that underwent BHR (chapter 4). Most pseudotumours (72.5 %) in THA BHR were asymptomatic. Failure of the BHR implant occurred in 5.6 % of the patients due to a symptomatic pseudotumour after an average follow-up of forty-one months. This was substantially lower than the incidence of pseudotumour formation (39 %) and subsequent revision (12 %) found with the Biomet M2a-Magnum/ReCap MoM. In 2016 Matharu et al reported a higher incidence of 11.2 % failure and subsequent revision due to pseudotumour formation in MoM HRA than Bisschop et al.
MC et al. recently published the result of 160 MoM THAs implanted in their clinic from 2006-2010. In total, 13 (8.1%) of the THAs were eligible for revision after the recall. In most patients the reason for revision was pseudotumour formation. A total of 14 (8.75%) pseudotumours were diagnosed at the first recall. The revision percentage is in line with our findings. The detection of capsular abnormalities however is higher in our cohort. This seems to indicate the strong capacity of CT in detecting capsular abnormalities. Overall, these results show that a comprehensive follow-up strategy is essential for MoM THAs to promptly identify and manage early complications.

A full comparison between the different types of MoM bearings is beyond the scope of this thesis but it is clear that design is an important factor.

Interestingly, it was recently shown in a randomised controlled trial (RCT) that pseudotumour formation is not solely confined to MoM bearings. Van der Veen et al. found that when the established vigorous CT pseudotumour protocols designed for MoM THA are applied to patients with a metal-on-polyethylene (MoP) articulation, 20% are likely to be diagnosed with a pseudotumour.

**RISK FACTORS FOR DEVELOPING A PSEUDOTUMOUR**

Several risk factors for developing a pseudotumour such as component positioning, gender, elevated serum ion levels, clinical complaints were identified and investigated in numerous studies. We found, however, that in the decision process for revision, imaging seems to be the most important predictor of all different THA related parameters investigated (chapter 3). Serum ion levels such as cobalt and chromium are poor unique predictors for pseudotumour presence. Importantly, pain seems to be an important predictor besides imaging results and hence further investigations in these patients is warranted. Even in the presence of normal ion levels, radiological imaging is considered mandatory as strong capsular reactions can be present without complaints. This was recently confirmed by Hjorth et al. They found no association between pseudotumour formation and serum metal-ion levels, metal patch test reactivity, and atopic dermatitis in 5-7 years follow-up. In addition, Liow et al. recently found that there was no significant correlation between aseptic lymphocytic vasculitis-associated lesions (ALVAL) scores and prerevision surgery, metal ion levels or intraoperative tissue damage, suggesting that the biological mechanism of histologic morphology cannot be solely attributed to elevated metal ion levels and is likely multifactorial, reflecting a complex interplay between implant and patient factors. Nevertheless, we have shown that there seems to be a high concordance between a morphological detectable reactive capsule and serum ion levels in a large screening cohort (chapter 3). The perceived importance of elevated ion levels in these patients by clinicians and patients
was confirmed in a systematic review on metal ion concentrations in body fluids after implantation of hip replacements with MoM bearing.\textsuperscript{28} In this review it was concluded that after hip replacement with contemporary MoM bearings the release of metal ions is highest in stemmed implants with large heads followed by resurfacing devices and also - but on a lower level - small heads. The authors of this review concluded that deposition of metal products may not only lead to local but possibly also systemic adverse health outcomes.\textsuperscript{28}

\section*{Revision and Bone Mineral Density}

Revisions are being undertaken mainly when complaints, capsular reactions and high serum ion levels are present. The main reason for this reticence is the high impact on the patient.

In addition to the consequences of revision, the revision itself is also a challenge. Due to the increasing number of THAs, the amount of hip revision procedures continues to rise. Careful patient selection and bone loss evaluation is crucial for a correct management of femoral revision procedures. The key point in femoral revision is to obtain a reliable primary stability of the stem, with the least invasive implant as possible, to preserve and if possible to restore the bone stock.\textsuperscript{29} In the various MoM THA populations assessing bone stock is of interest to the orthopaedic surgeon when planning the surgical revision procedure in which it is necessary to restore the acetabulum with plates and screws and in some cases transplantation of autologous bone after excision of the cup.

Because of the MoM THA screening program we had access to numerous CT scans with a unilateral MoM THA. This gave us the opportunity to investigate whether bone mineral density (BMD) can be quantified using conventional CT. We showed that there is no need to use an external phantom to quantify CT BMD measurements of body tissue (chapter 5).\textsuperscript{30} Furthermore, a statistically significant bone density difference was found by means of CT analysis when the MoM THA implanted hip was compared with the contralateral side. Pseudotumour formation did not correlate with bone density differences. Only the in situ time of the MoM THA showed a significant correlation with the bone density difference (chapter 6).\textsuperscript{31} Another way to use CT for bone integrity assessment was introduced by Pitto et al. They used quantitative CT-assisted osteodensitometry to predict bone remodeling and the quality of implant fixation using prostheses with different design and / or biomaterials. Quantitative CT-assisted osteodensitometry provides three-dimensional (3D) volumetric analysis with a standard CT scanner protocol. Additional software measures the relative density of the bone in Hounsfield units (HU) of each CT slice. A calibration phantom with a cylindrical section
with a known content of hydroxyl-apatite is needed and scanned together with the patient. This allows conversion of radiological density measurements to true volumetric mineral density measurements (mg CaHA/ml). In the future, this tool could be used for pre-clinical validation of new implants before their introduction on the market. Conversion of radiological density measurements into true volumetric mineral density measurements might also be the case for conventional non-iodine CT scans because in CT the contrast to noise ratio (CNR) and overall image quality seems to improve with each CT scanner generation including newly implemented iterative reconstruction protocols. We have shown that no phantom is needed with the phantomless bone mineral density (PLBMD) method (chapter 5).

We believe that in the future a conventional non-iodine CT scan will provide the orthopaedic surgeon with information whether there is a need for harvesting bone in order to reconstruct the acetabulum. Nevertheless, a reference standard needs to be developed for age, gender and body mass index (BMI) if we want to measure BMD in the pelvis without the use of an external phantom (chapter 5 and 6).

Follow-up

After the first screening round there was a substantial percentage of patients without capsular reactions and a smaller percentage of patients with pathological capsular reactions that did not meet the criteria for revision or who did not want to be revised. Therefore, we do not know the natural history in extenso of the capsular reactions from available large screening prospective cohort studies yet. There is also no international consensus on follow-up schemes yet. All data presented in this thesis are from a first line screening protocol. In a time course analysis based on CT results in a cohort of 706 hips it was estimated that the majority of Isala patients implanted with a MoM THA is likely to develop a pseudotumour in the near future. Future follow-up studies will show whether the estimation in this study population is indeed correct. A 10 year follow-up study of the Isala population will soon add knowledge on the progression of capsular pathology over time in a population that was initially screened by CT.

Kwon et al. recently found that the natural history of type I cystic pseudotumours continues to be nonprogressive in most ”asymptomatic” MoM HA patients at minimum 4 years, indicating the importance of patient symptoms and MRI characteristic features in the clinical decision-making process. Routine follow-up MARS-MRI evaluation of “asymptomatic” patients with low-grade cystic pseudotumours in the absence of interval clinical changes may therefore not be indicated. Low et al. used US for follow-up and found ultrasonic progression in 19 % of cases. Briant-Evans et al. used MRI for follow-up and found 10 % of cases to be progressive. In asymptomatic cases van der Weegen et al. found little change within one year after MoM hip resurfacing with the use of MARS-MRI. Based on the expected small chance on progression after a
short interval we decided to follow-up our patients using CT at 1 year for identifying immediate positive cases and 5 and 10 years for patients that did not receive a revision after one year.

The question on mechanism of failure in MoM HA defined as a need for revision has been extensively investigated over the last years. This question is recently eloquently addressed by Langton et al. in 2016 in BMJ open. It appears to depend in summary on four factors: device-related factors regarding design, device related factors regarding manufacturing, surgical factors and host factors.25

O-MAR

Metal artefacts cause a large disturbance in the image which make it often impossible for the radiologist to assess the surrounding soft tissues and also the surrounding bone. Up to 2010 the communis opinion amongst radiologists regarding the pelvis with pelvic implants was that these CT scans were almost unable to be read due to the metal artefacts. The improvement in CT hardware and subsequent evolution of reconstruction methods such as hybrid iterative reconstruction techniques and full model-based iterative reconstruction (MBIR) techniques have increased CNR and seem to decrease metal artefacts. Newly introduced MAR techniques immediately show their subjective advantage since black areas in the CT scan without any information become suddenly visible.

Quantification of the strength of the MAR technique was nevertheless not yet established. We found that a significant reduction of metal artefacts that were caused by MoM THA, was dependent on the amount of disturbance in attenuation caused by the metal artefacts and relatively improved between 32 and 68 % using O-MAR. O-MAR showed a significant improvement in CNR as well. The improvement in CNR was also dependent on attenuation disturbance by the metal artefact and varied between 52 and 72 % (chapter 7).36

Whether spectral CT imaging alone without dedicated MAR protocols is superior to conventional CT imaging that can make use of established dedicated metal protocols, needs to be investigated in the future.

FUTURE PERSPECTIVE OF MOM THA IMAGING

It would have been interesting to combine our CT scans with PET imaging by means of photon emission tomography (PET) CT instead of CT alone to study the inflammatory activity of the hip capsule, as well as bone single photon emission computed tomog-
raphy (SPECT) CT to study local bone activity around the implant. In this way we would have gained insight in the inflammatory nature of the morphological changes of the hip capsule, which in turn potentially discriminates active lesions from steady state lesions.

Due to increased computing power by the latest Teraflop processor chips that were introduced recently, even a full iterative reconstruction technique, Iterative Model based Reconstruction (IMR), became available. In 2011 IMR showed already the potential of clinically acceptable reconstruction times with an image quality better than achieved before. Nowadays there are several publications on the effect of IMR on image quality and its capacity to reduce dose. The combined improvement in hardware and software has improved the quality of CT scans dramatically. The combination of O-MAR and IMR has the potential to further improve visualisation of surrounding tissue in CT scans containing metal implants.

A recent study of Boudabbous et al. (2015) showed that MBIR reduces the size of metal artefacts on CT images and allows a better analysis of the soft tissue surrounding the metal implant when compared with Filtered Back Projection (FBP). This is the only study investigating metal artefacts using MBIR, however without the use of MAR software and without investigating dose reduction capabilities. Boudabbous et al. (2015) found that boundaries between water and the pellets and between the prosthesis and the surrounding water seem to be sharper. Dedicated metal artefact post processing protocols improve CNR and decrease metal artefacts even more. Therefore, overall CT quality will improve, and reading MoM related disease in CT will be less challenging for the general radiologist.

Thus the use of up-to-date model-based iterative reconstruction techniques allows significant dose reduction while maintaining and even increasing image quality resembling state of the art imaging of the pelvis with large metal implants. In combination with dedicated MAR post processing software IMR has the potential to improve readability of the pelvis with metal hip implants dramatically. Unfortunately, this is not widely implemented yet because it is more expensive than current CT imaging and it needs extra investments from health institutions and their subsequent imaging departments who already need to reduce costs for each scan due to relative budget cuts in a demographically aging population. Nevertheless, in general over time multiple detector computed tomography (MDCT) systems have become more widely available and reconstruction techniques necessary to create images from rough physical photon-extinction data evolved from FBP to iDose (hybrid iterative reconstruction technique).

Various dual energy CT techniques that are already available have decreased metal artefacts in comparison to conventional CT imaging. Overall image contrast may be reduced when optimizing MAR using dual energy techniques. These techniques only do not handle photon starvation.
The next step in combining spectral monochromatic CT imaging techniques with dedicated MAR protocols has been taken by GE and Siemens. This is not commercially available yet for the dual detector CT technique of Philips. Now that we have used different photon energies to reconstruct images from distinctive extinction data, the next step could be to actually count the amount of photons that reach the detector from a certain energy level and use this information in addition to reconstruct images. This photon counting technique in CT is a recent, highly experimental CT technique.\textsuperscript{68-70} Nevertheless, theoretically it is very promising because photon counting will give the preferred input to reconstruction techniques to only use information from those photons one wants to use for reconstructing images in the total spectrum of photons generated.

Overall, we can be confident that in the future better images will be available with further radiation dose reduction: We will just see more with less dose. Heavy reading in metal implants will be something we can leave behind us in the future because of the recent CT developments.

O-MAR holds an unique place amongst the newly developed CT techniques as it handles photon starvation. Being more able to actually read the CT scans of the pelvis in large metal implants will pave the way for future readers to truly quantify their observations in CT and thus unravel current mysteries of changes of body tissue after THA in general.
REFERENCES


HEAVY READING IN HEAVY METAL
Unraveling the mystery of hip tissue in Metal on Metal Total Hip Arthroplasty

In this thesis we described our radiological experience with pathological capsular reactions after metal-on-metal (MoM) hip arthroplasty (HA) using computed tomography (CT) (chapter 2). We showed that CT is an accurate and reliable method for the pre-operative evaluation of femoral head and neck deformities, for the diagnosis of femoro-acetabular impingement either pre-operatively or post-resurfacing and for diagnosing post-operative capsular and bursal reactions when evaluating HA. CT imaging is superior in detecting and delineating osteolytic lesions compared to plain x-radiography. Since current CT scans are acquired in supine position, measurements of the inclination and version of the acetabular component do not take the pelvic tilt into account and cannot be simply extrapolated to the standing position or compared to measurements on standing radiographs. When the ipsilateral knee is included, adequate measurement of femoral anteversion relative to the retrocondylar axis of the knee can be performed (chapter 2). In this way we can identify malpositioning of HA components and the need for a revision in one CT scan session.

We established a CT grading scale for diagnosing post-operative capsular and bursal reactions found in patients with HA (chapter 2). This grading scale was used in two different patient cohorts: 1. large head MoM total hip arthroplasties (MoM THA; chapter 3) and 2. MoM hip resurfacing arthroplasties (MoM HRA) with the so-called Birmingham Hip Resurfacing (BHR; chapter 4). The presented CT classification of the hip capsule in capsular reactions showed good intra- and interobserver reliability and was independently associated with revision surgery. In a multiple logistic regression prediction model together with other unilateral significant MoM-related variables of interest when considering revision, a simplified version of grading scale showed to be the most reliable independent predictor for revision (chapter 3). Our results with the BHR HRA showed that pseudotumour formation occurs in 28 % of the patients as seen on CT scans after an average follow-up interval of forty-one months but most pseudotumours (72.5 %) in BHR HRA are asymptomatic. Failure of the BHR implant occurred in 8.4 % of the patients (5.6 % due to a symptomatic pseudotumour) after an average follow-up of forty-one months (chapter 4).

In addition, we investigated whether it was feasible to investigate bone mineral density (BMD) of the acetabular roof without the use of a phantom. We have shown that internal references of fat and muscle are of similar accuracy when compared to references obtained from an extra-corporal phantom at the level of the acetabular roof in patients with a one-sided MoM THA. The intra-class correlation coefficient showed excellent agreement between the two different references. Thus, there is no need to use an external phantom to quantify CT density measurements of body tissue.
(chapter 5). We combined the specific CT based findings of the post-operative hip capsule and bursa with clinical outcome parameters such as revision (chapter 3) and BMD. With the use of CT a statistically significant bone density difference with respect to the contralateral side between the acetabulum at the side of the prosthesis and the contralateral side after 2.8 year postoperative follow-up in patients with unilateral MoM total hip replacements was shown. Only the in situ time of the MoM THA showed a significant correlation with the bone density difference. Pseudotumour formation did not correlate with bone density differences (chapter 6).

A challenge in reading MoM bearings by means of CT are the metal artefacts for which a dedicated orthopaedic metal artefact reduction software tool is available named O-MAR. We quantified the visual clearly positive effect of O-MAR on metal artefacts in a hip phantom. Our phantom study shows significant reduction of metal artefacts by O-MAR caused by MoM THA. The reduction is relatively dependent on the amount of disturbance in attenuation caused by the metal artefacts and the strength was dependent of the location and severity of metal artefacts between 32 and 68 %. O-MAR showed a significant improvement in contrast-to-noise-ratio (CNR) as well. The decrease in CNR decrement is also dependent on attenuation disturbance by the metal artefact and varies between 52 and 72 % (chapter 7).

We are confident that in the near future the combined use of O-MAR with up-to-date model-based iterative reconstruction techniques will allow significant dose reduction while maintaining and even increasing image quality and thus resemble state of the art CT imaging of the pelvis with large metal implants. We will just see more with less radiation dose. This will be beneficial for quantification of CT findings in general and will also result in a better positioning of CT imaging in orthopaedics as it can more easily be applied in clinical outcome studies.
Chapter 10

Dutch summary / Nederlandse samenvatting
MOEILIJK BEELDBEOORDELING DOOR VEEL METAAL
Ontrafelen van het mysterie van heupweefsel bij metaal-op-metaal
totale heup artroplastiek

In dit proefschrift beschreven we onze radiologische ervaringen met pathologische
 capsulaire reacties na metaal op metaal (MoM) heupartroplastiek (HA) die werden
detecteerd met behulp van computer tomografie (CT) (hoofdstuk 2). We hebben laten
zien dat CT een precieze en betrouwbare methode is voor de pre-operatieve evaluatie
van femorale kop en nek/steel misvormingen, voor de diagnose van heupinklemming
ofwel femoro-acetabulair impingement zowel pre-operatief als ook post-resurfacing en
voor het diagnosticeren van post-operatieve capsulaire en bursale reacties bij de evalu-
atie van een HA. CT scans zijn beter dan gewone röntgenopnames in het detecteren
en afbakenen van osteolytische laesies. Omdat de huidige CT scans in rugligging verkre-
gen zijn, houden metingen van de helling en kanteling van de acetabulaire component
geen rekening met de natuurlijke bekkenkanteling en kunnen deze dus niet eenvoudig
geëxtrapoleerd worden naar een staande positie of vergeleken worden met röntgen-
foto’s die genomen zijn in staande positie. Wanneer de ipsilaterale knie meegescand
wordt, kunnen adequate metingen van femorale anteversie in relatie tot de retrocond-
dylaire as van de knie vervaardigd worden. Op deze manier kunnen onjuist geplaatste
HA componenten en de noodzaak van een revisie in één CT scan sessie geïdentificeerd
worden (hoofdstuk 2). We hebben een indelingsschema ontwikkeld voor het diagnos-
ticeren van post-operatieve capsulaire en bursale reacties zoals die gevonden worden
in patiënten met HA (hoofdstuk 2). Deze indeling is gebruikt in twee verschillende
patient cohorten. 1. Grote kop MoM totale heupartroplasties (MoM THA; hoofdstuk 3)
en 2. MoM heup resurfacing artroplasties (MoM HRA) met de zogenaamde Birmingham
Heup Resurfacing (BHR; hoofdstuk 4). De ontwikkelde CT classificatie van het heupkap-
sel bij capsulaire reacties liet een goede intra- en interobserver betrouwbaarheid zien
en was onafhankelijk gecorreleerd met revisie. In een multipele logistische regressie
analyse samen met andere unilaterale significante MoM-gerelateerde variabelen die
van belang zijn wanneer een revisie overwogen wordt, was een gesimplificeerde versie
van het indelingsschema de meest betrouwbare onafhankelijke voorspeller voor een
revisie (hoofdstuk 3). Onze resultaten met de BHR HRA lieten zien dat in 28 % van
de patiënten significante capsulaire reacties gevonden worden op CT scans na een
gemiddelde follow-up interval van 41 maanden maar de meeste capsulaire reacties
(72.5 %) in BHR HRA zijn asymptomatisch. In 8.4 % van de patiënten (5.6 % door een
symptomatische pseudotumor) trad er een significant klinisch probleem op met de
BHR prosthese na een gemiddelde follow-up van 41 maanden (hoofdstuk 4).

Daarnaast hebben we onderzocht of het mogelijk was om de botmineraaldichtheid
(BMD) te meten van het dak van het acetabulum zonder het gebruik van een buiten
de patiënt gelegen fantoom. We konden aantonen dat interne referenties van vet en spierweefsel eenzelfde nauwkeurigheid hadden in vergelijking met referenties verkregen door een extracorporaal fantoom op het niveau van het dak van het acetabulum in patiënten met een unilaterale MoM THA. De intra-class correlatie coëfficiënt liet zien dat de twee verschillende referenties perfect overeenkwamen. Ofwel, het is niet nodig om een extern fantoom te gebruiken om dichtheid metingen te doen van lichaamsweefsel met behulp van CT (hoofdstuk 5). We combineerden de CT bevindingen van het post-operatieve heupkapsel en slijmbeursafwijkingen met klinische outcome parameters zoals revisie (hoofdstuk 3) en BMD. Met behulp van CT konden we een statistisch significant botdichtheidsverschil met betrekking tot het acetabulum aan de kant van de prothese en de contralaterale kant vaststellen na 2,8 jaar postoperatieve follow-up van patiënten met unilaterale MoM THA. Alleen de lengte van de tijd dat de MoM THA zich in het lichaam bevond, liet een significante correlatie met het botdichtheidsverschil zien. Pathologische capsulaire reacties correleerden niet met botdichtheidsverschillen (hoofdstuk 6).

Het interpreteren van CT scans van MoM prostheses wordt bemoeilijkt door metaal artefacten. Hiervoor is speciaal ontwikkelde orthopaedische metaal artefact reductie software beschikbaar, bijvoorbeeld de zogenaamde O-MAR. Wij kwantificeerden het duidelijk zichtbare positieve effect van O-MAR op metaal artefacten in een heup fantoom. Onze fantoom studie liet een duidelijk significante reductie van metaal artefacten zien die veroorzaakt werden door MoM THA, door O-MAR. De reductie was relatief afhankelijk van de hoeveelheid verstoring in foton extinctie die veroorzaakt werd door de metaal artefacten. De mate van verbetering was afhankelijk van locatie en grootte van de metaal artefacten en lag tussen de 32 en 68 %. O-MAR resulteerde daarnaast ook in een significante verbetering van de contrast-noise (ruis)-ratio (CNR). De verbetering in CNR is ook afhankelijk van de foton extinctie verstoring door de metaal artefacten en varieert tussen 52 and 72 % (hoofdstuk 7).

We hebben er alle vertrouwen in dat in de nabije toekomst het gecombineerde gebruik van O-MAR met up-to-date model-based iteratieve reconstructie technieken ons in staat zal stellen om bij een significante reductie van de stralingsdosis de beeldkwaliteit te behouden of misschien zelfs wel te verbeteren. We zullen alleen maar meer kunnen zien met een lagere stralingsdosis. Dit zal de standaard worden voor CT scans van het bekken met grote metalen implanten. Dit zal het kwantificeren van CT scans in het algemeen ten goede komen en zal ook resulteren in een betere positionering van CT beeldvorming in de orthopedie omdat het eenvoudiger toegepast kan worden in klinische outcome studies.
Appendix

1. LIST OF ABBREVIATIONS
List of abbreviations

3D three-dimensional
ALARA as low as reasonably achievable
ALTR adverse local soft tissue reactions
ALVAL aseptic lymphocytic vasculitis-associated lesions
ARMD adverse reactions to metal debris
ASR articular surface replacement
BHR Birmingham hip resurfacing
BMD bone mineral density
BMI body mass index
CI confidence interval
CNR contrast-to-noise ratio
Co cobalt
Cr chromium
CT computed tomography
CTDI computed tomography dose index
DICOM digital imaging and communications
DEXA dual-energy x-ray absorptiometry
FAI femoro-acetabular impingement
FBP filtered back-projection
FOV field of view
HA hip atroplasties
HRA hip resurfacing arthroplasties
HU Hounsfield unit
ICC intra-class correlation coefficient
IMR iterative Model based Reconstruction
MAR metal artefact reduction
MARS metal artefact reduction sequences
MAVRIC multiple acquisition variable-resonance image combination
MDCT multi detector computed tomography
MBIR model-based iterative reconstruction
MIS mini-incision surgery
MoM metal-on-metal
MoP metal-on-polyethylene
MR magnetic resonance
MRI magnetic resonance imaging
NA not available
NICE National Institute for Health and Clinical Excellence
OA osteoarthrosis
O-MAR orthopedic metal artefact reduction post-processing protocol
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>PET</td>
<td>photon emission tomography</td>
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<tr>
<td>PLBMD</td>
<td>phantomless bone mineral density</td>
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<tr>
<td>ROI</td>
<td>regions-of-interests</td>
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<tr>
<td>RCT</td>
<td>randomised controlled trial</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SEMAC</td>
<td>slice encoding for metal artifact correction</td>
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<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<tr>
<td>THA</td>
<td>total hip arthroplasties</td>
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<tr>
<td>THR</td>
<td>total hip replacement</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
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<tr>
<td>WED</td>
<td>water-equivalent diameter</td>
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</tbody>
</table>
Appendix

2. LIST OF PUBLICATIONS


Boomsma MF. Referaat: Penetrantie belangrijke mutatie voor hemochromatose is slechts 1%. Ned Tijdschr Geneeskd. 2002;146 (19)


Appendix 2.


van der Veen HC, Reininga IH, Zijlstra WP, Boomsma MF, Bulstra SK, van Raay JJ. Pseudotumour incidence, cobalt levels and clinical outcome after large head metal-on-metal


Appendix

3. LIST OF CONTRIBUTING AUTHORS
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Appendix

4. PHD PORTFOLIO
**Name Ph.D. student:** Martijn F. Boomsma  
**Ph.D. period:** January 2010 - October 2016  
**Promotor:** Prof. dr. M. Maas  
**Co-promotors:** Dr. C.C.P.M. Verheyen and Dr. G.J. Streekstra

**1 - Ph.D. TRAINING**

**General courses:**
- **2001** Basic course Biostatistics and Epidemiology  
- **2001** Ethical dimensions of human research  
- **2001** Basic course SPSS  
- **2003** Linear regression and analysis of Variance  
- **2012** Interactive presentations  
- **2014** TED worthy Presentations  
- **2014** Good Clinical Practice (GCP)  
- **2009-2012** Teach the teacher I, II, III and Entre-Nous  
- **2016** Teaching on the Run

**Presentations and workshops:**
- **2011** Radiologendagen, Maastricht, The Netherlands  
  “Pseudotumoren bij metaal op metaal totale heup arthroplastiek.”  
- **2013** ESSR, Marbella, Spain  
  “CT classification of pseudotumours in metal-on-metal total hip arthroplasty.”  
- **2014** NVVR Sandwichcursus MSK, workshop, Ede, The Netherlands  
  “Hot Topic: Metal-on-Metal Heupprothesen: is imaging zinvol en hoe te interpreteren?”  
- **2016** NVVR Sandwichcursus MSK, plenary session, Ede, The Netherlands  
  “Intra-articulaire schouder letsel: MRI met arthroscopische correlatie”  
- **2016** Symposium Nederlandse Orthopaedische vereniging werkgroep VS/PA “De sterkste schouders”, Zwolle, The Netherlands  
  “Beeldvormende technieken van de schouder” & “Correlatie van beeldvormende diagnostiek en schouder-pathologie per-operatief”
Appendix 4.

(Inter)national conferences related to MSK Radiology:

2010    ESSR annual meeting, Lille, France
2010    Erasmus Course Musculoskeletal II, Torino, Italy
2011    Erasmus Course Musculoskeletal I, Leiden, The Netherlands
2013    ECR, Vienna, Austria
2013    ESSR annual meeting, Marbella, Spain
2013    RSNA, Chicago, USA
2014    ECR, Vienna, Austria
2014    ESSR annual meeting, Riga, Latvia
2015    Stoller Course, Las Vegas, USA
2015    ECR, Vienna, Austria
2015    ESSR annual meeting, York, United Kingdom
2016    ESSR annual meeting, Zurich, Switzerland

2 - TEACHING

Tutoring / Mentoring

Bachelor students Medical imaging and Radiation Therapy from Hanzehogeschool Groningen

2014    Martine Stol, Liza de Gier and Lynn Houkes. Prospective evaluation of diagnostic yield in CTPA.
2015    Judith Wiersema and Lisanne Meijering. COPD quantification in ISP7.
2015    Nikki Hendriks and Jildau Kussendrager. Automated peripheral Lung Embolus detection in ISP 7.
2015    Annelies Breeuwsma and Lisa Kamping. Use of CT in trauma of the cervical spine.

Master students in Medicine from University Medical Centre Groningen

2013    Minke A. Leijstra. Retrospective analysis of diagnostic yield in CTPA.
2014    Sanne Jansen. COPD quantification in ISP 6 with clinical Gold Standard
Ph.D. portfolio

Master students in Technical medicine, Technical University Twente


2016  Inge Slouwerhof. In depth analysis of biological tissue characteristics of uterine fibroids using new MRI Techniques.

Medical interns

2009 - present  Isala Program Director Radiology internships

Residents in Radiology and Nuclear Medicine

2015 - present  Isala Program Director in Radiology

3 - OTHER

2013 - present  Isala Research Coördinator in Radiology

2015  ESSR Diploma in Musculoskeletal Radiology

Memberships

Nederlandse Vereniging voor Radiologie (NVVR)
Nederlandse Vereniging voor Nucleaire Geneeskunde (NVNG)
European Society of Pediatric Radiology (ESPR)
European Society of Musculoskeletal Radiology (ESSR)
European Society of Thoracic Imaging (ESTI)
European Society of Cardiac Radiology (ESCR)
Society for Cardiovascular Magnetic Resonance (SCMR)
Appendix

5. ACKNOWLEDGEMENTS / Dankwoord
This is in my opinion the most important part of the thesis. It reflects the fact that all the achievements described in this thesis are the mutual effort of a lot of dedicated people. I believe it was Goethe who once said...” If one would take away from me everything I have achieved through the efforts of others, not much would be left over from me.”

**Patients**

Patients with metal on metal total hip arthroplasty problems screened by the orthopaedic department and subsequently the radiology department of Isala and Martini hospital have been the start of this journey and they will fuel future research. I would like to thank all patients that have enrolled in our studies. Your efforts have been fruitful.

**Mario Maas**

Op verzoek van Cees Verheyen raakte jij al snel betrokken bij dit onderzoek. Die radioloog in Isala zag wel van alles op die CT-scans, maar enige academische back up en validatie in het kader van de wetenschap was wenselijk. Voor jou waren de weke delen van het kleine bekken met al die metaal artefacten van al dan niet bilaterale heupprotheses tot dan toe ook een beetje “No Man’s land” geweest. Gaandeweg wisten we samen vooruitgang in beeldvorming van het bekken met totale heupprotheses te boeken. We waren het er achter de monitor al snel over eens dat het belangrijkste stuk metaal artefact reductie gereedschap toch wel tussen de oren zit.

Op de vooravond van een serieuze double reading sessie van de eerste 120 patiënten vroeg je wat er voor nodig was om mij te laten promoveren. Mijn antwoord was: “Laat me maar mijn gang gaan en help me als ik om hulp vraag of ongevraagd als jij denkt dat ik hulp nodig heb.” Dat heb je aldus gedaan.

Je verlegde de laatste jaren elke keer een grens voor mij in radiologisch onderwijsland, hebt een open geest t.a.v. suggesties en constateringen maar vraagt ook vaak actief naar andermans mening. Je bent daarnaast een man van je woord. Dat vind ik bewonderenswaardig. Ik beschouw het echt als een voorrecht dat ik dankzij je begeleiding en vriendschap me op vakinhoudelijk maar ook persoonlijk vlak verder heb kunnen ontwikkelen. Dank dat je wilt optreden als mijn promotor. Ik hoop dat we nog lang mogen samenwerken.

**Cees Verheyen**

Je communicatie is kort en krachtig. Wat ik aan je bewonder, is dat je zaken altijd op de juiste waarde weet te schatten. Ik herinner me nog dat we een keer samen achter de microscoop zijn gekropen bij de patholoog om alle heupkapselbiopten de revue te laten passeren. Dankbaar ben ik voor onze samenwerking in Isala. De relatie tussen de Orthopedie en Radiologie is niet alleen sterk qua volume, maar ook als het gaat om kwaliteit en nu ook research. Dat is in de eerste plaats ook aan jou te danken waarbij
je focus op het leveren van kwaliteit een duidelijke stimulator is 'to do well'. Je energie om het hele metaal–op-metaal heup gebeuren nader te onderzoeken getuigt van professionaliteit waarbij jij op nationaal en internationaal niveau je input hebt geleverd. Dank dat je wilt optreden als mijn copromotor.

Geert Streekstra
Je raakte gaandeweg (toen het pas echt ingewikkeld werd op CT-gebied!) steeds meer bij dit onderzoek betrokken. Je vriendelijkheid, je rust en daarmee gepaard gaande stevige inhoudelijke op- en/of aanmerkingen zijn heel behulpzaam geweest. Ik heb het enorm gewaardeerd dat ik nog eens goed met je heb kunnen praten over fysische CT-onderwerpen en ik vind het mooi om te zien dat je met Ruud Wellenberg verder de diepte in kan gaan. Dank dat je wilt optreden als mijn copromotor.

Special thanks to all the other members of the Ph.D. Committee for their time and expertise in reading the manuscript and that they have agreed upon taking place in the Ph.D. committee: Prof. dr. F. Nollet, Prof. dr. R.J. Oostra, Prof. dr. J. Stoker, Dr. M.U. Schaafroth (University of Amsterdam) en Prof. dr. ir. C.H. Slump (Technical University of Twente) en Prof. dr. J. Hodler (Universität Zürich).

Co-auteurs
Ik wil alle co-auteurs bedanken voor de altijd prettige samenwerking. Zoveel expertise gecondenseerd in 1 artikel is elke keer weer een wonderlijke constatering. Zaken zijn altijd ingewikkelder dan je in eerste instantie denkt en het resultaat is elke keer weer beter na de vele iteraties over en weer. Ik krijg ook het idee dat tele-onderzoek een begrip is dat in de dikke van Dale zou kunnen worden opgenomen als je ziet hoeveel communicatie tegenwoordig via e-mail gaat. Als er op het laatste moment nog wat moet gebeuren voelt iedereen zich verantwoordelijk en doet zijn of haar “ding”. Dank!

Maatschap leden van de Medische Diagnostische en Therapeutische Beeldvorming Groep Nederland
Ik heb oprechte steun ervaren van veel van mijn directe collega’s die het belang van het doen van wetenschappelijk onderzoek in een niet academische setting binnen de radiologie in de 21e eeuw hebben onderkend. In het bijzonder ben ik onze Nucleair Geneeskundigen dankbaar voor hun voorbeeldfunctie waarmee zij historisch gezien de basis hebben gelegd voor de infrastructuur van onze gezamenlijke wetenschappelijke activiteiten. Er is echter één collega die ik hieronder in het bijzonder wil bedanken.
Corné van der Worp

Jij bent een van de steunpilaren van onze vakgroep. Vanaf het begin van de PACS-implementatie heb je gestreden voor het bewaren van de dunne coupes. Dit is achtereaf enorm waardevol gebleken. We hebben het grotendeels aan jou te danken dat we een radiologie afdeling hebben met zoveel state-of-the art apparatuur. Jij stond aan de basis van het research partnerschap tussen de afdeling Radiologie en Philips. Jij bent het elke keer geweest die ad hoc de noodzakelijke oplossingen wist te bedenken in tijd, logistiek en financiële middelen om de onderzoekspatiënten een plek te geven binnen onze productieomgeving. Je uitmuntende Excel kwaliteiten leveren de noodzakelijke informatie waarmee we gefundeerd onze beslissingen kunnen nemen. Los daarvan heb je een groot menselijk inzicht in ieders kwaliteiten gekoppeld aan een groot gevoel van rechtvaardigheid. Hiermee geef je individuen de kans om te excelleren. Je politieke bestuurlijke eigenschappen hebben de transformatie van onze afdeling mogelijk gemaakt. Ideeën pakken beter uit na een of twee “van der Worp” iteraties.

Edwin Rozeman, Egbert Broers en Coen van Delden

Edwin jij was de eerste manager die ik ontmoette toen ik startte in Zwolle. Jij hebt ondersteuning geboden en gefaciliteerd om te starten met research in Zwolle. Ik heb je goed gehoord toen je zei dat we het onderzoek op de Radiologie in Isala moesten verankeren in het collectieve geheugen. Ik heb getracht dit vorm gegeven door alle echelons binnen onze afdeling bij het doen van onderzoek te betrekken. Egbert, samen hebben we na het vertrek van Edwin MR HIFU en IMR weten te implementeren op onze afdeling en daarmee hebben we onderzoek doen binnen het partnerschap met Philips op onze afdeling geconsolideerd. Coen, ik kan je transparante en terugkoppellende manier van werken enorm waarderen. Daarmee kunnen we temporiseren en zaken goed en snel voor elkaar krijgen.

Jochen van Osch en Jorn van Dalen

Jullie zijn klinisch fysici die midden in de dagelijkse radiologische en nucleair geneeskundige praktijk staan en volop meedoen in onze researchambities en die zelfs aanwakkeren. We delen een gezamenlijke toekomstvisie. Aanvankelijk gestart met Jorn ben ik gaandeweg steeds meer samen gaan werken met Jochen en onze stijl van “last-minute” acties die inmiddels gepaard gaan met salades en Sushi werpt nog steeds vruchten af. Ik vind het ongelofelijk plezierig samenwerken, maar bovenal leer ik enorm veel van jullie. Jullie participatie binnen de opleiding is ook het neusje van de zalm.

Laboranten Radiologie Isala

Jullie zijn de drijvende motor van onze afdeling. Zonder jullie allen waren er geen beelden om te beoordelen. Ik bewonder hoe jullie de combinatie van zorg voor de pa-

**Gesubspecialiseerde echo-laboranten**


Dank voor alle hulp bij het verrichten van de diagnostische echografische onderzoeeken gecombineerd met histologische biotopen van het aangedane heupgewrichtskapsel. Jullie flexibiliteit en verantwoordelijkheidsgevoel maken het plezierig om met jullie samen te werken, maar geeft bovenal energie!

Mijn speciale dank gaat uit naar Irma Dartel-Ogink, operationeel leidinggevende echografie voor al haar inzet om de echo afdeling zo goed te laten werken. Onze samenwerking is me erg dierbaar en ik weet zeker dat we ons niveau van diagnostische performance kunnen uitbouwen door nieuwe innovatieve echo-technieken te implementeren in ons dagelijks werkpatroon.

**Gesubspecialiseerde CT-laboranten**


Heel veel dank voor niet alleen de grote hoeveelheid CT-scans die vervaardigd zijn bij het screenen van de patiënten, maar ook voor het verrichten van alle follow up scans. Dit was veel werk. Dank voor alle additionele fantoomplaatstingen, reconstructies en het toepassen van post processing software op bestaande datasets. Ik ben ervan overtuigd dat de dagelijks CT-werkprogramma’s de komende decades zullen evolueren in niet alleen scannen, maar steeds meer reconstrueren en kwantificeren.

Mijn speciale dank gaat uit naar Robbert Smit, operationeel leidinggevende CT, die altijd tijd vond om me behulpzaam te zijn als additionele metingen moesten worden verricht.

**Gesubspecialiseerde MRI-laboranten**

Aaron Noordstra, Erik Visscher, Evenita Polinder, Hein Eghuizen, Jack Hein, Jasper van der Bij, Jeffrey van Zanten, Lea Busweiler-Dickhof, Margreet ten Broeke- Bakker, Mari-
anne Jorna, Monique Dekker, Nick Zegger, Paulien van Wilsem, Renske Faber en Tessa Smits.

Dank voor het vervaardigen van de goede MRI-scans van de heupen ondanks de aanwezigheid van metaalartefacten. De scans zijn zeer behulpzaam geweest bij het begrijpen van de relatie van de vochtcollecties rondom het heupgewricht met de totale heupprothese. Hierbij wil ik ook de kans nemen om jullie te danken voor jullie inzet voor de niet aflatende druk op de MRI “tuin”. Jullie blijven altijd professioneel. Dank voor het helpen van onze patiënten binnen de gestelde termijnen.

**Overige Radiologie laboranten**


Jullie hebben heel veel conventionele opnames gemaakt voor Dr. Trial en deze werden trouw aan mijn verslagbakje toegevoegd. Daarmee hebben jullie me echt wel beziggehouden!

**Mirjam van der Streek**

Van het begin af aan kon ik het goed met je vinden. In de transformatie van onze afdeling was jij in het begin een welwillende katalysator. Jij hebt ervoor gezorgd dat de hele logistiek van de screening van zoveel patiënten met vele onderzoeken op een ordentelijke manier is verlopen. Je stond ook open voor nieuwe ontwikkelingen op CT-gebied. Ook op het gebied van de opleiding ben jij de persoon op wie we kunnen bouwen als het gaat om het aanleveren van de cijfers voor het Concilium Radiologicum en de RGS. Je hebt de directe radiologie verlaten, maar het is goed om te weten dat we nog steeds een beroep op je kunnen doen, al is het dan nu in de hoedanigheid van controller binnen de RVE ondersteunende specialismen in Isala.
Appendix 5.

Gardi Bloemhof
Als opleidingsfunctionaris ligt je hart al langer bij opleiden en je hebt praktische zaken rondom research de laatste twee en een half jaar met groot natuurlijk gemak in je portfolio verwerkt. Sinds anderhalf jaar werken we ook samen in het implementeren van de opleiding Radiologie op onze afdeling waarbij je voortvarendheid zijn vruchten afwerpt. Ik waardeer je prettige manier van communiceren en je uitstekend afgestelde sensor voor allerhande gevoelige zaken. Onze samenwerking beschouw ik als een werkelijk kostbaar kleinood binnen onze afdeling.

Rianne Eilander
Lang geleden kreeg ik het advies van ons toenmalig dagelijks bestuur bestaande uit Henk Boelhouwers en Zwenneke Flach om mijn agenda maar eens door jou te laten beheren. Dat is een goede beslissing geweest. Je inspanningen aangaande management rondom de opleiding maar ook het bewaken van de contacten binnen research zijn vruchtbaar.

Ingrid Nijholt
Ik leerde je voor het eerst kennen in de hoedanigheid van affiliatiecoördinator van de co-assistenten bij de Isala Academie. Ik verzorgde enkele klinische werkconferenties Radiologie op je verzoek.

Toen we de opleiding Radiologie definitief gingen aanvragen, bleek al snel dat je van onschatbare waarde was. Ik ken maar weinig mensen met een mate van afhechtend vermogen zoals jij dat laat zien. Je ziet allerlei kansen en laat geen steen onomgedraaid om doelen te bereiken. Ik beschouw jou echt als een "parel" van Isala. Je bent een groot voorstander en pleitbezorger geweest van het partnerschap van Isala met de TU Twente en je inspanningen om dit goed geïmplementeerd te krijgen werpen nu duidelijk hun vruchten af. Dat je me met de nodige regelmaat flink aan het werk zet omtrent allerhande opleidingszaken neem ik graag op de koop toe. Je bent voor mij nog steeds een "hordenloopster", en daarmee een "kei" in wat je dagelijks doet. Ik ben heel dankbaar dat we zo fijn kunnen samenwerken.

Harmen Ettema
Je enthousiasme om aan een promotie te gaan denken is vanaf het begin stimulerend geweest. Je hebt me echt bij het begin van dit onderzoek in 2011 een duw in de rug gegeven door korte bezoeken aan de verslagruimte op de locatie Weezenlanden te brengen. We doen goede zaken samen om wetenschappelijke vooruitgang binnen de Orthopedie te boeken waarbij beeldvorming een positieve rol kan spelen. Ik hoop dat onze toekomstige projecten net zo vruchtbaar zullen zijn.
Carine Gerritsma
Jij riep me in consult na mijn eerste ervaringen met de MoM THA in Zwolle en dat bood de kans om in het Martini samen met Roel de MoM BHR-populatie aan een kritische “CT-blik” te onderwerpen. Dat wierp al snel vruchten af. Jij was ook degene die als eerste de vraag stelde of het mogelijk was om m.b.v. CT de botdichtheid te gaan onderzoeken rondom de prothese i.p.v. de bekende DEXA-metingen. Zover zijn we nog niet, maar je hebt als eerste mijn interesse daarvoor gewekt en we hebben uiteindelijk een voorzichtig begin kunnen maken.

Roel Bisschop
In je huis in Laren hebben we een aantal avonden aan de keukentafel samengewerkt aan de totstandkoming van ons artikel. De diensten zijn handig om aan wetenschap te doen, hebben we onafhankelijk van elkaar “uitgevonden”. Last but not least, hebben we gemeen dat we niet vies zijn van een stukje autorijden!

Jos van Raay
Het woord “tele-research” is zeker op ons van toepassing. Het is ongelofelijk, maar we hebben elkaar nog nooit ontmoet, laat staan de handen geschud, daar moet verandering in komen! Ons e-mailcontact is echter vruchtbaar en met je AIOS is het goed samenwerken. Ik vind het mooi dat je je AIOS binnen de opleiding tot orthopeed zo tot ontwikkeling weet te brengen. We werken nu al enkele jaren samen en hebben diverse artikelen samen kunnen schrijven, er volgen er wellicht nog meer.

Christiaan van Lingen
Ik weet nog goed dat we op verzoek van een reviewer samen binnen een week ’s avonds nog een steekproef genomen hebben van de grote studie waarbij de classificatie afgezet werd tegen de revisies. Zonder jou had ik deze specifieke deadline niet gehaald. Jij had al die revisiepatiënten goed op je netvlies staan zodat we nauwkeurig de databases naast elkaar konden leggen. Je bent ook elke keer uiterst behulpzaam als we patiënten moeten identificeren uit je database als we nieuwe onderzoeksvragen willen beantwoorden.

Dean Pakvis
Harmen introduceerde jou in Zwolle als de orthopeed die zich bezighield met botdichtheid rondom de heup. We hebben heel wat nagedacht over hoe we botdichtheden in onze populatie konden en wilden gaan meten. Dat was echt een nieuw aspect om te onderzoeken. Het heeft wel even geduurd voordat het klaar was, maar uiteindelijk was het zeer de moeite waard.
Leon de Vries
Zonder jou was er geen onderzoek geweest binnen Isala. Ik had op dat moment geen idee hoe, waar en met wie te beginnen. Initieel vroeg je om aan de slag te gaan met metaal artefact reductie software gezien onze prille bezigheden met grote metalen implantaten. Jij introduceerde me bij Dirk Mueller en Alain Vlassenbroek en stelde voor om te investeren in het partnerschap met de TU Twente en de Hogeschool Groningen. In het begin was er geen geld, geen mankracht, maar jij zette de deur naar vooruitgang open door voormalige medewerkers van Isala, op dat moment werkzaam binnen Philips erbij te betrekken. Het was jouw idee om ons ontworpen fantoom, “de orthobox”, te onderwerpen aan spectraal CT-analyse.

Searske Woudstra
In het begin heb je op een gegeven moment letterlijk naast me gezeten achter de Barco monitor om een Clinical Research Agreement (CRA) op te stellen onder het wegwerken van een CT-programma. “Dat is gewoon echt even nodig Martijn!” Inmiddels hebben dit soort zaken gelukkig een wat meer geïnstitutionaliseerd karakter gekregen. Toch was je hands-on mentaliteit in het begin een geweldige stimulator. Jammer dat we elkaar niet meer zien nu je een nieuwe stap in je carrière hebt gemaakt.

Dirk Mueller
You were the big stimulator of starting to work/introduce myself into the field of metal artefact reduction quantification. You are always so polite and kind. It is admirable. You have left Philips and started a new career. I hope we can stay in touch.

Julien Milles
You are our “liaison officer”, you make things happen in the partnership between Isala and Philips. I appreciate your expertise in research and the remarks you make in the various study designs and articles we have come across. I hope we can keep on working together for a very long time.

Alain Vlassenbroek
Present when needed. Together with you and Julien we worked on a research plan that made it possible to get Ruud Wellenberg to Haifa, Israel to work on the dual detector Spectral CT.

Niek Warringa
Mijn eerste MBRT student in Isala. Ik bewonder je afhechtend vermogen. Ik mis je regelmatig nu je een nieuwe carrière stap hebt gemaakt in Nijmegen. Als ik kijk naar de vele zaken die we samen hebben bereikt, kan ik alleen maar dankbaar zijn dat we
hebben kunnen samenwerken. Jij was altijd positief over een goede afloop als er weer een paar “snelheidsdrempels” opdoemden onderweg. Dank dat je wilt optreden als mijn paranimf.

**Ruud Wellenberg**

Ik geloof dat je “in den beginne” graag af wilde studeren in Zwolle omdat je dan je semiprofessionele voetbalkarrière bij S.V. Berkum makkelijker kon combineren met je studie Technische geneeskunde. Je was heel erg duidelijk tijdens onze eerste kennismaking in wat je wilde in de laatste fase van je studie. We zijn vanaf het begin af aan open en duidelijk naar elkaar geweest. Ik bewonder je werkhouding en focus. Je bedrijft gewoon opnieuw topsport! Jij was de eerste technische geneeskunde student die bij mij afstudeerde en ik vind het heel bijzonder om je te hebben mogen begeleiden in de laatste fase van je studie. Gelukkig hebben we daarna elke keer weer een manier gevonden om je wetenschappelijk onderzoek bij ons voort te zetten en dat werpt nu zijn vruchten af. In het AMC ga je inmiddels ook weer als een “speer”. Je bent gewoonweg aan het “scoren” nu! Dank dat je wilt optreden als mijn paranimf.

**Inge Slouwerhof**

Als M2 student technische geneeskunde kwam je bij ons stage lopen. Al snel bleek dat deze rustige “ruwe diamant” niet voor de poes was. Samen zijn we enorm productief geweest. Ik heb gevraagd of je als M3 student je wilde gaan bezighouden met MR-HIFU. Dat avontuur ben je na rustig overdenken met ons aangegaan en dat project heeft ons vervolgens heel wat zweetdruppeltjes op ons voorhoofd doen bezorgen in de loop der tijd. Jij hebt enorme toewijding aan je opleiding en ons onderzoek getoond. Na je afstuderen heb je nog 6 maanden bij ons gewerkt aan de implementatie van MR HIFU. Zonder jou waren we nooit zover gekomen! Je hebt uiteindelijk besloten om je onderzoekscarrière in Nijmegen voort te zetten en ik hoop dat je het daar goed naar je zin hebt.

**Gerard Welten**

Vele onderzoekslijstjes van verschillende scans heb je gemaakt, altijd meedenken als we iets nodig hebben binnen onze PACS-omgeving. Binnen het MoM onderzoek hebben we het archief regelmatig laten “kreunen”. Dat hebben we nu anders ingericht.

**André de Vries**

In je rol als medische instrumentenmaker heb ik veel aan je creativiteit gehad en was je onmisbaar bij het ontwerp en de realisatie van de “orthobox!” Heel erg bedankt.
Appendix 5.

Wim Huurnink

Vele gevulde koeken hebben we gegeten in de Weezenlanden als ik weer eens "dienst" had en je hebt me laten kennismaken met de wondere wereld van Excel. Jij was vanaf het begin betrokken bij de steeds maar uitdijende database aangaande de MoM patiënten. Je steun in de rol van PACS en ICT-adviseur is enorm stimulerend geweest binnen de dagelijkse hectiek en je hebt vanaf het begin nieuwe ontwikkelingen op PACS en EPD-gebied en de integratie hiervan ondersteund. Dat je ondersteuning gaf bij het doen van research op onze afdeling was voor jouw holistische geest vanzelfsprekend.

Oom en collega Bernard Klaassen

Het was in jullie praktijk in de Tjalk 17 te Huissen dat ik als 5-jarig jongetje zei: " Ik wil ook dokter worden". Uit je oude Sobotta’s in het Duits heb ik de anatomie me eigen gemaakt. Je arbeidsethos, je medische ethiek, moraal en je feitelijke kennis van de geneeskunde is bewonderenswaardig. Ik vind het fantastisch dat ik ook nog met je heb kunnen samenwerken als collega en ik hoop dat je nieuwe gepatenteerde speculum een succes wordt. We zien en spreken elkaar gelukkig regelmatig. Dat we samen met Ilse en de kinderen aan de vooravond van de semi-Paris gedineerd hebben op de Seine en ik je zondagochtend op het nippertje nog kon vinden in de mensenmassa bij de finish van de semi-Paris bij Chateau de Vincennes vorig jaar, vond ik gewoonweg fantastisch! Onbetaalbaar.

Tante en collega Elisabeth van den Hengel

Jij stond er toen niemand anders er had moeten staan. Onmisbaar. Zonder jou had ik nooit de overstap van Antwerpen naar Amsterdam aangedurf. Jij hebt me mijn eerste fotocamera gegeven en de liefde voor de foto en, niet onbelangrijk, mijn historisch besef al van jongs af aan verder aangewakkerd. Voor deze maar ook vele andere zaken ben ik je werkelijk altijd dankbaar gebleven.

Oom en collega Jelle Boomsma

Lang geleden heb je weleens gezegd op een van de familiefeestjes in het Mastbos in Breda dat het de kunst was voor enkele Boomsma’s om onze "originele" gedachten en orale uiteenzettingen op papier te zetten. Dan zouden we meer kunnen bereiken. Ik herken deze familie-eigenschap bij eenieder meer of minder aanwezig en probeer om deze lang geleden gegeven wijze raad zelf dagelijks op te volgen. Ik vertaal het nu meer in het afhechten van allerhande zaken en dat gaat nauwkeuriger, zorgvuldiger en gaat dus inderdaad beter als je het opschrijft en documenteert. Je steun en interesse in wat we doen in Isala is hartverwarmend.
Tom Karsten, mindset trainer
Je mind’set’trainingen -met ‘vriendelijke ogen’- zijn enorm waardevol geweest. Hierdoor is onder andere het werk lichter geworden, heb ik makkelijker keuzes kunnen maken en ben bovenal effectiever geworden. Gevoel in plaats van gedachten! Ik kan iedereen die ook van tennis houdt, jouw mind’set’methode van harte aanbevelen.

Mijn maten van de NRC (Nigtevechtse Runners Club!) Dick Broekhuis en Jeroen Wilting
We hebben wat afgehold rondom de Aetsveldse Polder. Heerlijk. Zonder jullie op de oprit was ik nooit zo vaak gaan hollen. Het heeft me geholpen heel wat frustraties op het asfalt weg te trappen. De halve marathon van Parijs hebben we al gedaan. Nu nog een keer een hele!

Schoonouders Hans Nieuwenhuizen en Corrie Meiling
Al 15 jaar lang zorgen jullie samen of apart op afwisselende dagen voor onze kinderen als Ilse en ik aan het werk zijn. Dat is voor de kinderen natuurlijk heerlijk geweest, een bron van rust, daarmee hebben jullie ze wortels gegeven om te groeien en vleugels om uit te slaan. Ik vond het zelf altijd een rustig gevoel dat jullie de huiselijkheid verschaffen op de dagen dat wij er niet konden zijn. Daar heb ik de vele dagelijkse kilometerrijden naar het ziekenhuis wel voor over alsmede de regelmatige overnachtingen in de piketkamer. Het is niet in de laatste plaats aan jullie te danken dat de “ruimte” ontstond om dit proefschrift tot stand te laten komen. Dank voor al die zorgzame jaren en ik hoop dat we nog lang van elkaar kunnen blijven genieten.

Pleegouders Toon en Petronel Koevoets
Jullie hebben je huis en gezin voor mij als puber opengesteld. In de tijd dat ik bij jullie woonde, hebben jullie mij de rust en gemoedelijkheid geboden die ik nodig had. Jullie zijn onderdeel geworden van mijn identiteit. Ik ben ongelooflijk dankbaar voor en tevreden met de relatie die we met elkaar hebben opgebouwd en hoop nog lang van jullie nabijheid binnen ons gezin te kunnen genieten.

De Boomsma-tjes Sophia, Julianne, Justus en Benjamin
Sophia de oudste, je doet in alles wat je doet je best en als je viool speelt in de studeerkamer kan ik van de noten die ’s avonds door het huis vliegen echt enorm genieten. Julianne, kleine regelaar, je hebt je zaakjes altijd voor elkaar, altijd op tijd. Je rake observaties verwonderen mij elke keer weer en doen mijn mondhoeken krullen! Justus, de kleine “Bohemien” van de familie, het liefst zou je met je rugzak vandaag nog de wereld rond gaan trekken. Dat is iets waar je Papa en Mama zich wel een beetje in herkennen! Gelukkig is school iets wat je wel steeds meer lijkt te gaan waarderen.
Benjamin, de kleinste van het spul, je weet je goed staande te houden in al dat sociale geweld dat af en toe plaatsvindt in ons gezin. Jij staat duidelijk je mannetje! "Op naar de sterren en verder!"

Ilse Nieuwenhuizen-Boomsma
Lieve Ilse. Op het moment van schrijven ben ik al langer samen met jou dan dat ik geleefd heb zonder je nabijheid. Dankbaar en tevreden ben ik dat ik je al zo vroeg heb leren kennen en dat we sindsdien altijd samen zijn gebleven.

Behalve mijn levenspartner ben je ook een kritische collega. We delen dezelfde moraal en dat is wat ons verbindt. Je uittreksels tijdens onze studie waren voor mij van onschatbare waarde. Jij steunt me nu nog altijd in de dingen die ik wil en moet doen en dat ervaar ik als een enorme rijkdom.

Van het begin af aan wist je me echter ook altijd te wijzen op het belang van het hier en nu in ons privéleven. Aandacht voor ons innerlijke gevoelsleven, onze existentie. Je steun en kritische blik op allerlei zaken gaan eigenlijk hand in hand en plaatsen alles in een gezond perspectief en daardoor blijft ons leven goed in balans. Dat komt het werk ook allemaal ten goede.

De tijd is snel gegaan en we genieten nu dagelijks van het wel en wee van Sophia, Julianne, Justus en Benjamin. Het leven met jou is voor mij op werkelijk geen enkel moment saai geweest. Het is nog steeds een doorlopende ontdekkingsreis, waarbij we samen plannen maken, projecten aanpakken en we dagelijks zelf de slingers ophangen. Voor dit alles en nog veel meer heb ik je meer dan lief. Je Martijn.
Appendix

6. OVER DE AUTEUR


Aansluitend is hij toegetreden tot de Maatschap Radiologie in Isala te Zwolle. In Isala heeft hij zich vanaf april 2013 naast zijn dagelijkse klinische werkzaamheden als radioloog beziggehouden als researchcoördinator met de ontwikkeling van researchtrajecten binnen de radiologie Isala, hetgeen tot op heden heeft geresulteerd in onderzoekstrajecten voor 4 promovendi.

In deze periode heeft het wetenschappelijke deel van het partnership van Isala met Philips een aanvang genomen en is een partnership tussen de Radiologie en de TU Twente gerealiseerd. Dit heeft geleid tot succesvolle afstudeerprojecten van twee Technische Geneeskunde studenten onder zijn begeleiding.

Daarnaast behaalde hij in juni 2015 zijn Europese registratie als Musculoskeletaal Radioloog.

Hij heeft zich ingespannen om de fusie van de Radiologie met de Nucleaire Geneeskunde binnen Isala te realiseren eind 2014 voor de start van de CORONA opleiding. Onder zijn leiding verkreeg Isala in mei 2015 de opleidingsbevoegdheid voor de Radiologie. Sindsdien houdt hij zich als opleider bezig met de implementatie van de opleiding Radiologie binnen de oude HORA en nieuwe CORONA opleidingsstructuur.
HEAVY READING IN HEAVY METAL

Martijn Franklin Boomsma

Unraveling the mystery of hip tissue in Metal on Metal Total Hip Arthroplasty