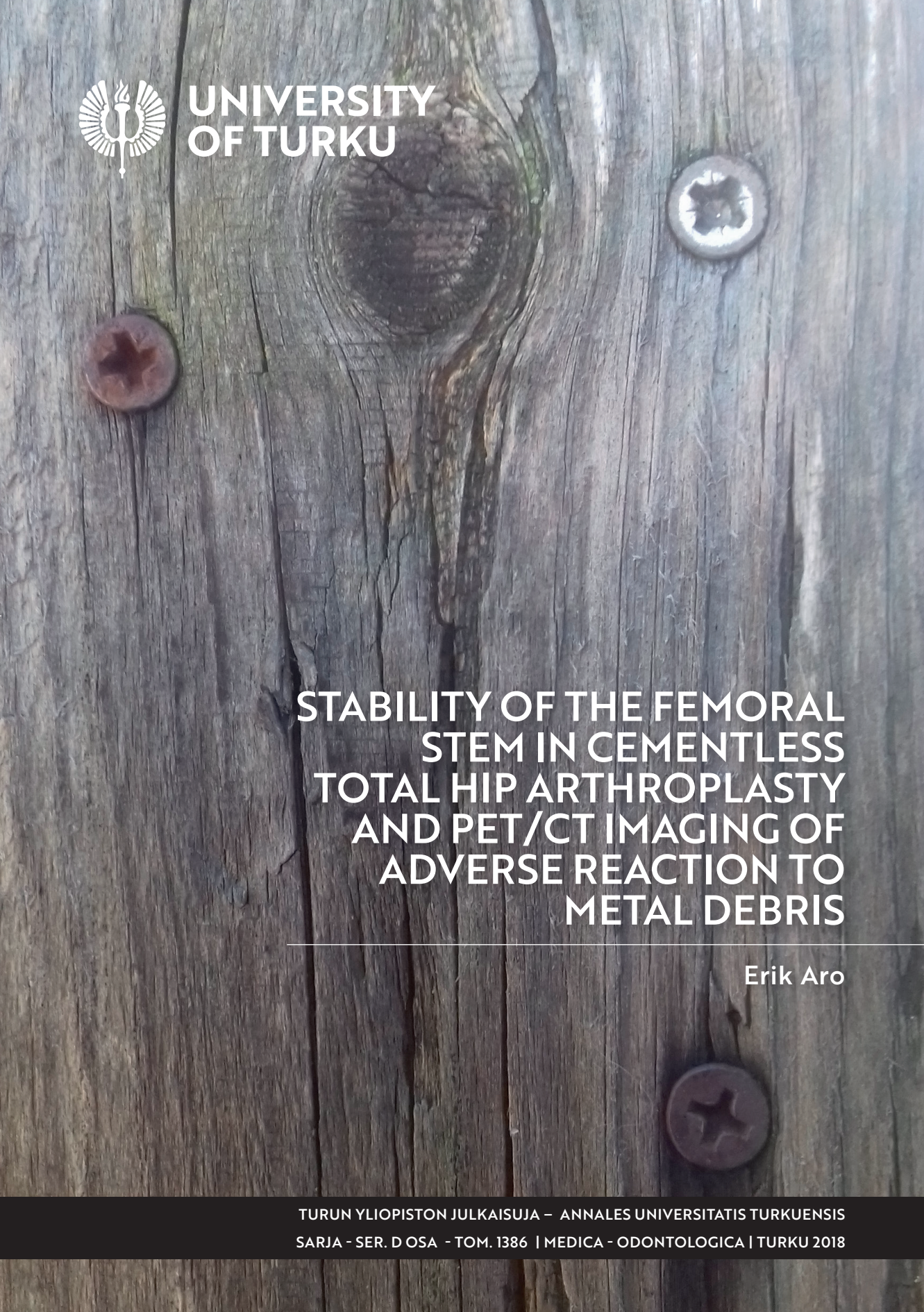

UNIVERSITY OF TURKU

# STABILITY OF THE FEMORAL STEM IN CEMENTLESS TOTAL HIP ARTHROPLASTY AND PET/CT IMAGING OF ADVERSE REACTION TO METAL DEBRIS

Erik Aro

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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To my mother Anne and to my father Hannu

# ABSTRACT

Erik Aro
STABILITY OF THE FEMORAL STEM IN CEMENTLESS TOTAL HIP ARTHROPLASTY AND PET/CT IMAGING OF ADVERSE REACTION TO METAL DEBRIS

University of Turku, Faculty of Medicine, Clinical Physiology and Nuclear Medicine, Orthopaedics and Traumatology, Doctoral Programme in Clinical Research, Turku PET Centre, Turku University Hospital

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The outcome of cementless total hip arthroplasty (THA) in aging women is challenged by impaired bone quality as it can jeopardize implant fixation and stability. Implant migration can be evaluated by means of radiostereometric analysis (RSA), which represents the first object of interest in this thesis. The second object of interest is the positron emission tomography with computed tomography (PET/CT) imaging of adverse reaction to metal debris (ARMD). Metal-on-metal hip arthroplasties generate wear debris that causes periprosthetic tissue inflammation and damage. PET/CT detects sites of inflammation, and therefore could be applicable in the diagnostics of ARMD.

In the first two studies, aging females suffering from hip osteoarthritis underwent cementless THA. Preoperative bone mineral density (BMD) assessment showed low BMD in most of the subjects. The first study evaluated the stability of the femoral stems in a nine-year follow-up. The second placebo-controlled trial evaluated the effects of an antiresorptive drug, zoledronic acid, on femoral stem migration and periprosthetic BMD in a four-year follow-up. The third exploratory, controlled, open-label study characterized the PET/CT imaging findings of symptomatic ARMD patients with [$^{18}$F]FDG and [$^{68}$Ga]Citrate.

The femoral stems did not show significant late migration. Zoledronic acid did not inhibit early implant migration but it reduced periprosthetic bone loss. The cementless femoral stems are stabile even in aging women. The inflammatory ARMD is better visualized with [$^{18}$F]FDG than with [$^{68}$Ga]Citrate.

**Key words:** Cementless total hip arthroplasty, bone quality, radiostereometric analysis, implant stability, zoledronic acid, adverse reaction to metal debris, positron emission tomography

# TIIVISTELMÄ

Erik Aro
SEMENTITTÖMÄN LONKAN TEKONIVELEN STABILITEETTI JA METALLIHIERREKOMPLIKAATION PET/TT-KUVANTAMINEN

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen fysiologia ja isotooppilääketiede sekä Ortopedia ja traumatologia, Kliininen tohtoriohjelma, Turun PET-keskus, Turun yliopistollinen keskussairaala

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Sementittömän lonkan tekonivelleikkauksen onnistumista ikääntyvillä naisilla voi uhata heikentynyt luunlaatu, joka on riski tekonivelen kiinnittymiselle ja stabiliteetille. Tekonivelen liikettä voidaan arvioida radiostereometrisellä analyysillä. Sementittömän lonkan tekonivelen stabiliteetti ikääntyvillä naisilla on väitöskirjan ensimmäinen tutkimusaihe. Toisena tutkittavana aiheena on metallihierrekomplikaation kuvantaminen positroniemissiotietokonetomografialla (PET/TT). Metalli-metalli-liukupintaisista lonkan tekonivelistä irtoaa metallihierrettä, joka voi aiheuttaa tekoniveltä ympäröivien kudosten tulehdusta ja vaurioita. PET/TT soveltuu tulehduksen kuvantamiseen, ja se voisi auttaa metallihierrekomplikaatioiden diagnostiikassa.

Kahteen ensimmäiseen osatyöhön valittiin lonkan nivelrikkoa sairastavia naisia. Suurella osalla potilaista todettiin alentunut luuntiheys ennen tekonivelleikkausta. Ensimmäisessä osatyössä arvioitiin sementöimättömän lonkan tekonivelen varsiosan myöhäisvaiheen stabiliteettia yhdeksän vuoden seurannassa. Toisessa osatyössä arvioitiin, vähentääkö luukatolääke tsoledronihappo varsiosan leikkauksen jälkeistä liikettä sekä estääkö tsoledronihappo luuntiheyden laskua varsiosan ympärillä neljän vuoden seurannassa. Kolmannessa osatyössä arvioitiin PET/TT:ssa käytettävien tulehdusmerkkiaineiden, [$^{18}$F]FDG:n ja [$^{68}$Ga]sitraatin, kerääntymistä oireisilla metallihierrekomplikaatiopotilailla.

Tekonivelen varsiosassa ei tapahtunut merkittävää myöhäisvaiheen liikettä. Tsoledronihappo ei pienentänyt varsiosan alkuvaiheen liikettä, mutta vähensi luuntiheyden laskua varsiosan ympärillä. Sementitön lonkan tekonivel on stabiili myös ikääntyvillä naisilla. Tulehduksellinen metallihierrekomplikaatio kuvautuu paremmin [$^{18}$F]FDG:lla kuin [$^{68}$Ga]sitraatilla.

**Avainsanat:** Sementitön lonkan tekonivelleikkaus, luun laatu, radiostereometrinen analyysi, tekonivelen stabiliteetti, tsoledronihappo, metallihierrekomplikaatio, positroniemissiotietokonetomografia

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# ABBREVIATIONS

| | |
|---|---|
| [$^{18}$F]FDG | 2-deoxy-2-[$^{18}$F]fluoro-D-glucose |
| [$^{68}$Ga]Citrate | $^{68}$Gallium-citrate |
| 95% CI | 95% confidence interval |
| ABG | Anatomic Benoist Girard |
| ALVAL | Aseptic lymphocytic vasculitis-associated lesion |
| ARMD | Adverse reaction to metal debris |
| BMD | Bone mineral density |
| CN | Condition number |
| CRP | C-reactive protein |
| DXA | Dual X-ray absorptiometry |
| EBRA-FCA | Einzel-Bild-Roentgen-Analyse-femoral component analysis |
| ESR | Erythrocyte sedimentation rate |
| HHS | Harris hip score |
| HRA | Hip resurfacing arthroplasty |
| MARS MRI | Metal artifact reduction sequencing magnetic resonance imaging |
| ME | Mean error of rigid body fitting |
| MoM | Metal-on-metal bearings of hip arthroplasty |
| P | Probability |
| PAFF | Periprosthetic atypical femoral fracture |
| PET/CT | Positron emission tomography with computed tomography |
| RMANCOVA | Repeated measurement analysis of covariance |
| ROI | Region of interest |
| RSA | Radiostereometric analysis |
| SD | Standard deviation |

| | |
|---|---|
| $SUV_{max}$ | Maximum standardized uptake value |
| THA | Total hip arthroplasty |
| VAS | Visual analogue scale |
| WOMAC | Western Ontario and McMaster Universities Osteoarthritis Index |

# LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I–III.

I Aro E, Alm J, Moritz N, Mattila K, Aro H. Good stability of a cementless, anatomically designed femoral stem in aging women: A RSA study of 32 patients. Acta Orthop. 2018 Jul 10. Epub ahead of print.

II Aro E, Moritz N, Mattila K, Aro H. A long-lasting bisphosphonate partially protects periprosthetic bone but does not enhance initial stability of uncemented femoral stems: A randomized placebo-controlled trial of women undergoing total hip arthroplasty. J Biomech. 2018 Jun 25;75:35-45.

III Aro E, Seppänen M, Mäkelä K, Luoto P, Roivainen A, Aro H. PET/CT to detect adverse reaction to metal debris in patients with metal-on-metal hip arthroplasty: an exploratory prospective study. Clin Physiol Funct Imaging. 2018 Sept 38;5:847-855.

# 1 INTRODUCTION

Over 250000 people in Finland have functional impairment due to hip osteoarthritis, a disease that earlier used to turn patients bed-ridden. The treatment of hip osteoarthritis, has been revolutionized by total hip arthroplasty (THA), accounting for more than 86% of the indications for primary THA in Finland. It is considered as one of the most successful and frequently undertaken elective surgeries with over 9000 annual primary THA implantations in Finland (Finnish Arthroplasty Register, 2017). Excellent functional outcomes are reported in terms of pain relief and restored function.

It is of primary importance to avoid revision surgery as its outcome is significantly worse than in primary implantations. Two major factors contributing to the survival of THA are (1) the successful fixation of the prosthesis to the surrounding bone and (2) to minimize the wear of the weight-bearing surfaces.

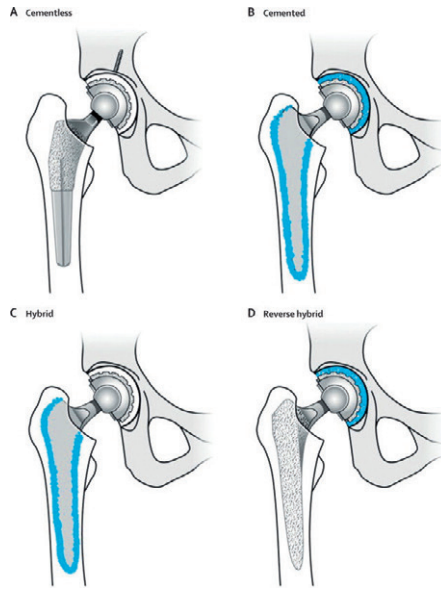


**Figure 1** Total hip arthroplasty (THA) consists of a femoral stem and an acetabular cup. Their fixation design can be either (A) fully cementless, (B) fully cemented, (C) hybrid design with a cemented stem and cementless cup, or (D) reverse hybrid design with a cemented cup and cementless femoral stem (Pivec et al. 2012).

One of the main advantages of cementless THA is the theoretical life-long biologic fixation of the prosthesis to the bone. As a living tissue, the bone first integrates the prosthesis into itself in a biological process called osseointegration. It was described more than 100 years ago: "-- in the course of time, the bone would grow in, around and through the frame --". The long-term stability of the cementless THA is based on a stable bone-prosthesis interface that is maintained intact by bone remodeling under the constant cyclical loading forces to "-- be held securely in position" (Greenfield 1909).

Bone quality is essential ensuring the long-term outcome of the THA (Russell 2013) as osteoporosis has been found as risk factor for complications (Stihsen et al. 2017). Cementless THA was originally designed to patients with normal bone structure and healing capacity. Due to the aging population, the coexistence of conditions treated by arthroplasty, such as osteoarthritis, and conditions leading to decreased quality of bone, such as senile osteoporosis, presents a growing challenge for the clinical outcome of arthroplasty (Huang et al. 2016). Despite the growing use of cementless THA in low bone quality, little is known about the osseointegration and stability of the cementless femoral stem in this high-risk population for complications (Aro et al. 2012).

In addition to having preoperatively low quality of bone, patients undergoing THA are subject to further periprosthetic bone loss postoperatively. Two main factors leading to periprosthetic bone loss are stress shielding, which is a physiologic response to the changing biomechanical forces applied to the bone leading to a bone remodeling process (Behrens et al. 2017). Another factor for periprosthetic bone loss is osteolysis due to inflammatory wear debris released from the prosthesis (Santavirta et al. 1990). The periprosthetic bone loss has two possible complications leading to implant failures: aseptic loosening and periprosthetic fractures (Arabmotlagh et al. 2009), which account up to 75% of the indications for revision arthroplasties (Furnes et al. 2001).

Bisphosphonates inhibit bone resorption and are approved for the prevention and treatment of osteoporosis. In cementless THA, bisphosphonates have shown to reduce periprosthetic bone loss. However, there is still lack of direct evidence that bisphosphonates improves clinically relevant outcomes, despite cohort studies have associated bisphosphonate use to improved THA survival (Friedl et al. 2009).

Radiostereometric analysis (RSA) is the golden standard for the measurement of implant migration – a biologic phenomenon that is thought to contradict osseointegration (Ryd 2006). In cementless femoral components, RSA-measured stem migration has good diagnostic capabilities to detect risk for later aseptic loosening and therefore RSA has a role predicting implant survival (Streit et al. 2016).

The choice of bearings is essential in hip arthroplasty as materials have different properties. As a low wear option, metal-on-metal (MoM) hip arthroplasties became quickly popular early in this millennium to achieve better function, less dislocations and improved survival of the prosthesis especially for the physiologically demanding and physically active young population.

Surprisingly, the premises turned out to be flawed. The bearings create metal wear debris that formed a new disease entity, adverse reactions to metal debris (ARMD). Due to its inflammatory and necrotic nature, it is locally destructive and is associated with early failures of the prosthesis. The wide clinical presentation challenges the differential diagnostics, follow-up and treatment of ARMD (Haddad et al. 2011).

Positron emission tomography with computed tomography (PET/CT) can be used for the imaging of infectious and noninfectious foci. There are no previous controlled studies on the PET/CT imaging on the emerging disease of ARMD.

# 2 REVIEW OF LITERATURE

## 2.1 Stability of the femoral stem in cementless total hip arthroplasty

The cementless design represents a truly biologic method of fixation of the prosthesis to the bone. During surgery, an initial press-fit fixation is applied for the early stability of the implant. The lack of early stability has been considered to increase implant migration and interfere the final bone ingrowth, osseointegration (Friedl et al. 2009). The stability and therefore survival of uncemented THA is excellent being over 90% at 10 years, especially the uncemented femoral component performs well (Hailer et al. 2010, Mäkela et al. 2014).

### 2.1.1 *Osseointegration: what the bone does to the prosthesis*

Osseointegration derives from the Greek *osteon*, bone, and the Latin *integrare*, to make whole. Osseointegration defines the phenomena of bone's ability to biologically integrate an implant to the bone by forming a direct osseous interface without intervening soft tissue leading to long-term mechanical stability (Albrektsson et al. 1981, Kienapfel et al. 1999).

The history of osseointegration begins in 1909 in dentistry when a patent was applied for a metallic cage-like framework for an artificial tooth for implantation. It was suggested that "in the course of time, the bone would grow in, around, and through the frame, and the latter would, therefore, be held securely in position" (Greenfield 1909).

In 1940 osseointegration was introduced to orthopedics as researchers applied titanium screws in rat femur. They noted that at the end of six weeks, the screws were tighter fused to the femur than when originally put in. At 12 weeks, the screws were difficult to remove and at 16 weeks, the screws were so tight that in one specimen the femur fractured attempting to remove the screw. Microscopic evaluation of the bone showed no reaction to the implant (Bothe et. al 1940).

Biomechanically the most important parameters for a successful osseointegration of cementless THA are gaps at the implant-bone interface implying the importance of direct bone and implant contact (Sandborn et al. 1988, Dalton et al. 1995) and micromotions (Engh et al. 1992, Jasty et al. 1997). Periprosthetic micromotions under 40 μm have been implicated in the successful bone formation and osseointegration, while micromotions over 150 μm causes the excessive formation of fibrous tissue periprosthetically (Jasty et al. 1997). In addition, the strength of

the osseointegration increases with time after implantation and bone ingrowth depth (Tarala et al. 2013). It is maintained under the constant cyclical loads by remodeling of the bone in areas of disruption (Kienapfel et al. 1999, Garino and Beredjiklian 2007).

Different prosthesis designs are used to maximize early stability and osseus contact for osseointegration (Khanuja et al. 2011). The prosthesis are designed to have irregular surfaces, which encourage the establishment of a rigid bone-prosthesis interface by two mechanisms: in-growth and on-growth of bone. In-growth of the bone happens in the microscopic pores of varying depth in the porous coating. On-growth of the bone happens on the indentations created by plasma spray or grit blasting of the prosthesis (Mirza et al. 2010).

Physiologically the bone responses to a porous-coated implant by occupying the void spaces of the porous implant with hematoma formation and subsequent development of mesenchymal tissue. Later it is replaced with woven bone followed by the final lamellar bone remodeling without an intermediate fibrocartilaginous stage (Kienapfel et al. 1999). The implant coatings differ in the capabilities to induce bone-forming cells to proliferate, differentiate and produce extra-cellular matrix (Wilke et al. 1998).

Osseointegration of the cementless femoral component can be assessed from plain radiographic images using Engh's classification (Engh et al. 1990). In addition, radiostereometric analysis (RSA) has been used to evaluate the osseointegration of cementless femoral stem (Ryd 2006).

#### 2.1.1.1 *RSA imaging of the migration of the cementless femoral stem*

Radiostereometric analysis (RSA), developed in 1974 (Selvik 1989), is a method that allows *in vivo*, three-dimensional measurement of migration of orthopedic implants, such as THA. Migration is an important predictor of long-term fixation and therefore it can be used as an early warning sign for failure (Bottner et al. 2005). It has been stated that the late-occurring aseptic loosening is rather a consequence of late detection than late loosening (Mjöberg 1991). For this indication, RSA allows as early as 1-2 years postoperatively evaluate future aseptic loosening and therefore the long-term survival of the implant (Valstar et al. 2005).

In cementless THA, RSA has been applied in the development of implants and their coatings, and in stydying the weight-bearing regimes in the postoperative mobilization of THA patients (Soballe et al. 1993, Kärrholm et al. 1994, Bottner et al. 2005).

For RSA measurements, patients receive intraoperatively an implant with RSA markers and respective tantulum markers in the periprosthetic bone. During the RSA measures, two x-ray beams are used determine the position of the markers, and later their relative movement (Bottner et al. 2005). Due to its dependency on markers, RSA is applicable only for prospective studies evaluating implant migration.

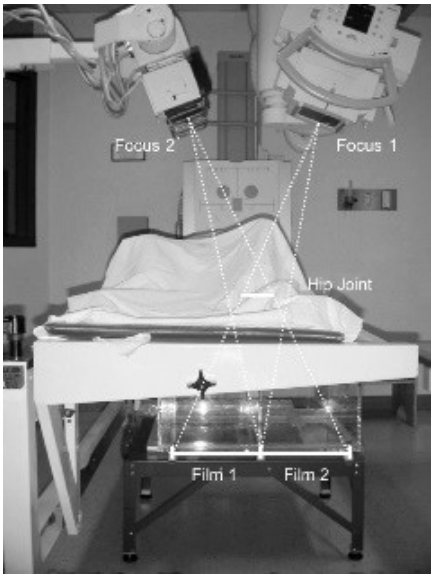


**Figure 2** Set-up for an RSA X-ray. The hip joint is positioned in the focus of two X-ray machines for an exact location of the object in space (Bottner et al. 2005).

RSA is extremely accurate and can detect migrations with an accuracy of 0.2 mm for translations and 0.5 degrees for rotations (Soballe et al. 1993). Therefore, RSA can be used in relatively low numbers of subjects, e.g. 15-25 patients in each group in randomized studies to predict future aseptic loosening. In comparison, Einzel-Bild-Roentgen-Analyse-femoral component analysis (EBRA-FCA) and plain radiograph need respective movements of 1.0-1.5 mm and 5 mm to detect a change in position. In addition, EBRA-FCA and plain radiographs cannot detect rotation of the femoral stem (Sutherland et al. 1982, Biedermann et al. 1999).

Unlike with cemented femoral stems (Kärrholm et al. 1997), there is very limited data on the correlation of early migration, defined as the migration during the first two postoperative years, of the cementless femoral component and later aseptic loosening. A recent meta-analysis concluded that the data is insufficient to provide robust conclusions (van der Voort et al. 2015). Absolute early migration is different depending on the stem design, implant design, fixation method and other circumstances, such as if bone graft has been used (Kärrholm 2012). However, the

data gathered suggest that femoral stems migrate to some extent during the first year, but in well-functioning stems the migration slows down, while continuing rapid early migration is said to predict loosening (Streit et al. 2016).

RSA studies conducted up to 6 years postoperatively show on cementless femoral stems that clinically successful stems stop migrating after the stabilization period of 3-6 months (Thien et al. 2007, Callary et al. 2012, Sköldenberg et al. 2014). However, there can be small micromovement, the amount of which tolerated depends on patient- and implant related factors (Viceconti et al. 2006), which can be seen in clinically stable stems (Nysted et al. 2014). Especially in the y-axis, there can be translation (proximal / distal) and rotation (retroversion / anteversion) movement without associated clinical problems (Wolf et al. 2010).

The quality of interpretation of RSA data is of utmost importance. Results should be assessed by an experienced reviewer. Defining specific thresholds should be nuanced and related to stem fixation and design as excessive average migration does not always predict implant failure in general. The interpretation of RSA results should be describing the migration pattern of the specific stem design. Therefore, the expected migration pattern of the stem should be stated in the hypothesis. In addition, an universal way of interpreting outliers could improve the predictive value of RSA (de Vries et al. 2014).

Krismer et al. studied with EBRA-FCA method both cemented and cementless femoral components up to 96 months (Krismer et al. 1999). They found a similar 1.5 mm threshold migration during the first two years predicting later aseptic failure. More importantly, they recognized different migration patterns, which are illustrated in the figure below.

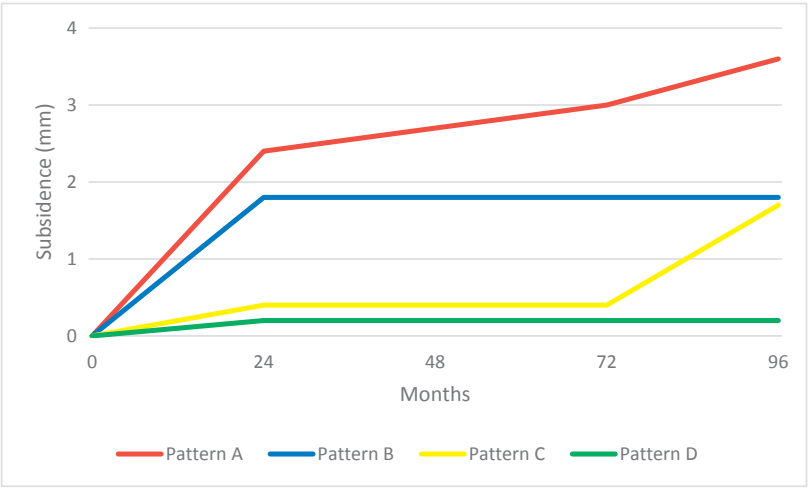


**Figure 3** In cementless designs, Krismer et al. found four migration patterns. A pattern represents early onset with continued subsidence (8% of patients), B represents early onset with subsequent stabilization (21%), C represents initial stability with late onset of subsidence (3%), and D represents stability throughout the whole period of observation (68%). Patterns B and D did not lead to any subsequent revisions, while 20-29% of patterns A and B were revised during the 10-year follow-up. The authors discussed that the lack of initial fixation is not the only cause of failure of the stem, but also wear, foreign-body reactions and granulomas can explain the late-occurring migration and failures in pattern C. In addition, the data show that cementless designs do not always subside to obtain better bone contact like in pattern D, while in pattern B secondary stabilization occurs (Krismer et al. 1999).

After the meta-analysis by van der Voort, one thorough study of 158 cementless femoral stems studied by EBRA-FCA on the early migration of the stem and later aseptic loosening with a 21-year follow-up has been published (Streit et al. 2016). The study revealed that at 24 months postoperatively, stems that had aseptic loosening had significantly higher migration than components that remained well-fixed (4.2 mm ± 3.1 mm vs 0.8 mm ± 0.9 mm). Early migration, measured at 24 months, had good diagnostic capabilities to detect aseptic loosening during the first and early second, but not late second or third, decades of surgery. Stems that have

sufficient stability initially may be compromised later by other factors such as bone loss and remodeling or osteolysis.

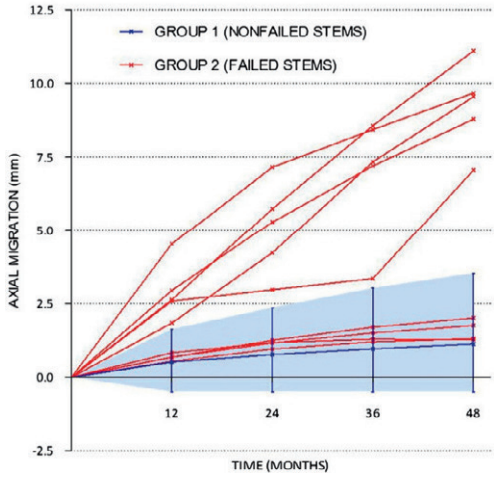


**Figure 4** Not all stems showing later aseptic failure migrate early. The graph shows axial migration of the individual components during the first 48 postoperative months. All failed components (n = 9) are shown by solid red lines. Mean migration of well-performing stems (n = 73) is shown by the solid blue line. The blue shaded area contains the 95% range of axial migration shown by all well-performing stems (Streit et al. 2016).

### 2.1.2 *Bone quality in the stability of cementless THA*

Bone quality is defined as the sum of characteristics that affect the resistance of bone to fracture (Fyhrie 2005). Osteoporosis is a phenomenon defined by decreased bone mass and alterations of microarchitecture. Such changes lead to an increased fragility of bone and subsequently increased the risk of fracture matching the definition of lowered quality of bone (Russell 2013).

Osteoarthritis and osteoporosis are the two most common joint and bone conditions in the elderly (van Staa et al. 2001). Dual-energy X-ray absorptiometry (DXA) studies have shown that roughly 2/3 of patients scheduled for cementless THA have a low bone mass density (BMD) indicating osteopenia or osteoporosis (Glowacki et al. 2003, Mäkinen et al. 2007).

The relationship between aging and lowered bone quality is evident. All structural materials that undergo cyclical loading are subject to fatigue. To prevent these fatigue changes from progressing, bone induces repair of microdamage by

remodeling so that the damaged bone is removed and is replaced by new undamaged bone (Parfitt 2001). However, the remodeling of the bone is imperfect after the age of 40 years, because each cycle replaces less bone that was removed (Riggs and Melton 1992).

Lowered quality of the bone may compromise longevity of the cementless THA. Excessive amounts of periprosthetic bone loss may result to (1) intra- and (2) postoperative periprosthetic fractures, (3) implant migration and (4) aseptic loosening. In addition, revision surgery may be complicated with less bone stock (Kröger et al 1998, Russell 2013, Stihsen et al. 2017).

The bone-implant interface has to withstand high shear stresses of physiological loading and poor peri-implant bone quality may be a risk for successful osseointegration (Gabet et al. 2010). There are only few clinical studies on the effect of bone mass density in the migration of the cementless femoral stem.

Rhyu et. al studied whether osteoporosis, defined as age more than 70 years or DXA T-score under -2.5, affected the early subsidence of cementless femoral component compared to patients with age less than 50 years with no disease affecting the quality of bone (Rhyu et al. 2012). At 1 year, osteoporotic patients had an average subsidence of 0.94 ± 0.74 mm, while the control group had 1.19 ± 1.18 mm. There was no statistical difference between groups in the terms of the occurrence of migration more than 3 mm.

Aro et. al studied in a 2-year RSA follow-up study whether low BMD, defined as T-score under -1.0, affects the implant migration in cementless THA due to osteoarthritis compared to patients normal BMD. Patients with low BMD had higher subsidence of the stem during the first three postoperative months, after which it stabilized in both groups at 0.5 mm in normal BMD and 1.3 mm in low BMD in the 2-year follow-up (Aro et al. 2012).

Sköldenberg et al. showed in a 2-year RSA and DXA study in patients operated on cementless THA due to femoral neck fracture that low BMD correlates with more postoperative migration. Patients with low BMD, defined as T-score under -1.0, had higher mean maximum total point movement of 2.4 mm compared to 1.4 mm in patients with normal BMD at three months, after which the migration stopped (Sköldenberg et al. 2011).

Another study conducted by Sköldenberg et al. showed in a 4-year RSA and DXA follow-up study that patients with a femoral neck fracture treated with a reverse hybrid THA with a cementless stem fixation suffer considerable periprosthetic bone loss. This bone loss did not affect the implant stability measured with RSA, however the clinical problem was high number of late-occurring periprosthetic

fractures. This study suggests that stress-shielding leads clinically to the high incidence of periprosthetic fractures in high-risk patients, even though the stem can easily achieve firm fixation even in osteoporotic bone (Sköldenberg et al. 2014).

#### 2.1.2.1 *Complications of low bone quality in cementless THA*

##### *2.1.2.1.1 Osteolysis and aseptic loosening*

Prosthesis form particulate wear debris of its material. Especially component malposition, but also patient activity level, implant material, and component design affect the amount of wear debris (Callanan et al. 2011). If the prosthesis is not stable and has enough mobility to increase the effective articular space, it enables the migration of inflammatory debris particles in the bone-prosthesis interface (Schmalzried and Callaghan 1999).

Such debris recruits and activates osteoclasts and macrophages releasing osteolytic cytokines (Tuan et al. 2008) and inhibits osteoblastic activity leading osteolysis. Osteolysis is therefore presented as an osteoclast-mediated bone resorption at the bone-implant interface. It allows further micromotion of the prosthesis leading to more particle wear, loosening and possibly subsequent implant failure (Wang et al. 2004).

Osteolysis can be diagnosed from plain radiographs (Figure 5). It may be asymptomatic, while pain might be a sign that the bone loss has lead implant migration with decreased mechanical support. Complications of osteolysis include aseptic loosening and periprosthetic fractures leading ultimately to a failure of the prosthesis (Iannotti et al. 1986).

Aseptic loosening is diagnosed clinically with patient-reported start-up pain. However, differential diagnostics with periprosthetic joint infection is important (Parvizi et al. 2011). Aseptic loosening is a sum of multiple pathways leading to implant failure including osteolysis and mechanical failure of the fixation (Canale and Beaty 2013). It is treated by replacement of loose components and correction any component malalignment. Aseptic loosening accounts for over 50% of the revision surgeries in THA (Sadoghi et al. 2013). Femoral stem revision with long-stem cementless component has shown good outcomes (Hartman and Garvin 2011).

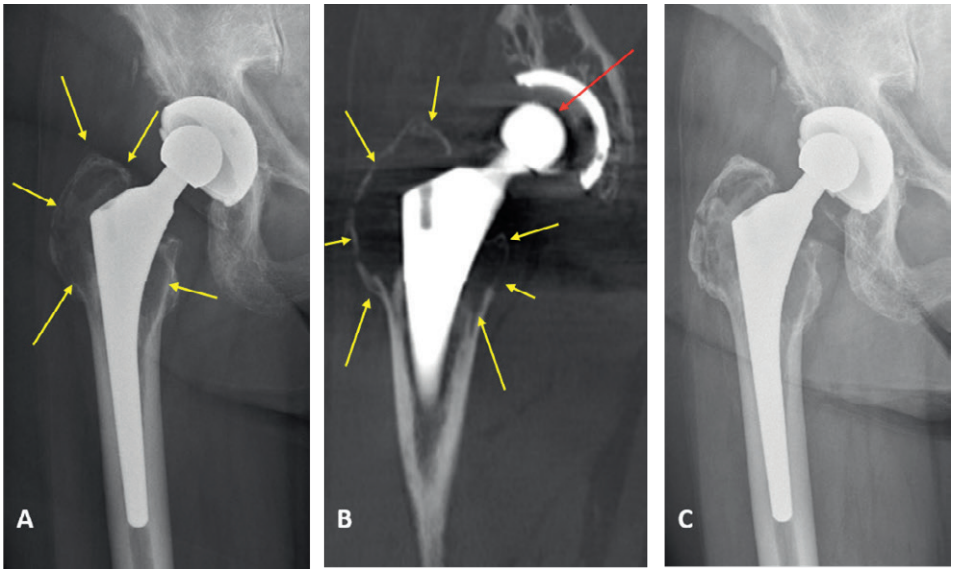


**Figure 5** 81-year-old women with osteoathritic of the right hip. (A) 10 years after cementless THA there were large osteolytic lesions of the greater and lesser trochanteric regions of the proximal femur (yellow arrows) due to wear of the polymer liner of the acetabular cup (red arrow). (B) CT imaging confirmed osteolysis and thinning of the cortical bone with an undisplaced fracture (yellow arrows) and the asymmetric position of the femoral head due to wear of the cup liner. (C) After two annual infusions of zoledronic acid, given partly for treatment of Paget disease of the contralateral hip, the osteolytic lesions showed progressive consolidation and the patient was asymptomatic at 15 years postoperatively.

#### *2.1.2.1.2 Periprosthetic fractures*

Periprosthetic bone loss can adversely affect the survival of the prosthesis causing periprosthetic fractures, which can occur both intra- and postoperatively (Huang et al. 2016). Even though some periprosthetic fractures can be treated nonoperatively, periprosthetic fractures can be difficult to repair and recovery is slow. Complications and mortality are associated to periprosthetic fractures (Lindahl et al. 2007), and survivors often do not reach their previous level of mobility and suffer from pain (Russell 2013).

Periprosthetic fractures are the third most common reason, after aseptic loosening and infection, for revision surgery, with an overall incidence of approximately 4.1% and higher rates linked with revision THA and uncemented design (Berry 1999).

Typically, postoperative periprosthetic fractures occur years after implantation in low-energy trauma. In an arthroplasty registry study, periprosthetic fractures occurred 7.4 years after primary THA surgery, and 70% of the cases occurred in the presence of a loose component (Lindahl et al. 2005). In presence of severe osteolysis, more than 50% of patients will develop spontaneous fractures without pre-fracture symptoms (Lewallen and Berry 1998). Thus, loosening is the principal cause of periprosthetic fractures (Robinson et al. 2016).

### 2.1.3 *Periprosthetic bone loss: what the prosthesis does to the bone*

Bone tissue is biologically active with a continuous physiological turnover, which refers to the total volume of bone that is both resorbed and formed over a period of time (Parfitt 2002). In adults, this process leading to a turnover is called the remodeling of the bone. It is performed by basic multicellular unit containing clusters of bone-resorbing osteoclasts and bone-forming osteoblasts. Their cross-talk between other cells is mediated by hormones to maintain the integrity of human skeleton and mineral homeostasis. Mechanical stimulus affect highly this process of bone remodeling (Raggatt and Partridge 2010).

German anatomist and surgeon Julius Wolff stated in 1892 that “every change in the form and function of bone or of their function alone is followed by certain definite changes in their internal architecture, and equally definite alteration in their external conformation, in accordance with mathematical laws” (Frost 1994).

This is known as Wolff's law, which states that a bone in a healthy person will adapt to the loads under which it is placed. In hip arthroplasty, the clinical application of Wolff’s law is called stress shielding. It is a mechanical phenomenon, where implantation of the femoral component leads to an adaptive response in the structure and density of the periprosthetic bone to match the altered mechanical stimulus.

In stress shielding, a well-fixed femoral component, which is stiffer than the surrounding femur, bears the majority of the load originally directed on the proximal femur leading to bone resorption clinically seen as periprosthetic bone loss (Sumner 2015).

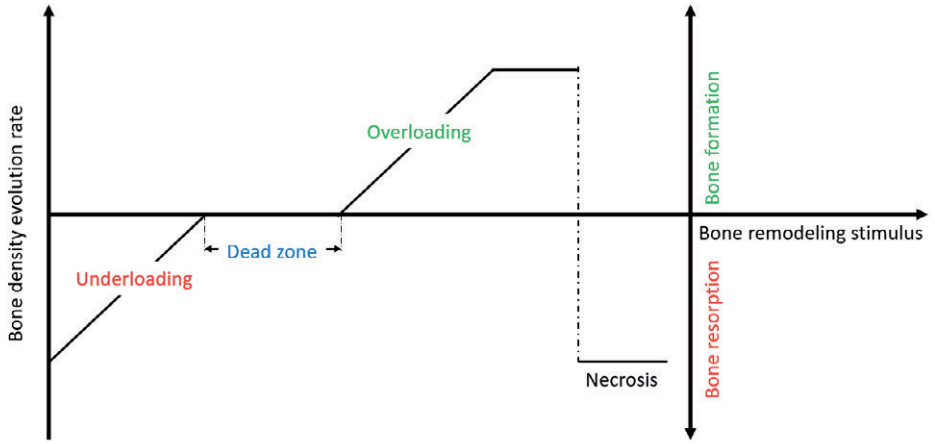


**Figure 6** Overloading of the mechanical stimulus leads to bone formation, where the bone will remodel itself to become stronger. Underloading leads to bone resorption, where the bone will become less dense and weaker due to the lack of stimulus required for continued remodeling. There is a so-called dead zone where the change of the mechanical stimulus doesn't lead to changes in bone density (Behrens et al. 2017).

Increased osteoclastic activity seems to be associated with periprosthetic bone loss (Willert and Buchhorn 1999). Periprosthetic bone loss occurs due to two main factors: (1) stress shielding discussed previously (Oh and Harris 1978) and (2) osteolysis caused by the inflammatory wear debris (Santavirta et al. 1990). In addition, the global effect of decreased loading of the limb may advance disuse atrophy of the bone (Bobyn et al. 2006) and the implantation itself may damage periprosthetic bone (Muratore et al. 2012).

Typically, in non-cemented femoral stems the periprosthetic bone loss varies between 0-30% (Knutsen et al. 2017), while the strongest bone resorption takes place on the proximomedial side of the prosthesis, calcar region, leaving distal parts unaffected (Behrens et al. 2017). Most of the periprosthetic bone loss happens during the first postoperative year, peaking at 3-6 months postoperatively, with little change thereafter (Brodner et al. 2004).

This local osteopenia progresses faster than the natural age-related loss of femoral bone (Boden et al. 2006). There are studies showing that low preoperative BMD aggravates periprosthetic bone loss (Nishii et al. 1997, Rahmy et al. 2004), however conflicting results exist (Aldinger et al. 2003, Sköldenberg et al. 2006).

Other factors influencing periprosthetic bone loss are stem design, including the shape, size, stiffness, surface type and its extent. Host factors influencing the bone

remodeling include the patient's diagnosis, health status, age, sex, medications, activity level as well as the physical properties of the femur receiving the stem (Engh et al. 1999, Sköldenberg et al. 2006).

However, whether periprosthetic bone loss around femoral stem truly has any influence on the survival of the THA, is still under debate as larger observational studies evaluating BMD with long follow-up are needed (Muren et al. 2015). Although there is no evidence that periprosthetic bone loss causes symptoms or complications, it is evident that large amount of – or continuous – bone loss may reduce the stability of the stem (Sköldenberg et al. 2006).

#### 2.1.3.1 *Bone quality assessed by DXA*

Clinically, bone quality is assessed by bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA). It is the preferred method for the early detection and treatment of osteoporosis to prevent osteoporosis-related fractures (Cosman et al. 2014). DXA measures the areal density (mass per area, $g/cm^2$) of hydroxyapatite, the main mineral component of the bone. Other factors contributing to bone quality are bone macro- and microarchitecture, tissue composition and microdamage (Seeman and Delmas 2006, Chapurlat and Delmas 2009).

As DXA measures only the areal density of hydroxyapatite in the bone, BMD explains only 70% of the variance in bone strength. Therefore it gives only a surrogate measurement of bone quality in the diagnosis, prognosis, and treatment of bone fragility syndromes, most notably postmenopausal osteoporosis (Ammann and Rizzoli 2003, Roux and Briot 2017). To date, there are no studies indicating the extent of periprosthetic BMD to account for periprosthetic bone quality.

With DXA, the intraindividual reproducibility of the BMD results is in the range of 1.8-7.5% (Iolascon et al. 2010). In addition, there are systemic discrepancies between the results that different densitometers produce (Hui et al. 1997).

Compared to patients without osteoarthritis, osteoarthritic patients have increased BMD (Hannan et al. 1993, Nevitt et al. 1995), however, their risk for fractures is increased (Arden et al. 1996, Bergink et al. 2003, Arden et al. 2006). One possible explanation for this is that osteoarthritic patients have a lower quality of bone due to changes in microstructure (Kamibayashi et al. 1995, Mansell and Bailey 1998).

Despite the importance of bone quality in THA, according to an international survey of practicing orthopedic surgeons 96% of which do not routinely measure BMD preoperatively (Maier et al. 2016).

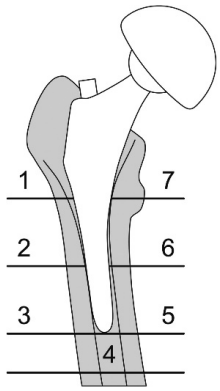


**Figure 7** DXA has been extended also to measure periprosthetic bone density and its loss. Periprosthetic bone density is measured in seven zones, named Gruen zones 1-7. Measuring the BMD at these respective regions of interest (ROI) allows the quantification of the periprosthetic bone loss at these areas (Alm et al. 2009).

### 2.1.4 *Bisphosphonates in cementless THA*

Bisphosphonates are antiresorptive drugs that tend to affine to the major constituent of bone, hydroxyapatite. They locally inhibit osteoclast activity leading to less bone resorption and suppressed bone turnover. Bisphosphonates are effective in the treatment of conditions characterized by extensive osteoclast-mediated bone resorption, such as senile and glucocorticoid-associated osteoporosis (Morris and Einhorn 2005).

Bisphosphonates are available orally and intravenously, which allows faster maximal suppression of bone resorption. A single dose of intravenous infusion of zoledronic acid, a later-generation bisphosphonate (Kennel and Drake 2009), leads to a continued suppression of biochemical markers of bone resorption 2 years after drug administration (Grey et al. 2009). The precise biological half-life of the later-generation bisphosphonates is still unknown, but estimated to be at least 10 years (Khan et al. 1997).

In cementless THA, bisphosphonates have been studied to prevent periprosthetic bone loss and implant stability. Such changes may turn to better outcomes in terms of aseptic loosening and periprosthetic fractures and, ultimately, implant failure and revision surgery (Khatod et al. 2015).

Clinical studies concerning the effects of bisphosphonates in THA have been promising, but conflicting. Many trials have shown beneficial short-term effects on the periprosthetic BMD (Thillemann et al. 2010). The clinical effect of these changes is still mostly unknown and still, there is no direct evidence that improvement of BMD will also improve implant function or survival.

There are two studies conducted with the EBRA-FCA method regarding the effects of bisphosphonates on the migration of femoral stem in cementless THA. In patients receiving cementless THA due to osteonecrosis of the femoral head, a condition where the outcome of THA is compromised due to a higher incidence of aseptic loosening, a single infusion of zoledronic acid did not affect the femoral stem migration (Friedl et al. 2009). In osteoarthritic patients, a 6-month risedronate therapy neither did affect the femoral stem migration (Muren et al. 2015).

In animal models, bisphosphonates have shown to enhance osseointegration, protect from periprosthetic bone loss, wear debris osteolysis and subsequent aseptic loosening and ultimately improve survival rates (Shanbhag et al. 1997, Millett et al. 2002, Wedemeyer et al. 2005, von Knoch et al. 2005, Muratore et al. 2012, Chen et al. 2013).

Given the already excellent results of cementless THA, the possible adverse events associated with any new intervention, such as bisphosphonates, lead easily to lowered patient and physician satisfaction (Hamilton 2011). Most common adverse effects of bisphosphonates are upper gastrointestinal tract effects and pyrexia (Kennel and Drake 2009).

More concerningly, as bisphosphonates suppress bone turnover, there is an apparent link to atypical fractures. Animal studies on beagle dogs receiving bisphosphonates have shown a dose-dependent accumulation of microdamage in bone, with conflicting results regarding the consequences on bone mechanical properties (Chapurlat and Delmas 2009).

Clinically, long-term use bisphosphonates are associated with atypical femoral fractures in diaphyseal and subtrochanteric regions (Goh et al. 2007, Lenart et al. 2008, Abrahamsen et al. 2009). Respectively in THA patients, there has been found similar periprosthetic atypical femoral fractures (PAFF) in long-term bisphosphonate users. PAFFs are considered as stress fractures, are often Vancouver type B1 (near the tip of the stem and well-fixed stable implant (Figure 8)) and especially hard to treat. PAFF share more characteristics in common with atypical femoral fractures than other types periprosthetic fractures (Robinson et al. 2016). Whether bisphosphonates have a causal role in atypical fractures or not, it is clear that they have capability to impair remodeling of developing stress

fractures and prolong healing times (Solomon et al. 2009, Saito et al. 2010, Robinson et al. 2016).

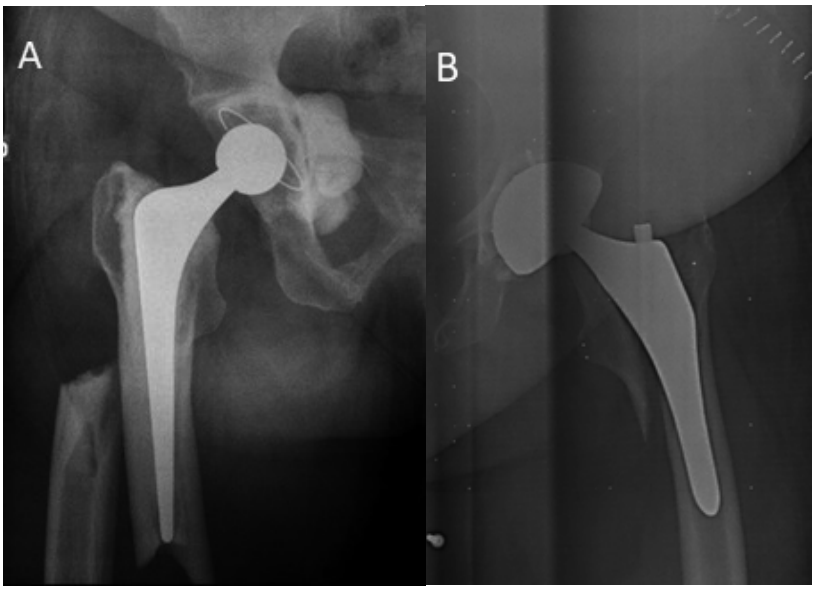


**Figure 8** 72-year-old woman with a osteoporotic T-score of -3.4 and Dorr type A femur morphology. Alendronate treatment started for osteoporosis in 2004. Due to osteoarthritis, bilateral THA were implanted, to the right hip with cemented design in 2003 and to the left hip with cementless design in 2004 for the ABG-II study. In the early postoperative period the patient sustained a B3 type periprosthetic fracture according to the Vancouver classification in the left hip (Figure 8B). The next year the patient presented on the right side a Vancouver B1 type fracture (Figure 8A), which is a fracture type seen in atypical periprosthetic femoral fractures of bisphosphonate users.

#### 2.1.4.1 ***Bisphosphonates in preventing periprosthetic bone loss***

A recent meta-analysis has studied the effect of bisphosphonates in preventing femoral periprosthetic bone resorption after primary cementless THA. Results for the changes in postoperative BMD at 3, 6 and 12 months after surgery were in some Gruen zones heterogenous: bisphosphonate group showed significantly higher BMD in Gruen zones in 1, 2, 3, 4, 6 and 7, while zone 5 showed mixed results. At 5 years bisphosphonate group showed higher BMD in Gruen zones 6 and 7, the main load-bearing areas, while no statistical difference was found in the rest of the zones (Zhao et al. 2015).

A similar meta-analysis has been conducted on the effect of zoledronic acid on reducing femoral BMD following cementless THA. 4 randomized, controlled trials were included, with a maximum follow-up time of 2.8 years. At one year, zoledronic acid showed significantly reduced BMD loss in Gruen zones 1, 2, 4, 6, and 7. However, high-quality randomized controlled trials with large sample size and long follow-up are needed (Gao et al. 2017).

Even though postoperative bisphosphonates have been shown in several studies to reduce periprosthetic bone loss, studies are inconsistent in what happens after discontinuation of treatment in mid-term. There is evidence that bisphosphonate-treated group return to the same BMD than control group (Tapaninen et al. 2010, Muren et al. 2015), but long-lasting effects have been also reported (Arabmotlagh et al. 2009).

The timing of the administration of bisphosphonate might relate to its efficacy, however current clinical data are insufficient to provide answers for the optimal length of treatment (Zhao et al. 2015). Some investigators have warned that preoperative bisphosphonate therapy might be harmful for the osseointegration of the implant due to reduced bone remodeling and prevention of regeneration of underlying bone, while postoperative treatment would reduce the inflammation-mediated osteolysis (Prieto-Alhambra et al. 2014, Teng et al. 2015).

#### 2.1.4.2 ***Bisphosphonate use in cohort studies***

Bisphosphonate use, determined (Prieto-Alhambra et al. 2011) as medication prescription with refills indicating at least 6 months of high adherence treatment, has been linked with an improved survival of cemented and cementless THA in cohort studies.

A large, retrospective cohort study of nearly 13000 patients studied the association of bisphosphonate use and risk of revision after primary THA stratified by patient BMD and age (Khatod et al. 2015). Bisphosphonate use was associated with a nearly 50% lowered risk for all-cause and aseptic loosening revision, which was more pronounced in older and more osteoporotic patients. However, bisphosphonate use was associated with an almost two-fold risk of periprosthetic fractures, and this effect was even more profound in younger patients with normal BMD.

Another large, retrospective cohort study found a similar reduced risk for revision in bisphosphonate users and almost twofold increase in implant survival time. Over five years with an assumed 2% failure rate, the study estimated that the number

needed to treat to avoid one revision was 107 oral bisphosphonates (Prieto-Alhambra et al. 2011).

A population-based nested case-control study showed that a long-term, but not short-term, postoperative use of bisphosphonates was associated with a reduced all-cause risk of revision. Further, postoperative use of bisphosphonates increased the risk of revision to deep infection 2.6-fold (Thillemann et al. 2010). In hip fracture repair patients, zoledronic acid has in addition shown to reduce new clinical fractures and mortality (Lyles et al. 2007). This decreased overall fracture risk has been shown also in patients undergoing elective THA receiving bisphosphonates (Prieto-Alhambra et al. 2011).

## 2.2 PET/CT in the diagnostics of adverse reactions to metal debris (ARMD)

### 2.2.1 *Overview of MoM hip arthroplasties and ARMD*

Young, active patients with osteoarthritis are a demanding population for arthroplasty as their surgical outcome is markedly decreased. UK's National Institute for Health and Care Excellence (NICE) has a benchmark criteria for hip arthroplasty survival in young patients at 10 years of 95%, while the Scandinavian registry has shown in patients younger than 50 years old a 10-year survivorship only at 83% (Mäkelä et al. 2014).

To meet these challenges, hip arthroplasty with metal-on-metal (MoM) bearings were re-introduced in the end of 1990s. For MoM bearings, wear simulator data suggested 100-fold lower volumetric wear rates compared to conventional bearings (St John et al. 2004). Long-term clinical studies suggest a direct relationship between wear and periprosthetic osteolysis leading to fatigue failures of the prosthesis (Manley et al. 2002). This lead to an assumption of fewer failures due to aseptic loosening, which was considered as one of the principal advantages for MoM bearings (St John et al. 2004).

MoM hip arthroplasties became popular as they were considered as an intriguing option for younger and more active patients with long life expectancy (Triclot 2011). Due to concerns over strength associated with other bearings (Cuckler et al. 2004), MoM bearings allowed the possibility to use larger femoral heads (e.g. 38mm) instead of smaller heads (e.g. 28mm). These larger heads were supposed to provide better function, fewer dislocations, less wear and prolonged prosthesis survival despite higher activity demands (Zywiel et al. 2011).

Moreover, the possibility to perform a bone-conserving hip resurfacing arthroplasty (HRA) instead of a conventional THA accounted for a great increase in the popularity MoM bearings. Compared to THA, HRA theoretically should have reduced risk of dislocation, easier replication of hip mechanics and easier revision (Amstutz and Le Duff 2015, Gaillard and Gross 2017).

**Figure 9** Hip resurfacing arthroplasty: Birmingham hip resurfacing system (Smith & Nephew; Andover, Massachusetts, USA) (van Lingen et al. 2016). In HRA the damaged joint articulations from the femoral head and acetabulum are removed and shaped for the resurfacing articulations.

The use of MoM bearings peaked late in the first decade of 2000 (Borroff et al. 2014). In the United States, in 2008 over 40% of all primary THA procedures were performed with MoM bearings (Bozic et al. 2009). Worldwide over 1,5 million MoM hip implantations have been made. In Finland approximately 20000 patients have been implanted with MoM bearings, 15000 with THA and 5000 with HRA (Finnish Arthroplasty Register, 2017).

However, this fundamental premise of lower wear and subsequently reduced osteolysis and aseptic loosening was flawed. The wear simulator results and theoretical promises did not apply clinically. MoM bearings actually produce a greater number of debris particles as they are in the nanometer-size range (Jacobs et al. 2009). Moreover, MoM bearings produce irregular-shaped metal particles that promote inflammation and tissue damage (Caicedo et al. 2013). The metal debris is believed to cause local adverse reactions to metal debris (ARMD) leading to early failures of the prosthesis and need for revision surgery (Haddad et al. 2011).

This emergence of early failures led to a subsequent fall in use of MoM bearings and intervention from several regulators including, but not limited to, the US and UK regulators. In accordance, the Finnish Arthroplasty Society has discouraged the use of MoM bearings since May 2012. Several prostheses has been withdrawn from market (Wagner et al. 2012).

Currently, the reported 10-year prosthesis failure rates for MoM bearings are higher for other bearing surfaces ranging from 1% to 29% depending on the prosthesis types (Amanatullah et al. 2016). These rates are two to threefold higher than in contemporary bearings.

MoM THAs were not rigorously tested by the European and US authorities as they were considered to be similar to parts used conventionally (Cohen 2012). The exposure of millions of patients to unknown risk can be considered as a regulatory failure. Concerningly, a meta-analysis found increased mortality in patients with MoM THA compared non-MoM THA (Pijls et al. 2016). MoM arthroplasties are considered among the least successful of modern hip arthroplasties (Haddad et al. 2011).

Therefore, MoM bearings have had a lesson to be taught for the medical society. It has been suggested that a phased introduction of the new prosthesis should be mandatory in the future (van Lingen et al. 2016). For example, the Dutch Orthopaedic Association has stated that any new hip prosthesis has to pass a phased introduction, including mandatory RSA studies (Nelissen et al. 2011, Poolman et al. 2015).

Surprisingly, RSA studies conducted on MoM arthroplasties showed no signs of early migration nor loosening and predicted good performance in the long-term (Itayem et al. 2005, Itayem et al. 2007, Glyn-Jones et al. 2009, Baad-Hansen et al. 2011, Penny et al. 2012, Itayem et al. 2014) suggesting that the typical failure mechanism of ARMD does not seem to be related to early implant migration (Malak et al. 2016).

### 2.2.2 *Current evidence of ARMD*

As the knowledge of ARMD is rapidly growing, the nomenclature and terminology are highly variable. However, the umbrella term of ARMD is the most common term to describe the wide range of local complications caused by metal debris leading possibly to the immature failure of the prosthesis (Haddad et al. 2011).

Two major subgroups of local complications of ARMD are soft tissue reactions and osteolysis (Amanatullah et al. 2016). Soft tissue reactions in ARMD are inflammatory including synovitis, extra-articular cysts, and masses named as pseudotumors (Reito et al. 2016), which are common in symptomatic MoM hips with a prevalence up to 69% (Berber et al. 2015). These can be large and destructive leading to necrosis of the surrounding soft tissue and gluteal area (Griffin et al. 2012).

The gluteal muscles and tendons are affected by a prevalence from 22% to 90% in symptomatic ARMD causing functional deficits. This irreversible soft tissue pathology, including gluteal muscle affection, is associated with poor outcome in revision surgery (Grammatopoulos et al. 2009, Daniel et al. 2012, Berber et al. 2015).

Osteolysis is a loss of bone near the femoral and acetabular components seen on plain radiographs as cystic lesions and radiolucent regions. Histologically these changes are similar seen in soft tissue reactions pointing it as an only bony continuum of ARMD (Amanatullah et al. 2016).

Histologically ARMD has shown to be a complex inflammatory response by macrophage-induced cytotoxicity leading to tissue destruction and necrosis (Jacobs et al. 2009). In addition to this macrophagic response, another inflammatory reaction has been described in ARMD mediated by lymphocytes, referred as the aseptic lymphocytic vasculitis-associated lesion (ALVAL). It is a type IV hypersensitivity reaction (Chalmers et al. 2016), which can be simplified in this case to a slow onset allergic response. However, the role of ALVAL in the pathogenesis of ARMD is debatable (Kwon et al. 2010). It must be noted that the exact cellular and molecular mechanisms behind the multifactorial pathogenesis of ARMD is not fully understood (Pandit et al. 2008).

In addition to causing locally ARMD, debris metal ions are also released systemically. It has been suggested that the inflammatory process of ARMD predisposes to a greater infection risk through immune response modification, remaining particulate debris or bacterial seeding of damaged tissue (Hosman et al. 2010, Wyles et al. 2014). Infection rates for patients with ARMD are not yet clearly established. However, registry studies have shown that MoM arthroplasties have infection as a cause for revision at a rate of 6-11%, almost two-fold than seen in conventional bearings (Lainiala 2016, National Joint Registry for England and Wales 2017).

As ARMD can be an expanding process, it has a potential to cause local pressure causing necrosis and compression of nearby blood vessels, nerves and muscles. Symptoms of ARMD often include discomfort or pain in the hip or groin area, where might also be a noticeable mass or swelling. In addition, catching, locking, crepitus, and clicking are common mechanical symptoms. Anamnestically the patient might tell about spontaneous dislocations and sensation of subluxation (Pandit et al. 2008, Mäntymäki et al. 2017). However, up to 61% of the asymptomatic MoM hips have ARMD lesions (Wynn-Jones et al. 2011, Hart et al. 2012, Fehring et al. 2014).

The diagnosis of ARMD is sometimes obscured due to the wide spectrum of clinical manifestations. ARMD may be present in symptomatic or asymptomatic patients, with high or low metal ion levels, in components that are malpositioned or well-positioned, in components with high or low rates of wear. Even patients with normal cross-sectional imaging and well-positioned components may present hip pain (Chalmers et al. 2016). Therefore, there are no definite criteria for establishing the diagnosis of ARMD.

Risk factors for ARMD are female gender, surgeons performing low numbers of procedures, underlying hip diagnosis other than primary osteoarthritis, different component sizes and suboptimal component alignment (Glyn-Jones et al. 2009, Jameson et al. 2012, Bosker et al. 2015).

### 2.2.3 *PET/CT imaging of ARMD*

Detection and localization of infectious and noninfectious foci in soft tissues are of primary importance for the management of patients with presumed or established inflammatory or infectious diseases. Ultrasound, computed tomography, and magnetic resonance imaging are applicable whenever the lesion has caused changes in local anatomy, capillary permeability or tissue water content (Ma et al. 1997). However, when normal anatomic landmarks are lost or obscured, localization of inflammatory foci can be best accomplished by nuclear imaging, such as combined positron emission tomography and computed tomography (PET/CT) (Pellegrino et al. 2005).

2-deoxy-2-[$^{18}$F]fluoro-D-glucose ([$^{18}$F]FDG), a radiolabeled glucose analog, is the most commonly used tracer for PET/CT. [$^{18}$F]FDG is a sensitive and widely used method for detecting inflammation and infection (Salomäki et al. 2017). Inflammatory processes attract by a variety of stimuli white blood cells: neutrophils in acute inflammation (Kaim et al. 2002), and macrophages and granulocytes in chronic inflammation (Sugawara et al. 1999). These cells are metabolically active and therefore uptake large quantities of glucose and respectively [$^{18}$F]FDG. In hip arthroplasty, [$^{18}$F]FDG PET/CT is in clinical use in selected cases in the diagnostics of periprosthetic infection (Della Valle et al. 2010).

$^{68}$Gallium-citrate ([$^{68}$Ga]Citrate) is another PET/CT tracer that has been shown to be sensitive and specific tracer in detecting inflammation and infection, although only few human studies exist (Nanni et al. 2010, Kumar et al. 2012, Salomäki et al. 2017). Its biological mechanism of accumulation at sites of infectious foci is not fully understood. [$^{68}$Ga]Citrate behaves as an *in vivo* iron mimetic. Once

injected, it dissociates into $Ga^{3+}$ and $citrate^{3-}$ within the blood. 99% of the $Ga^{3+}$ ions are attaches to transferrin (Tsan 1985, Kumar et al. 2011), which accumulates in inflammatory lesions. In addition, [$^{68}$Ga]Citrate may also attach to bacterial siderophores, lactoferrin inside neutrophils and free lactoferrin at infectious foci (Hoffer 1980).

There are no guidelines for the use of nuclear imaging modalities in ARMD (Lombardi et al. 2012). There is only one previous study on PET/CT imaging of ARMD. Imaging case report of ARMD with [$^{18}$F]FDG PET/CT showed a rim-like uptake in the inflammatory pseudo-capsule, whereas the necrotic interior was almost entirely photopenic (Makis et al. 2011). The authors discussed that the metal debris infiltrating into the surrounding tissues causes a profound macrophagic response. After being recruited, the macrophages phagocyte the debris leading to macrophage apoptosis and cell death releasing the metal debris into surrounding tissues. This leads to a cyclic process creating a macrophagic pseudo-capsule with a necrotic interior.

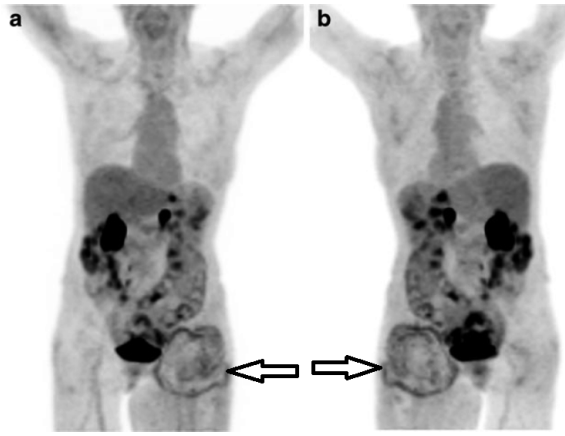


**Figure 10** [$^{18}$F]FDG PET/CT showing in (a) anterior and (b) posterior maximum intensity projection views a large irregular heterogenous pseudotumor caused by ARMD at the left hip with a maximum diameter of 16 cm with a maximum standardized uptake value ($SUV_{max}$) of 3.4 (Makis et al. 2011).

### 2.2.4 *Management of ARMD*

The unsatisfactory outcomes of ARMD are concerning as most of the patients are young and active. As the clinical presentation of ARMD is highly variable, the differential diagnosis of pain from ARMD can be challenging. Management of

MoM prosthesis is so complex that multidisciplinary teams have been suggested to assess patients and provide treatment recommendations (Berber et al. 2015).

Key factors assessing a patient suspected with ARMD are symptomology, prosthesis track record, metal ion levels, the positioning of the components, cross-sectional imaging, histopathologic analysis and the exclusion of other diagnosis, particularly infection (Kwon et al. 2014). Based on these risk stratifications, there are diagnosis and treatment algorithms for both asymptomatic and symptomatic ARMD patients (Lombardi et al. 2012).

Blood metal ion levels, especially cobalt and chromium, are useful in diagnosing, follow-up and treating ARMD. Even though there is no exact correlation between elevated metal ion levels and increased risk of ARMD, elevated metal ion levels are associated with increased wear and failed prosthesis (Lombardi et al. 2012). Although metal ion levels are elevated in most ARMD cases, a normal level does not exclude ARMD (Grammatopoulos et al. 2017).

Plain radiographs are the first imaging modality in the evaluation of MoM arthroplasties. Component malposition increases the risk of ARMD and other potential complications. However, in most cases of ARMD plain radiographs appear normal without major component malpositioning (Kwon 2014). Radiograph might give light to other potential causes of pain. Comparison of serial radiographs is important for the evaluation of osteolysis, component loosening or signs of prosthesis impingement (Lombardi et al. 2012).

MARS MRI is the main cross-sectional imaging modality used in the diagnosis and characterization of ARMD. MARS is a technique reducing the image distortion from surrounding metal prosthesis allowing soft tissue visualization (Kwon 2014). There are several grading systems for soft tissue changes seen in ARMD (Anderson et al. 2011). The variety of clinical presentations of ARMD can be seen also in MARS MRI as synovitis and pseudotumors have been detected in nearly equal proportions in painful and painless, well-functioning MoM hips (Hart et al. 2012).

Periprosthetic joint infection must be excluded when evaluating a painful arthroplasty, preferably following evidence-based guidelines (Parvizi and Della Valle 2010). There is no distinct guideline for the diagnosis of infection in ARMD. The inflammatory process of ARMD can mask the coexisting infectious symptoms and findings (Mikhael et al. 2009, Judd and Noiseux 2011). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be both elevated in ARMD mimicking infection. Joint, or any fluid collection, aspiration can help secure the diagnosis of ARMD as well as infection (Wyles et al. 2013). As the diagnosis of infection in ARMD is extremely difficult, a more aggressive approach

to the preoperative evaluation of infection is suggested, repeating aspiration if necessary (Yi et al. 2015).

Three most common reasons for failing and subsequent revision surgery of MoM arthroplasties are aseptic loosening, ARMD and infection (Fabi et al. 2012). As the total revision rate is increased in MoM bearings compared to traditional bearings, a lower risk of revision is found only due to dislocations (Kostensalo et al. 2013).

As the thresholds for revision are not determined, all regulatory authorities recommend revision in patients with imaging abnormalities, especially if progressive, and in patients with rising blood metal ions (Matharu et al. 2015). Early revision surgery is recommended to avoid irreversible soft tissue damage (De Smet et al. 2011) and in cases where osteolysis is progressive or periprosthetic fracture is apparent (Berber et al. 2016).

Revision surgery of the failed MoM prosthesis is individualized to the characteristics of the patient and the reason for the failure. In addition to component exchange, resection of necrotic tissue and soft tissue changes is recommended. Revision surgery of a failed MoM prosthesis due to ARMD can be technically challenging (Matharu et al. 2017).

The early results of revision surgery in MoM prosthesis due to ARMD were catastrophic (Grammatopoulos et al. 2009, Munro et al. 2014). However, the latest registry studies conducted on ARMD revision surgery outcome seems to be comparable all-cause non-MoM THA revision surgery. The same study showed that the exchange of MoM bearings to soft-on-hard materials, e.g. ceramic-on-polyethylene, decreased the risk for re-revision (Matharu et al. 2017).

# 3 AIMS OF THE STUDY

The purpose of this thesis was to investigate the stability of the femoral stem in cementless THA and characterize the PET/CT imaging findings of ARMD in MoM hip arthroplasties.

All studies were prospective and clinical using various outcome measures including functional, biochemical and imaging studies aimed specifically to:

1. study the mid-term stability of the femoral stem in cementless THA in aging women with low bone quality in a prospective cohort study.

2. study the effect of zoledronic acid in the stability of the femoral stem and periprosthetic bone loss in cementless THA in aging women in a randomized, double-blind, placebo-controlled trial.

3. characterize the PET/CT imaging findings with [$^{18}$F]FDG and [$^{68}$Ga]Citrate in patients with ARMD in MoM hip arthroplasty in an exploratory, prospective, open-label study.

# 4 MATERIALS AND METHODS

**Ethical issues**

Studies were conducted in accordance with the Declaration of Helsinki, and the study protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland. All patients provided their written informed consent.

## 4.1 Subwork ABG

This is a prospective cohort extension study of a 2-year single-center RSA study studying the osseointegration of aging female patients implanted with cementless THA due hip osteoarthritis (Aro et al. 2012).

**Patients and surgery**

The inclusion criteria for the original study were (1) a generally healthy female less than 80 years old with advanced primary hip osteoarthrosis, and (2) unremarkable medical history. Exclusion criteria were rheumatoid arthritis or any other inflammatory arthritis, hereditary skeletal disease, untreated parathyroid disease, ongoing osteoporosis or corticosteroid therapy, medication affecting bone metabolism and severe undiagnosed osteoporosis (T-score less than -3.5).

Female patients enrolled for the original study received a RSA-marked hydroxyapatite-coated hip implant (Anatomic Benoist Girard II [ABG-II], Stryker) with ceramic-on-ceramic bearings. During surgery, multiple RSA markers (n = 4–7) were inserted into the greater and lesser trochanters. The center of the femoral head was as one additional marker. After surgery, the patients were instructed to use crutches and partial weight-bearing up to 6 weeks.

Of the 53 original patients, 32 were able to attend this extension study at 9 years postoperatively.

**RSA imaging**

Stem migration was measured with the use of marker-based RSA (UmRSA software 6.03.7, Biomedical Innovations AB, Sweden). The clinical precision was determined based on double examinations. The mean error of rigid body fitting (ME), as a measure of RSA marker stability, and the condition number (CN), as the indicator of sufficient marker distribution, were calculated and the recommended cutoff points were adopted (Valstar et al. 2005). Four patients of the 32 were excluded from the RSA analysis due to high values of either ME or CN.

### Clinical assessment

Standard two-plane hip radiographs were taken at 2 and 9 years. Radiographic signs of osseointegration were evaluated and classified according to the published criteria (Engh et al. 1990). Hip function was evaluated with the Harris hip score (HHS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

### Statistical analysis

The data was tested for normal distribution. Parametric and non-parametric paired t-tests were applied to compare the significance of differences between 2 and 9 years. P-values $< 0.05$ were considered significant.

## 4.2 Subwork zoledronic acid

### Patients and surgery

This randomized, double-blind, placebo-controlled clinical trial consisted of aging women that were admitted to Turku University Hospital due to advanced degenerative hip osteoarthritis. The exclusion criteria included any inflammatory arthritis, disorders of parathyroid function, current use of drugs for osteoporosis or corticosteroids, hepatic or renal disease, skeletal disorder such as Paget's disease, malignancy within the past 5 years, and a history of dental infections or impending dental surgery.

Forty-nine patients (mean age 68.1 ± 8.7 years) were enrolled to receive a hydroxyapatite-coated uncemented stem (Symax, Stryker Inc, Netherlands) with metal-on-plastic bearings. The stem was marked for RSA by the manufacturer with 3 tantalum beads (1.0 mm). During surgery, 5 to 7 tantalum beads were implanted into the femur trochanter to serve as bone markers. After surgery, full-weight bearing with the use of crutches was encouraged.

Thirty-one patients of the original 49 (63%) completed the 4-year extension study, 19 from zoledronic acid and 12 from placebo group. 5 patients had died, 10 had poor general condition or malignancy and 3 declined to participate.

Implant survival was evaluated based on the review of electronic medical records at the median of 9 years (range 3.0 – 10.3 years).

### Randomization, intervention and blinding

Enrolled participants received calcium and D-vitamin supplementation. The participants (n = 49) were randomized to receive either a single intravenous

infusion of 5 mg of zoledronic acid (n = 25) or placebo (n = 24) prior to the discharge from the hospital (with the median of 5 days post-surgery). The physically indistinguishable active and placebo infusion vials (Novartis Inc., Switzerland) were coded by the hospital pharmacy according to the computerized randomization list provided by a third party (4Pharma Ltd, Finland). All patients, staff, and investigators were blinded to the treatment assignment.

**RSA and DXA**

The trial end-points were the change of periprosthetic femoral BMD (Gruen zone 7) and the femoral stem migration. The baseline measurements were performed within three days after surgery and repeated at 3, 6, and 12 months and 4 years.

Systemic BMD was measured with the use of dual X-ray absorptiometry (DXA) from the proximal femurs, the lumbar spine (L1 through L4), and the distal non-dominant radius during screening and at 12 months. Periprosthetic BMD was measured from seven Gruen zones of the proximal femur. Each patient was measured with the same DXA device (Hologic QDR 4500C, Hologic Inc, USA or Osteocore III, Medilink, France) on all occasions during the treatment period. During the extension study, all measurements was performed using Hologic QDR 4500C. The two groups showed no imbalance in the use of the two devices, and the device effect was included in the statistical analysis as a covariate. The agreement between the two devices was confirmed by means of double examinations of six trial participants ($r^2 = 0.879$, two anatomical locations) and the equation of the linear correlation was applied to adjust the measured BMDs.

Stem migration was measured with the use of marker-based RSA. The clinical precision was determined based on double examinations. The recommended cutoff points were adopted for ME and CN numbers (Valstar et al. 2005).

**Clinical assessment**

A standard gait laboratory system of a 3.8 meter long electronic walkway (GAITRite; CIR Systems, Franklin, NJ) was used to measure the self-selected walking velocity (Schwesig et al. 2011). Digital pedometers were used for the assessment of walking activity (Schmalzried et al. 1998). Each patient recorded the number of steps per day as counted by the pedometer for periods of 14 days.

In addition to the clinical assessment of range of motion and hip function, the participants completed the HHS, WOMAC, and the Rand-36 as a general health survey. Stem stability was assessed according to the criteria of Engh et al. (Engh et al. 1990) from standard hip radiographs. Bone turnover marker osteocalcin and

serum bone resorption markers were defined to confirm the bone resorption efficacy of zoledronic acid.

**Sample size and power analysis**

To be clinically relevant, zoledronic acid was expected to ameliorate this bone loss by at least 50% compared to placebo. With a power of 80% ($\alpha$=0.05) and a standard deviation (SD) of 5%, it was calculated that 17 participants were needed in each group in order to detect the expected difference. Allowing for dropouts, 25 participants per group were enrolled, giving a total sample size of 50 patients.

**Statistical analysis**

The study end points were analyzed using a repeated measurement analysis of covariance (RMANCOVA). In the analysis of periprosthetic BMD, the DXA device was modeled as a fixed effect with full interactions with treatment and clinic visit effects. Results are presented as mean values with corresponding 95% CIs.

## 4.3 Subwork ARMD

**Patients**

ARMD patients were recruited from a population of hip arthroplasty patients who were recalled for safety evaluation of MoM bearings at Turku University Hospital. Patients who had symptoms and/or functional impairment were selected to undergo MARS MRI according to national guidelines. If the MARS MRI indicated ARMD, the patient was asked to participate in the PET/CT study. The selected subjects represented a consecutive sample of eligible patients.

All 12 ARMD patients had MoM bearings in either total hip arthroplasty (THA) or hip resurfacing arthroplasty (HRA). THA implants were either large-diameter M2a-Magnum (Biomet, Warsaw, IN, USA) or Durom Cup (Zimmer, Warsaw, IN, USA). HRAs were Birmingham hip resurfacing implants (Smith and Nephew, Memphis, TN, USA). Eight ARMD patients had a unilateral MoM hip and four had bilateral MoM hips. Thus, the 12 patients had 16 MoM hips. The mean time from primary surgery to PET/CT was 6.8 (range 1.7-10.1) years.

Six symptomatic hip arthroplasty patients without ARMD were recruited as controls. There were five controls with unilateral THA and one control with bilateral THA. Due to unexpected changes in the study protocol, five patients with conventional bearings and one with MoM bearings served as controls for the study.

**Clinical assessment**

All patients underwent clinical examination and routine imaging of their hips. Local symptoms such as pain were assessed using a questionnaire and visual analogue scale (VAS) of pain. WOMAC was used to evaluate functional disability. Patients were excluded for having a periprosthetic joint infection by following the current guidelines of the American Academy of Orthopaedic Surgeons (Della Valle et al. 2010). Serum levels of cobalt and chromium were determined

**Imaging studies**

As a routine of the safety evaluation of MoM arthroplasty, the patients underwent metal artifact reduction sequence magnetic resonance imaging (MARS MRI) with contrast medium using 1.5 tesla scanners and recommended imaging protocols (Hart et al. 2009, Yanny et al. 2012). The severity of ARMD-related changes in periprosthetic soft tissue on MARS MRI was classified using a validated grading system (Anderson et al. 2011).

All 12 patients suffered from ARMD in at least one hip. Of the 16 MoM hips, 14 were affected by ARMD. In four patients with bilateral MoM hips, two of these cases had ARMD bilaterally and two had ARMD unilaterally. 12 (75%) hips showed moderate (grade C2) or severe (grade C3) ARMD. Using the Anderson grading, ARMD patients were divided into subgroups of no/mild ARMD and moderate/severe ARMD.

PET/CT (Discovery VCT; General Electric Medical Systems, Milwaukee, WI, USA) was done on the same day starting with [$^{68}$Ga]Citrate PET/CT and followed, six hours later, with [$^{18}$F]FDG PET/CT. Non-attenuation-corrected PET images were also analyzed.

Qualitative visual analyses of [$^{18}$F]FDG and [$^{68}$Ga]Citrate tracer distributions were classified according to the system of Reinartz (Reinartz et al. 2005), which was developed to evaluate [$^{18}$F]FDG PET images in patients with painful THAs.

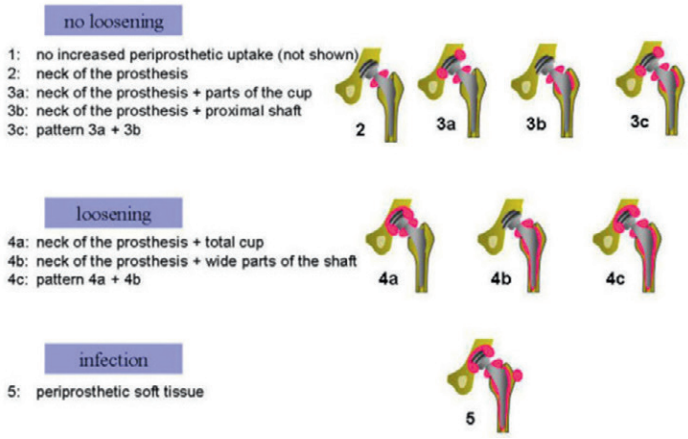


**Figure 11** Illustration of the Reinartz classification for the interpretation of [$^{18}$F]FDG uptake in the periprosthetic region (Delank et al. 2006).

In addition to classifying the tracer uptake pattern, measurements of the maximum standardized uptake value ($SUV_{max}$) were made in the gluteal muscle region to measure gluteal muscle region affision. A fixed-dimension circular region of interest (diameter 1.5 cm) was positioned manually over the gluteal muscle region with the highest uptake, where the $SUV_{max}$ was calculated.

**Follow-up for revision surgery**

During the follow-up (≥3 years after imaging and ≥5 years after implantation), seven patients underwent revision surgery. The time elapsed from PET/CT to revision surgery varied between one and 46 months (median four months). All intraoperative tissue samples were submitted for microbiological and histopathological analyses and were found negative for bacterial infection.

**Statistical analyses**

The $SUV_{max}$ data was tested for normality using the Shapiro-Wilk test. For analyses of data with a normal distribution, the independent-sample t-test was applied to test the significance of differences between two groups. The non-parametric Kruskal-Wallis test was applied for the comparison of two subgroups (no/mild and moderate/severe) of ARMD patients with the controls. A p-value $< 0.05$ (two-sided) was considered significant.

# 5 RESULTS

## 5.1 Subwork ABG

RSA showed no significant migration between two and nine years after surgery. One outlier showed a continuous migration until nine years. Based on a review of the electronic patient records up to 14 years after surgery, none of the patients had developed aseptic loosening. Patient-reported outcome scores did not differ between two and nine years. Radiographically all stems were classified as stable.

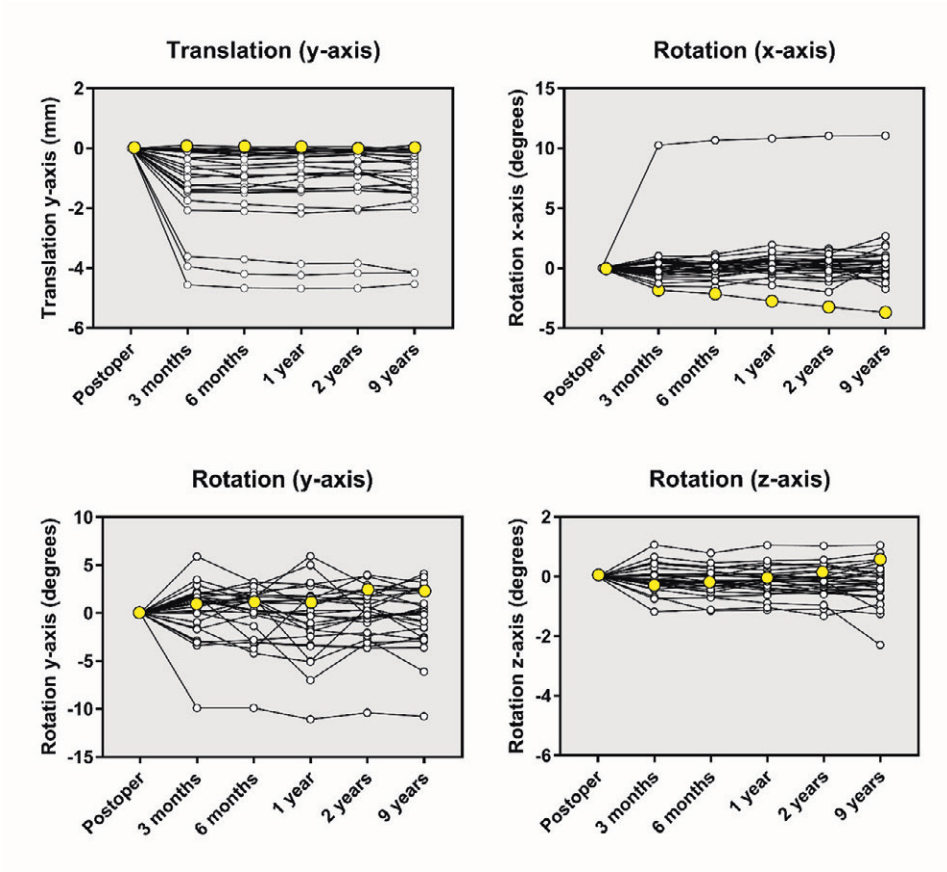


**Figure 12** Graphs showing the migration pattern of individual femoral stems (n = 28) during the 9-year follow-up. One outlier showing continuous migration until nine years is marked with yellow dots. At 14 years postoperatively the patient had not developed clinical signs of aseptic loosening.

## 5.2 Subwork zoledronic acid

Zoledronic acid did not affect femoral stem migration, walking speed, walking activity, HHS, WOMAC or Rand-35 score. Zoledronic acid suppressed serum bone turnover and resorption markers as expected. Radiographically all stems were classified as stable. No patient needed revision surgery in the follow-up. One patient from the placebo group suffered a late periprosthetic fracture, which was treated conservatively. Sixteen patients (64%) in the zoledronic acid group and 19 patients (79%) in the placebo group had preoperatively low BMD (T-score < -1).

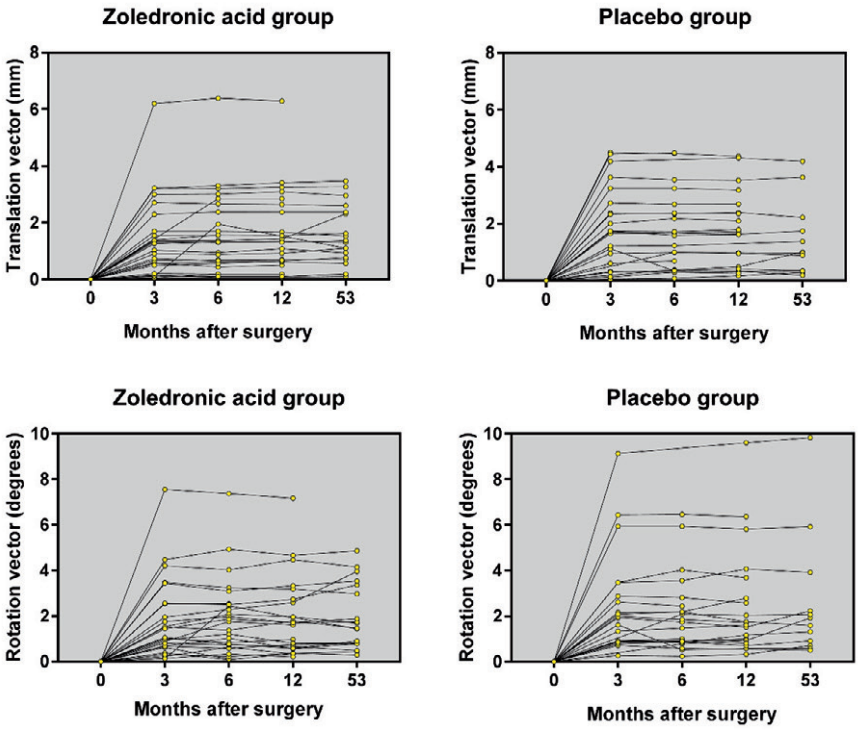


**Figure 13** Zoledronic acid treatment did not have a significant effect on femoral stem migration. Migration occurred predominantly within 3 first postoperative months.

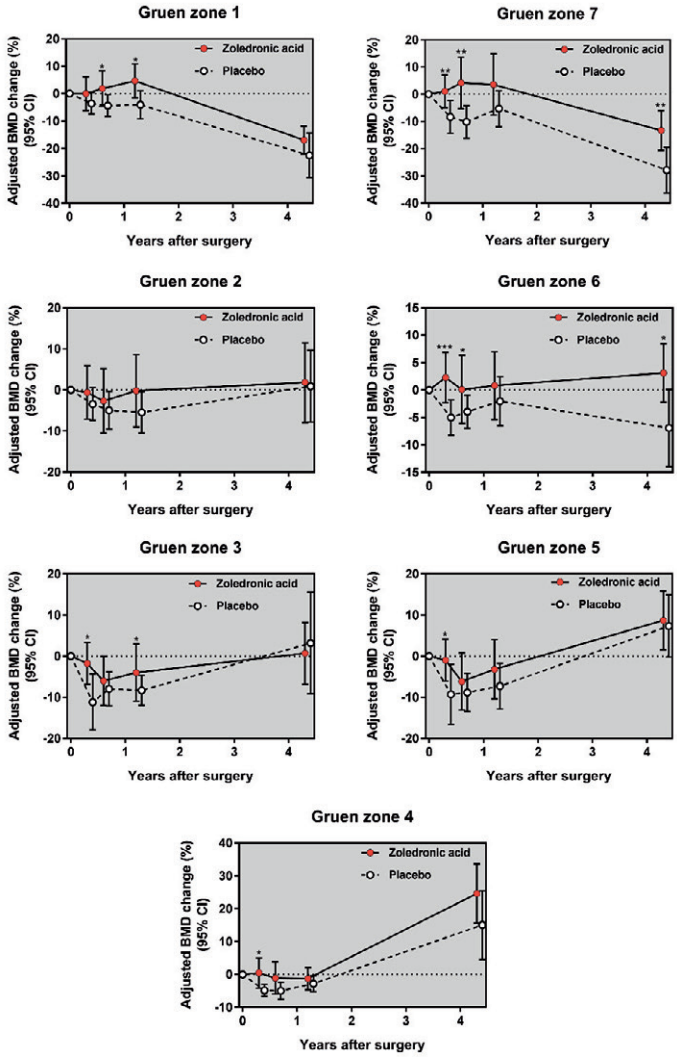


**Figure 14** Zoledronic acid reduced periprosthetic bone loss. This effect was evident especially in the Gruen zones 6 and 7, areas where periprosthetic fractures often occur. The error bars indicate 95% CI. The intergroup differences: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

## 5.3 Subwork ARMD

Only one hip did not show any [$^{18}$F]FDG uptake in the periprosthetic area (pattern 1). The distribution of [$^{18}$F]FDG uptake in the periprosthetic soft tissues (especially

in the gluteal muscles) resembled a pattern seen typically in infection of three (19%) hips (pattern 5).

In the gluteal muscle region, the $SUV_{max}$ values of [$^{18}$F]FDG were significantly greater in hips with moderate or severe ARMD compared with hips of the controls (3.29 ± 1.44 vs. 1.31 ± 0.32, p = 0.009). Patients who had necrosis in the gluteal muscles upon revision surgery showed significantly greater $SUV_{max}$ values of [$^{18}$F]FDG compared with patients who had no necrosis in the gluteal muscles (4.52 ± 1.00 vs. 2.02 ± 1.56, p = 0.039). There was no statistical significance in $SUV_{max}$ values of [$^{18}$F]FDG between patients who needed revision surgery within the follow-up period (n = 7) and patients who did not (n = 5).

There was no increased uptake of [$^{68}$Ga]Citrate in 13 (81%) of 16 hips (pattern 1) in the periprosthetic region. Three hips with increased uptake of [$^{68}$Ga]Citrate (pattern 3 or 5) were found in the same three patients who had wide periprosthetic soft tissue [$^{18}$F]FDG uptake (pattern 5).

In the gluteal muscle region, the $SUV_{max}$ values of [$^{68}$Ga]Citrate were not significantly different in hips with moderate or severe ARMD than in the control hips. Patients who needed revision surgery during the follow-up did not show a significantly increased $SUV_{max}$ value of [$^{68}$Ga]Citrate compared with those who did not need intervention. The $SUV_{max}$ values of [$^{68}$Ga]Citrate were not significantly different in patients with an intraoperative finding of gluteal muscle necrosis compared with patients with no necrosis of the gluteal muscles or who did not need revision surgery.

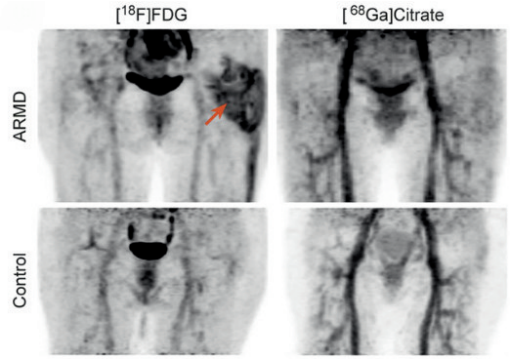


**Figure 15** ARMD patient showing extensive periprosthetic accumulation (Reinartz pattern 5) with both, [$^{18}$F]FDG and [$^{68}$Ga]Citrate, tracers on the symptomatic left hip. Especially the $SUV_{max}$ value of [$^{18}$F]FDG (area of red arrow) was high 4.44, also the respective value of [$^{68}$Ga]Citrate was elevated 1.75. MARS MRI indicated moderate severity of ARMD. No revision surgery was needed in the follow-up. Control patient showed no respective tracer accumulations.

# 6 DISCUSSION

## 6.1 Subwork ABG

In this prospective cohort study, we found that an anatomically designed cementless femoral stem (ABG-II) implanted for osteoarthritis in aging women, shows no further migration between two and nine years. Radiographic images and clinical status also suggested stability. Of the 53 original patients showing more early migration in patients with low BMD, 28 completed successfully the follow-up RSA study. No revision surgery was needed.

One patient showed continuous RSA migration from six months onward until the last RSA measurement at nine years. In electronic record follow-up 14 years after surgery the patient did not show signs of mechanical loosening in radiographic images or clinical status. It is plausible that this stem may show later clinically mechanical loosening that RSA detected early. However, it must be noted that the rotations exceeded just slightly the clinical precision of RSA.

This borderline case raises a question what is meant by the stability of cementless femoral stem? The following equations help simplify this question:

*All femoral stems = Stable femoral stems + unstable femoral stems,*

which can be reduced and turned into:

*Stable stems = All stems – unstable stems,*

as shown previously in literature, unstable stems equal to stems with continuous RSA migration:

*Stable stems = All stems – stems with continuous RSA migration,*

and stems with continuous RSA migration will show signs of unstability sooner or later in radiographic images:

*Stable stems = All stems – stems with roentgenographic signs of mechanical loosening,*

and stems with roentgenographic signs of unstability show sooner or later clinical signs of mechanic loosening:

*Stable stems = All stems – stems with clinical signs of mechanical loosening.*

These equations show that the stability of cementless femoral stem is contradictory phenomenon to the instability of cementless femoral stem. Stability includes all the stems that do not show instability in RSA, radiographic images or clinical signs of mechanical loosening.

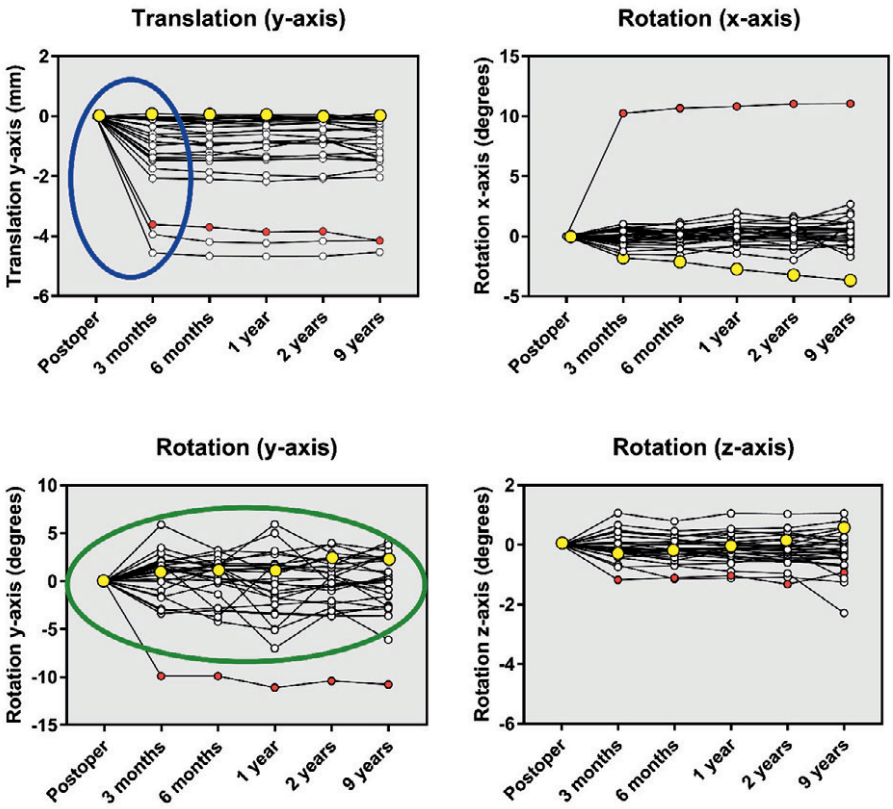


**Figure 16** Analyzing RSA migration patterns of individual stems for implant stability. An unstable stem showing continuous minor migration marked with yellow dots. The following characteristics can be recognized from the RSA migration data of stable stems. The slight wavy movement of lines represent a combination of imprecision and micromotion. Blue circle represents early migration (in this case subsidence) ending in the first three postoperative months. Green circle represents predominantly imprecision at y-axis rotation, a variable known for imprecision in RSA studies (Li et al. 2014). This is due to the shorter distance between the mediolateral markers detecting y-axis rotation compared to markers in proximomedial direction that have longer distance detecting z-axis ja x-axis rotations. Patient marked with red dots possibly

accounts for a patient with age-related widening of the medullary canal in the proximal femur (Noble et al. 1995) that has allowed the stem to rotate before stabilization. In conclusion, RSA results are ambiguous regarding the stability of the cementless femoral stem giving little information.

Migration depends on the stem design, implant design, fixation method and other circumstances, such as if bone graft has been used (Kärrholm 2012). Previous studies suggest that low BMD aggravates implant migration, however conflicting results exist (Sköldenberg et al. 2011, Aro et al. 2012, Rhyu et al. 2012). Clinical significance and the reason for this finding are unknown. Some experts say that uncemented stems should preferably not migrate at all, but many designs still do (Kärrholm 2012).

It must be noted that this is an untested hypothesis. So far, there is no direct evidence that shorter time or less migration before the cessation of early migration would be directly linked with improved survival of the cementless femoral stem. This raises questions, whether the amount of force applied during the press-fit implantation affects the amount of early migration. It is plausible that there is a J shaped adverse outcome curve of the THA regarding the early migration of the prosthesis as a tighter intraoperative press-fit fixation might reduce, or even diminute, the migration before the stabilization of the stem, but at the same time applied forces to the bone, especially at high-risk patients, may lead to periprosthetic fractures intraoperatively or in the early postoperative phase leading to exclusions in RSA studies. This might explain, why younger and active patients are supposed to have lower limits of acceptable amounts of migration (Kärrholm 2012) as their press-fit fixation can be achieved assumable with greater forces. Thus, one can question the relevance of efforts to prevent early stem migration detected by RSA.

Hypothetically, if there is an amount of early migration, where the clinical outcome of the prosthesis is at its best, its' verification may turn impossible. As RSA studies typically include less than 50 patients (de Vries et al. 2014), combining RSA data to clinical end points for correct biological conclusions can be difficult as uncemented femoral stems show over 90% survival at 10 years (Hailer et al. 2010, Mäkela et al. 2014). At such survival rates, RSA studies with few patients produce rather circumstance-related RSA data than results that can be turned into clinical practice.

The use of RSA to study osseointegration of a cementless femoral stem is based on an assumption that the cessation of the migration of the femoral stem component can be seen as a sign of complete and successful osseointegration leading to implant stability. This migration should seize during the first

postoperative year to achieve osseointegration rather than a fibrous fixation or loosening (Kärrholm 2012).

It is difficult to prove that a femoral stem which does not migrate at all, is osseointegrated to the bone. However, the detection limit for migration in RSA is in the range of one tenth of a millimeter. Our study shows that after excluding migration outliers, despite the migration is on average under the detection limit, only few stems show no migration at all after a time point. This makes it impossible to point out a time for an osseointegration matching the definition of Ryd *et al.* of radiographical signs of osseointegration and no migration detected by RSA (Ryd 2006). This implicates that on a population level a time point for stem osseointegration can be found, but not for individual stems. Therefore, it is questionable whether the relative motion of RSA markers is a suitable method for bone-implant interface.

For the stability of cementless THA, the most important biomechanical parameters are gaps and micromotion at the implant-bone interface. Periprosthetic gaps under 1 mm and micromotions under 40 µm implicate successful bone formation and osseointegration, while micromotions over 150 µm cause excessive formation of fibrous tissue periprosthetically (Sandborn et al. 1988, Engh et al. 1992, Dalton et al. 1995, Jasty et al. 1997). The clinical precision of our RSA measurements for translations (y-axis 130 µm, x-axis 100 µm, z-axis 290 µm) was typical for RSA (Soballe et al. 1993). However, they are greater than the limit of 40 µm in micromotion of osseointegration making their evaluation difficult. Especially in the case of repeating measurements at several time points, the micromovement evaluation is complex as it can be diminished behind variation.

Validity tells how well the method used in the study measures the phenomenon it was supposed to study (Sedgwick 2012). Even though previous studies have been conducted to study the osseointegration or stability of the cementless femoral stem with RSA (Aro et al. 2012, Nysted et al. 2014, Sköldenberg et al. 2014)**,** these studies have not discussed whether RSA is valid study for addressing stability despite being a valid method for evaluation of mechanical loosening.

Therefore, lack of validity of RSA for implant stability can be considered as a limitation for this study. It seems that despite being able to detect mechanical loosening of millimeter range of movements, RSA might not be an ideal method for implant stability and osseointegration, which need the accuracy of micrometer range. In addition, linking RSA results into clinical end points data need large patient samples – a quality which laborious RSA is not known for.

The two main patterns of stem migration were either initial migration with subsequent cessation of migration or no migration at all. These patterns have been

described earlier (Krismer et al. 1999) and they have been linked with cementless femoral designs with good outcome, which is supported by our study. The RSA migration pattern of the ABG-II stem has not been described previously (de Vries et al. 2014). Each implant has its unique pattern of migration and when the long-term survival results are available, most probably there are already new prosthesis designs in use.

ABG-II, developed in 1996, has not been implanted in Finland after 2012 (Finnish Arthroplasty Register 2017) making the implant-related data obsolete. Therefore, this study fails to give generalizable information. This study can be considered rather as a descriptive data of the RSA migration pattern of ABG-II as there is no clearly defined outcome that is used to measure a certain biologic phenomenon.

To achieve the accuracy and preciseness RSA is known for, the implanted tantalum markers have to be adequately numbered, adequately configured and have a stable fixation (Kärrholm 1989). Our study used a low number of 4-5 bone markers in each patient and periprosthetic bone loss, namely calcar atrophy, caused unstable markers leading to the exclusion of three patients.

ABG-II prosthesis is known to be at risk for periprosthetic fractures (Mäkela et al. 2010, Catanach et al. 2015). In our study of the 61 original operated patients, 4 (7%) suffered a postoperative periprosthetic fracture. Of the 53 included patients mean age of 62 at the beginning of the study, by the 9-year extension study 13 patients (25%) were not able to participate due to health problems: 4 deceased and 9 had poor general condition. No stem was revised during the follow-up. Such numbers point out that periprosthetic fractures, general health problems and death seem to be clinically more important than the stability of the cementless femoral stem.

There is still no consensus about the best fixation method of THA. Historically, cemented design has been the primary choice for prosthesis fixation in patients with osteoporotic bone (Rhyu et al. 2012). The cementless fixation has quickly reached popularity of cemented design even in THA patients over 55 years. No biological explanation has been attributed for this current trend for cementless fixation (Mäkelä et al. 2014).

In younger population cementless design seems to perform better, while cemented seems to be more applicable in older population, while 55-64 years of age seems to be an equivocal (Moskal et al. 2016). Elderly THA patients show less aseptic loosening than younger patients, while recurrent dislocations, periprosthetic fractures, and infections are more common in the elderly (Ogino et al. 2008).

This raises the question if cemented fixation would be more ideal for this patient population. Cementless designs have more intra- and postoperative periprosthetic fractures than the cemented design (Russell 2013), while cemented design has more aseptic loosenings (Berger et al. 1997). As periprosthetic fractures have devastating consequences and often need revision surgery, it is questionable whether this elderly patient population benefits for the theoretically life-long biological fixation of the cementless design over the cemented design.

## 6.2 Subwork zoledronic acid

In conclusion, this randomized, double-blind, placebo-controlled study demonstrated that postoperative zoledronic acid treatment does not affect the femoral stem migration in elderly women undergoing cementless total hip arthroplasty due to osteoarthritis.

Such result does not support the possibility of decreased stem migration as an associated finding for improved THA survival found with perioperative bisphosphonate use (Thillemann et al. 2010, Prieto-Alhambra et al. 2011, Prieto-Alhambra et al. 2014, Khatod et al. 2015).

The lack of the effectiveness of zoledronic acid in prevention of stem migration is in line with previous studies (Friedl et al. 2009, Muren et al. 2015). However, it must be noted that these studies were conducted with both sexes and with the less accurate EBRA-FCA method, which is not able to measure stem rotation. There are also other major differences between these studies. Our study population consisting of osteoarthritis patients showed an early cessation of migration, while the avascular necrosis patients of the study of Friedl *et al*, a patient group in great risk of later aseptic failure after THA implantation, showed a continuous increase of subsidence up to 3 years. This suggests that the migration of a cementless THA can be affected by the indication of arthroplasty.

Zoledronic acid reduced periprosthetic bone loss throughout our 4-year study period. This effect was seen in Gruen zones 6 and 7 representing the calcar area and lesser trochanter, which are of clinical interest as most periprosthetic bone loss and fractures occur in these areas (Capello et al. 2014, Behrens et al. 2017). These results are consistent with previous studies (Zhao et al. 2015). It must be noted that some studies doubt the long-term efficacy of bisphosphonates to preserve the periprosthetic bone from losing its density (Tapaninen et al. 2010, Muren et al. 2015).

The rationale for measuring BMD is to evaluate the quantity and the quality of the periprosthetic bone, but there are some limitations with DXA. Firstly, the BMD explains only 60-70% of the quality of the bone that is ability to resist fracture. In addition, DXA has limitations in measuring BMD: it is confounded by bone size, projection artifacts, amount of overlaying soft tissue and interdevice differences (Crabtree et al. 2007, Gluer 2017).

DXA has shown its validity in the diagnosis, prognosis, and treatment of osteoporosis (Cosman et al. 2014, Gluer 2017). It has weaknesses as there are no BMD targets for the treatment of osteoporosis and as a preoperative study for THA there are no BMD levels, when e.g. consideration has to be made between cementless or cemented THA design (Chapurlat 2016).

The clinical use of DXA in the evaluation of periprosthetic bone is scarce. Despite more than of three decades of extensive research on periprosthetic bone loss with DXA, no robust conclusions have been made. Results are inconclusive on regarding how much, where, when and what is the clinical significance of periprosthetic bone loss.

It is plausible that despite being able to predict the risk of fracture in naïve bone, the changing biomechanical environment in the case of an implantation of a femoral stem can make the measurement of areal hydroxyapatite density on the thin cortex an invalid study for periprosthetic bone quality.

It is of primary importance to avoid reoperations. At 9 years postoperatively, only one patient had undergone reoperation due to a periprosthetic fracture in the placebo group in our study. Cohort studies have shown improved implant survival in bisphosphonate users (Thillemann et al. 2010, Prieto-Alhambra et al. 2011, Prieto-Alhambra et al. 2014, Khatod et al. 2015). The current study with small sample size did not allow to evaluate the efficacy in the prevention of periprosthetic fractures.

Whether periprosthetic bone loss around femoral stem truly has any influence on the survival of the THA, is still under debate as larger observational studies evaluating BMD during long follow-up are needed (Muren et al. 2015). Although there is no evidence that periprosthetic bone loss causes symptoms or complications, it is evident that large amount of – or continuous – bone loss may reduce the stability of the stem (Sköldenberg et al. 2006).

It has been shown in the osteoporotic bone of femoral neck fracture patients that the femoral component can be successfully fixated with a cementless design. However, periprosthetic bone loss was evident and the clinical problem was periprosthetic fractures (Sköldenberg et al. 2014). It is tempting to think that as

bisphosphonates have shown to reduce periprosthetic bone loss (Zhao et al. 2015), they would protect from detrimental periprosthetic fractures, also. Conversely, the long-term use of bisphosphonates have been linked to periprosthetic atypical femoral fractures (PAFFs) (Khatod et al. 2015, Robinson et al. 2016).

Considering the significant role of the physiological response of stress shielding behind periprosthetic bone loss, plausible dose-dependent accumulation of microdamage in bone with bisphosphonates (Chapurlat and Delmas 2009) and the alleged findings of increased risk of PAFF in bisphosphonate users, it is questionable whether bisphosphonates are the proper treatment for periprosthetic bone loss as they cannot fix the underlying cause, stress shielding or general frailty with lowered quality of bone as a finding. Prospective studies are attributed to study whether the increased BMD due to bisphosphonate treatment outweighs the downsides of disrupted bone metabolism and drug-related side effects.

Zoledronic acid did not affect the functional or patient-related outcome measures. This finding is in line with other another study conducted with zoledronic acid in patients undergoing cementless THA (Huang et al. 2017).

As a limitation to this study, in cementless femoral component, RSA is a golden standard method to predict later aseptic loosening, which is important safety measure introducing new components. However, RSA is not a validated study method for other indications, such as enhancement of femoral stem stability.

In randomized controlled trials prospective sample size calculation is important to determine the number of participants needed to detect a clinically relevant treatment effect (Charles et al. 2009). The sample size was not based on a power analysis regarding RSA. Considering the great variation in implant migration, possible treatment effects on implant stability might be diminished. Post-hoc analysis showed that 70 patients per group would have been needed to detect a 50% reduction of the 1.4 mm migration observed in the placebo group.

The idea of randomized-controlled trials is to produce studies where groups differ only with respect to the interventions being compared (Bubbar and Kreder 2006). However, studies with small sample sizes are prone to failures of randomization. In this study ($n = 49$), the placebo group was significantly older ($71.0 \pm 9.0$ vs $65.3 \pm 8.0$ years, $p = 0.03$), had preoperatively lower scores of Harris Hip Score ($43.2 \pm 16.0$ vs $55.5 \pm 18.8$, $p = 0.02$) than the zoledronic acid group. This presents a limitation for the internal validity of the study.

Another limitation for the internal validity of the study is selection bias as 15 of the 49 patients were unable to complete the study protocol due to health problems or death, 11 of which from the placebo group with older patients. Elderly women,

even though are a group at risk for THA complications, are also prone to general health problems, making their eligibility for follow-up studies questionable. In other words, the survival of the cementless femoral component is better than the survival of an elderly woman as an eligible follow-up study subject and implant recipient.

## 6.3 Subwork ARMD

This study was the first prospective study to characterize local ARMD complication related to MoM hip arthroplasties with PET/CT. The management of this entirely new host tissue reaction is complex and patients show highly variable clinical presentations (Berber et al. 2015). There are two major issues in the management of ARMD: the inflammatory pathophysiology of ARMD makes the infection diagnostics challenging (Mikhael et al. 2009, Judd and Noiseux 2011) and the timing of revision surgery to avoid ARMD progressing into soft tissue necrosis (De Smet et al. 2011).

Both studied tracers, [$^{18}$F]FDG and [$^{68}$Ga]Citrate, are used to detect sites of inflammation and infection. [$^{18}$F]FDG accumulates in metabolically active cells, such as white blood cells, while [$^{68}$Ga]Citrate seems to be an *in vivo* iron mimetic accumulating at inflammatory and infected lesions. In moderate and severe cases of ARMD, [$^{18}$F]FDG, but not [$^{68}$Ga]Citrate, showed significantly higher uptake at the gluteal muscle region compared to controls. Such results indicate that [$^{18}$F]FDG could be useful monitoring the disease activity of ARMD.

Head-to-head comparisons of [$^{18}$F]FDG and [$^{68}$Ga]Citrate have been made in infectious conditions (Jodal et al. 2017, Salomäki et al. 2017), malignant tumors (Tan et al. 2015, Jing et al. 2017, Orunmuyi et al. 2017) and in atherosclerotic inflammation (Tarkin et al. 2017). [$^{68}$Ga]Citrate seems to provide excellent macrophage specificity, while [$^{18}$F]FDG shows higher sensitivity as it lacks cell specificity. Our imaging results with the highly inflammatory ARMD support these findings that [$^{18}$F]FDG is more sensitive to detect inflammatory lesions than [$^{68}$Ga]Citrate.

Gluteal muscle region was chosen for region of interest for $SUV_{max}$ measurements due to the clinical relevance for normal function of the joint. Detecting changes in the gluteal muscle region are important to identify patients that need immediate surgical intervention before irreversible muscle atrophy or necrosis that are linked with worse outcome (Grammatopoulos et al. 2009, De Smet et al. 2011). Serial MRI imaging has been suggested to detect these changes (Berber et al. 2015). As MRI produces only topographic images of the lesions, PET/CT produces

functional imaging possibly showing the activity of the progressing lesions. Our results support this as increased uptake of [$^{18}$F]FDG, but not [$^{68}$Ga]Citrate, which was associated with gluteal muscle necrosis in the revision surgery.

Only patient that didn't show neither [$^{18}$F]FDG nor [$^{68}$Ga]Citrate accumulation in the periprosthetic region. MARS MRI showed moderate ARMD, but during the 9.5-year follow-up the symptoms had not progressed and no revision surgery was needed. It is plausible that negligible tracer uptake predicted in this case correctly slow disease progression.

The detection of periprosthetic joint infection is of primary clinical importance as its treatment differs greatly from non-infected cases. Infection must be excluded when evaluating a painful arthroplasty, preferably following evidence-based guidelines. Basic laboratory measurements of ESR and CRP are applied, followed by the gold standard of joint aspiration. However, in patients in whom the diagnosis of infection cannot be reached, nuclear imaging, such as PET/CT, is applicable (Parvizi and Della Valle 2010).

There is no distinct guideline for the diagnosis of infection in ARMD. The inflammatory process of ARMD can mask the coexisting infectious symptoms and findings (Mikhael et al. 2009, Judd and Noiseux 2011). As the diagnosis of infection in ARMD is extremely difficult, a more aggressive approach to the preoperative evaluation of infection is suggested, repeating aspiration if necessary (Yi et al. 2015).

Most widely used method to diagnose infection with [$^{18}$F]FDG PET/CT is the uptake pattern introduced by Reinartz et al (Reinartz et al. 2005), which seems to be more applicable than the intensity of uptake (Yue and Tang 2015). There are no studies conducted with [$^{68}$Ga]Citrate for the detection of periprosthetic joint infection.

Even though our study was not aimed for infection diagnostics, some conclusions can be made concerning the applicability of [$^{18}$F]FDG and [$^{68}$Ga]Citrate PET/CT in diagnosing infection in ARMD. As it is an inflammatory condition, neither of the tracers are applicable as they lack specificity to distinguish the inflammation related to ARMD from infected cases.

As a limitation of this study, the small sample size with a high variety of clinical presentation of ARMD make the results ambiguous.

## 6.4 Future aspects

To transform migration detected by RSA into clinically beneficial data of the biological attachment, *osseointegration*, or the stability of the cementless femoral stem has obvious limitations that does not warrant further studies in the current form. The movements from one tenth of a millimeter to millimeters present more instability of the implant, while the evaluation of micromovements of micrometer range could be seen as a better marker of implant stability.

A measurement of micrometer-range movement at the bone-implant interface during walking would allow a deeper look at the stability of the stem. Such measurement needs an extremely accurate method, the accuracy of more than 40-year-old RSA method is not enough. For example, acceleration sensors or sensors measuring directly their distance placed in the bone and the implant might give useful information during gait.

Different type of connections – bony, fibrous or even loose – should provoke different kind of accelerations and distances between the sensors telling how large are the micromotions and indirectly the quality of the fixation. Therefore, after validation of histologic studies, it could be used to evaluate the implant-bone interface and successfulness of osseointegration.

It is plausible that DXA as a method of periprosthetic BMD is not sufficient for the periprosthetic bone quality measurement – outcome important for the patient as it defines the ability to resist fractures – in the complex biomechanical setting of THA. In other words, it can be concluded that the periprosthetic BMD has not been validated to periprosthetic bone quality. This should be conducted successfully to warrant further studies on periprosthetic BMD studies *per se*.

To produce clinically useful data on the quality of the periprosthetic bone, a study that would accurately address that question would be essential. To date, it seems that the two-dimensional radiographic evaluation of areal density of bone minerals does not produce sufficient data. Three-dimensional quantitative computed tomography are studied to improve the accuracy of bone quality studies (van Hamersvelt et al. 2017, Burt et al. 2018).

Moreover, there is even less knowledge what should be done to increase the quality of periprosthetic bone. Decreased periprosthetic bone quality in aging patients can be seen as the bony part of multiorgan incompensation due to frailty syndrome (Chen et al. 2014). One interesting research topic would be to explore how much of the periprosthetic fractures are explained by frailty and how much of the changing biomechanics of the arthroplasty. Furthermore, a study could be addressed to find out how does arthroplasty itself affect to the risk of a having a

femoral fracture of any type. It is plausible that patients having a periprosthetic fracture would have had a similar femoral fracture due to frailty, and especially due to its deteriorating effect on musculoskeletal condition.

It is clear that a healthy and active lifestyle is of primary importance when avoiding fractures and frailty in general. So far, drugs used for the treatment of osteoporosis have not been studied in large-scale randomized, controlled trials for the outcome of THA. These studies should include safety analysis of drug-related side effects, namely PAFFs. Even if the causality of bisphosphonate use and improved survival of THA could be confirmed, these detrimental fractures should be better studied before any conclusions can be made of the usage of bisphosphonates in cementless THA.

Another area to focus in THA studies is to concentrate on patient-important outcomes. Theoretically, even though RSA studies might show reduced implant movement or DXA might show increased areal bone mineral density, they have limited clinical interest if they cannot be linked with a beneficial outcome for the patient.

As a limitation to RSA and DXA studies for the future, the distinct prosthesis designs lead to different biomechanical properties that create unique patterns of RSA migration and changes in periprosthetic BMD limiting the generalization of the results. Therefore, it would be of major importance to give sufficient power and adequate follow-up to the studies to also investigate the outcome of the arthroplasty in randomized controlled trials. In such setting, RSA and DXA are probably too complex suggesting it might be of clinical interest to concentrate on larger samples instead of non-validated, complex imaging studies.

The popularity of MoM arthroplasties has significantly decreased. However, ARMD will present a challenge for clinicians for still quite a while. Recurrence of ARMD can occur if the revision excision is incomplete or there is another potential source of metal wear debris and/or corrosion. ARMD recurrence is at the moment the second most common reason for re-revision in MoM hip arthroplasties (Matharu et al. 2018).

Emergingly, there has been also reported failures in non-MoM THA due to ARMD attributed to wear and taper corrosion (Whitehouse et al. 2015, Plummer et al. 2016, Della Valle et al. 2018). Analysis of the world's largest arthroplasty database showed that 7.5% of ARMD revisions were performed on non-MoM bearings (Matharu et al. 2016). Compared to MoM hips, the non-MoM ARMD revisions were performed earlier and were more complicated. Moreover, the risk for re-revision is higher in non-MoM ARMD revisions (Matharu et al. 2017). Concerningly, the exact etiology and clinical significance of non-MoM ARMD

will become apparent by time (Matharu et al. 2016). Such reports emphasize the need for basic characterization of this local destructive complication of ARMD in hip arthroplasty. It is plausible that PET/CT can be integrated in the future to the diagnostics of non-MoM ARMD.

Further studies are needed to warrant whether [$^{68}$Ga]Citrate is feasible as an alternative to [$^{18}$F]FDG PET/CT in the diagnostics of periprosthetic joint infection. In meta-analysis [$^{18}$F]FDG has shown a wide variation of sensitivity from 28% to 91% and specificity from 9% to 97% diagnosing periprosthetic joint infection (van der Bruggen et al. 2010). [$^{68}$Ga]Citrate might be a more specific option for [$^{18}$F]FDG. The wide variations of [$^{18}$F]FDG are explained by the differences in the criteria used to diagnose infection pointing out how problematic is the diagnosis of periprosthetic joint infection. However, more infection-spesific tracers, such as radiolabeled antibiotics and antimicrobial peptides, would be applicable in clinical practice (Palestro 2014).

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# 7 SUMMARY AND CONCLUSIONS

Our findings support the following conclusions:

1. In mid-term follow-up of nine years, after THA in an elderly female cohort, all uncemented femoral stems were clinically stable, and only one out of the 28 femoral stems showed continuous migration.

2. Zoledronic acid reduces periprosthetic bone loss, but the clinical significance of this finding remains unknown. Zoledronic acid does not seem to reduce the amount of migration of the femoral stem in the elderly female.

3. The inflammatory disease of ARMD can be better visualized with [$^{18}$F]FDG than with [$^{68}$Ga]Citrate PET/CT after MoM hip arthroplasty.

As a summary, cementless THA achieves clinical stability even in aging women that are at risk for low bone quality. RSA can detect implant migration and therefore aseptic loosening, but the validity of migration data for implant stability is an untested hypothesis. Respectively, DXA can detect periprosthetic bone loss. However, its validity for periprosthetic bone quality is unknown. PET/CT can be used to detect various sites of inflammation, which was confirmed by our results with ARMD patients.

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