



**UNIVERSITY  
OF TURKU**

# **RADIOSTEREOMETRIC ANALYSIS OF INITIAL FEMORAL STEM MIGRATION IN CEMENTLESS TOTAL HIP ARTHROPLASTY OF POSTMENOPAUSAL WOMEN**

**Exploring contributing factors in  
initial femoral stem migration**

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**Sanaz Nazari Farsani**





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*To my father and mother*

UNIVERSITY OF TURKU

Faculty of Medicine

Department of Orthopaedics and Traumatology

Sanaz Nazari Farsani: Radiostereometric analysis of initial femoral stem migrations in cementless total hip arthroplasty of postmenopausal women

Doctoral Dissertation, 143 pages. September 2020

Doctoral Programme in Clinical Research (DPCR)

## ABSTRACT

In cementless total hip arthroplasty (THA), femoral stems rely on the initial press-fit fixation against the cortical bone to achieve osseointegration. In aging women, structural changes of the proximal femur may jeopardize the stem stability. Preoperative screening of bone quality and exploring the factors that cause stem migration may help in the selection process of patients for the use of cementless fixation techniques. Antiresorptive denosumab therapy might be efficient in preventing periprosthetic bone loss and reducing femoral stem migration in postmenopausal women.

Sixty-five postmenopausal women with primary hip osteoarthritis (60 to 85 years old and Dorr A-type or B-type femur morphology) underwent cementless THA with implantation of a parallel-sided femoral component in a randomized double-blind placebo-controlled trial. The patients randomly received denosumab or a placebo 1 month before and 5 months after the surgery. The three-dimensional stem migration was measured using model-based radiostereometric analysis (RSA). Patient's baseline characteristics, local and systemic bone mineral density (BMD) values measured by dual-energy X-ray absorptiometry (DXA), cortical-bone thickness measured by pulse-echo ultrasonometry, surgery-related factors, and postoperative walking activity were examined for the association with stem migration.

The accuracy and clinical precision of model-based RSA were comparable to those of marker-based RSA. Denosumab significantly decreased periprosthetic bone loss but did not reduce stem migration which occurred predominately during the first 3 months. DXA and pulse-echo ultrasonometry of the distal radius helped to identify patients at high risk of stem subsidence of more than 2 mm. Walking activity and local BMD dictated the direction and magnitude of stem rotation around y-axis.

Femoral stem stability is sensitive to adequate bone stock. In postmenopausal women, stem migration is predominantly due to impaired bone quality. Inhibition of periprosthetic bone resorption did not prevent stem migration. Preoperative evaluation of the skeletal status is recommended for all postmenopausal women with hip osteoarthritis before scheduling cementless THA.

**KEYWORDS:** Cementless total hip arthroplasty, Postmenopausal osteoporosis, Model-based radiostereometric analysis, Denosumab, Bone mineral density, DXA, Pulse-echo ultrasonometry

# TURUN YLIOPISTO

Lääketieteellinen tiedekunta

Ortopedia ja traumatologia

Sanaz Nazari Farsani: Lonkan tekonivelen biologinen kiinnittyminen

ikäntyvillä naisilla: varsiosan liikkeen radiostereometrinen analyysi

Väitöskirja, 143 s. Syyskuu 2020

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## TIIVISTELMÄ

Sementitön lonkan tekonivelleikkaus perustuu implantin biologiseen kiinnittymiseen. Kantavan varsiosan luutumisen edellyttää, että implantti saadaan leikkauksessa tukevasti paikoilleen kuoriluuta vasten. Tämän saavuttaminen voi olla vaikeaa naisilla, joille on kehittynyt vaihdevuosisen jälkeen reisiluun kuoriluun ohentumista ja huokoistumista. Tästä johtuen on tärkeää selvittää ennen leikkausta potilaan luuston kunto. On myös arvioitava muita tekijöitä, jotka voivat lisätä varsiosan liikettä. Ennen leikkausta aloitettu luukatoa estävä lääkitys voi vahvistaa kuoriluuta ja näin parantaa varsiosan tukevuutta.

Satunnaistettuun kliiniseen potilastutkimukseen osallistui 65 lonkan nivelrikkoa sairastavaa naispotilasta (keski-ikä 69 vuotta). Potilaille tehtiin sementitön lonkan tekonivelleikkaus. Ennen leikkausta aloitettiin luulääkitys (denosumabi), jonka tiedetään vahvistavan reisiluun kuoriluuta osteoporoosia sairastavilla naisilla. Potilaiden subjektiivista toipumista seurattiin kuvaavilla kyselykaavakkeilla ja myös objektiivisilla mittauksilla (kävelynopeus, kävelyaktiiviteetti, luuntiheysmittaus, kuoriluun ultraäänimittaus ja luuaineenvaihdunnan merkkiaineet). Varsiosan kolmiulotteista liikettä seurattiin 3D-mallinnukseen perustuvalla radiostereometrisellä analyysillä. Menetelmän tarkkuus ja toistettavuus varmistettiin prekliinisessä kokeessa muoviluumalleilla.

Lääkehoito esti reisiluun yläosan paikallisen luukadon varsiosan ympärillä, mutta se ei vähentänyt varsiosan painumista ja kiertymistä. Liikettä tapahtui ensimmäisten kuukausien aikana leikkauksesta. Varsiosat luutuivat ja hoitoryhmien välillä ei ollut eroa kliinisessä toipumisessa. Ennen leikkausta tehty ranteen kuoriluun paksuuden ultraäänimittaus (Bindex®) ja luuntiheysmittaus auttoivat tunnistamaan kohtalaisen hyvin ne potilaat, joille kehittyi varsiosan yli 2 mm painuminen leikkauksen jälkeen. Varsiosan kiertymisen suunta ja määrä heijastivat kävelyaktiivisuutta leikkauksen jälkeen.

Tulokset vahvistivat aiempia tuloksia, että biologisesti kiinnittyvä lonkan tekonivelen varsiosa vaatii hyvää luuainesta. Luulääkkeellä (denosumabi) voidaan estää paikallista luukatoa, mutta luuresorption esto ei vähennä varsiosan alkuvaiheen liikettä. Luuston kunnan seulontaa suositellaan kaikille vaihevuosi-ikä ohittaneille naisille, joille suunnitellaan sementitöntä lonkan tekonivelleikkausta.

**AVAINSANAT:** Lonkan tekonivel, radiostereometrinen analyysi, osteoporoosi, denosumabi, luuntiheys, luun ultraäänimittaus

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# Abbreviations

3D	Three dimensional
AE	Adverse event
AO	Acetabular offset
AP	Anteroposterior
ASA	American Society of Anaesthesiologists physical status classification
AUC	Area under the curve
BMD	Bone mineral density
BMI	Body mass index
BPI	Brief pain inventory
CAD	Computer-aided design
CFI	Canal flare index
CI	Confidence interval
CN	Condition number
CONSORT	Consolidated standard of reporting trials
CT	Computed tomography
CV	Coefficient of variation
DI	Density index
DXA	Dual-energy X-ray absorptiometry
EBRA-FCA	Einzel-Bild-Roentgen-Analyse-femoral component analysis
EGS	Elementary geometric shapes
FO	Femoral offset
FRAX	Fracture risk assessment
GO	Global offset
HA	Hydroxyapatite
HHS	Harris hip score
IQR	Interquartile range
ISCD	International Society for Clinical Densitometry
LS	Least square
ME	Mean error of rigid body fitting
MRI	Magnetic resonance imaging

OA	Osteoarthritis
OP	Osteoporosis
OR	Odd ratio
P	Probability
PROMs	Patient-reported outcome measures
QUS	Quantitative ultrasound
RCT	Randomized clinical trial
ROC	Receiver operating characteristic
RSA	Radiostereometric analysis
SAE	Serious adverse event
SD	Standard deviation
SF	Short form
THA	Total hip arthroplasty
VFA	Vertebral fracture assessment
WHO	World health organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

# List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

- I **Nazari-Farsani S**, Finnilä S, Moritz N, Mattila K, Alm JJ, Aro HT. Is model-based radiostereometric analysis suitable for clinical trials of a cementless tapered wedge femoral stem? *Clinical Orthopaedics and Related Research*, 2016; 474:2246-2253.
- II Aro HT, **Nazari-Farsani S**, Vuopio M, Löyttyniemi E, Mattila K. Effect of Denosumab on Femoral Periprosthetic BMD and Early Femoral Stem Subsidence in Postmenopausal Women Undergoing Cementless Total Hip Arthroplasty. *JBMR Plus*, 2019; 3:e10217.
- III **Nazari-Farsani S**, Vuopio M, Löyttyniemi E, Aro HT. Contributing factors to the initial femoral stem migration in cementless total hip arthroplasty of postmenopausal women. manuscript.
- IV **Nazari-Farsani S**, Vuopio M, Aro HT. Bone mineral density and cortical-bone thickness of the distal radius predict femoral stem subsidence in postmenopausal women. *Journal of Arthroplasty*, 2020; 35:1877-1884.e1.

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# 1 Introduction

Total hip arthroplasty (THA) is known as the most successful surgical procedure which helps to relieve pain and restore functionality in patients suffering from disabling primary or secondary hip osteoarthritis (OA). THA is frequently performed globally. In Finland alone, over 9000 primary THAs are performed annually (Finnish Arthroplasty Register, 2019).

Cementless THA was introduced to avoid complications involved in cemented THAs. Uncemented stems were initially designed for young, active patients because of their extraordinary longevity (Dutton & Rubash, 2008). Nowadays, the majority of THA patients receive uncemented implant components in many countries. However, in Finland, the use of cementless fixation decreased from 43% to 24% between 2010 and 2017 (Bunyoz et al., 2020). Cementless THA has been successfully applied even in octogenarians (Keisu et al., 2001; Riley et al., 2016). In cementless THA, initial stability is of great importance for the successful biological fixation. Initial stability might be affected by patient-related factors such as a low systemic BMD (Aro et al., 2012) and surgery-related factors including stem design, material, coatings, and surgical technique (Khanuja et al., 2011). Excessive migration at the bone-implant interface delays and even inhibits osseointegration (Jasty et al., 1997; Pilliar et al., 1986) and failure of osseointegration can lead to clinical loosening of the implant (Mavrogenis et al., 2009). Therefore, it is important to identify patients prone to excessive initial femoral stem migration.

Postmenopausal women suffer from unfavorable changes of the cortical bone including endosteal trabeculation and increased intracortical porosity (Zebaze et al., 2010). This remodeling process leads to disproportionate changes in intraosseous dimensions of the femur, causing a gender issue in THA (Casper et al., 2012). Postmenopausal women with osteoporosis or osteopenia are prone to periprosthetic bone loss (Alm et al., 2009; Venesmaa et al., 2003) which might predispose them to periprosthetic fractures. Revision surgery of periprosthetic fractures is highly costly and have detrimental effects on morbidity and mortality of THA patients (Lindahl et al., 2007; Toogood & Vail 2015). Consequently, it is important to identify high-risk patients before performing cementless THA. In order to reduce the risk of revision

surgery, cemented fixation of femoral stems is recommended in patients 75 years or older (Tanzer et al., 2018; Bunyoz et al., 2020).

Bisphosphonates are currently widely used antiresorptive therapies in the treatment of osteoporosis (Baron et al., 2011). In cementless THA, bisphosphonates have shown to reduce periprosthetic bone loss (Aro et al., 2018; Bhandari et al., 2005; Sköldenberget al., 2011). However, bisphosphonates have not improved the primary stability of uncemented femoral stems in randomized clinical trials (Aro et al., 2018; Sköldenberget al., 2011). Clinical studies have also associated bisphosphonate use to improved survival and lowered revision risk of uncemented and cemented THAs (Prieto-Alhambra et al., 2011; Khatod et al., 2015). No previous study has investigated if denosumab, which is an approved therapy for postmenopausal osteoporosis (Cummings et al., 2009), can prevent periprosthetic bone loss and thereby improve femoral stem stability.

Radiostereometric analysis (RSA) is an accurate technique for the assessment of the postoperative stability of femoral stems. Initial femoral stem migrations measured by RSA has a diagnostic capacity to detect long-term aseptic loosening of the cemented femoral stems (van der Voort et al., 2015) and knee prostheses (Pijls et al., 2012). However, the published research is not sufficient to form a conclusion regarding such an association for uncemented femoral stems (van der Voort et al., 2015).

This doctoral study investigated the impact of patient-related and surgery-related factors on the initial femoral stem migrations after cementless THA in postmenopausal women with primary hip osteoarthritis. The thesis was based on a randomized clinical trial, which compared periprosthetic femoral bone loss and femoral stem migration in denosumab-treated and placebo-treated patients. The feasibility of the model-based RSA for the femoral stem migration measurement was examined, and following that, femoral stem migration was monitored for 2 years postoperative. The impact of a wide range of patient-related and surgery-related factors on femoral stem migration was thoroughly investigated.

## 2 Review of the Literature

### 2.1 Cementless total hip arthroplasty

Total hip arthroplasty (THA) is a reproducible operation for the treatment of hip OA and late conditions of other hip diseases such as avascular necrosis. THA is highly cost-effective and is considered to be one of the most successful medical interventions in the orthopedics field (Learmonth et al., 2007). THA has a great impact on the health-related quality of life of the patients. The patients scheduled for THA are either middle-aged or aged. THA aims to retain working capacity in middle-aged and to restore physical activity and maintain functional independence in the elderly population.

The first attempt to perform a THA occurred in Germany in 1891, and was recorded by Professor Themistocles Glück who replaced the femoral head with ivory. Later, in the late 19th and early 20<sup>th</sup> century, surgeons applied different materials including fascia lata, skin, and pig bladders submucosa in between the articulating hip surfaces of the arthritic hip (Learmonth et al., 2007). In the mid-20<sup>th</sup> century, American surgeon Marius Smith-Petersen created the first mold arthroplasty out of glass which failed to withstand the great forces going through the hip joint and shattered (Knight et al., 2011). In 1953, English surgeon George McKee introduced the first metal-on-metal prosthesis which had a good survival rate. However, it suffered from the local effect of metal particles. Eventually, in the early 1960s, surgeon Sir John Charnley, known as the father of modern THA, designed low friction arthroplasty which had similar ideas to the current THA in terms of components; metal femoral stem, polyethylene acetabular component, and acrylic bone cement. It was called low friction because the design of the femoral head was small in order to minimize wear due to its smaller surface area (Knight et al., 2011).

In 1980, when total hip arthroplasty became more popular and was known as an established approach for the treatment of hip OA, concerns about the use of cement start to arise (Corten et al., 2011). The early failure of cemented stems was initially considered to be due to the infection but was later recognized as a local inflammatory response originating from the cement particles and/ or polyethylene wear which lead to a premature loosening of the cemented components (Learmonth et al., 2007).

Due to the complications involved in cemented THA including aseptic loosening (Hearn et al., 1995), bone resorption, (Jones & Hungerford, 1987) and osteolysis (Maloney et al., 1990) cementless femoral stems were designed to provide adequate initial stability and to encourage the bone to biologically integrate the implant (Learmonth et al., 2007). The first generation of the cementless femoral stems caused problems related to initial fixation failure, thigh pain, wear, and osteolysis (Banaszkiewicz & Kader, 2014). Consequently, the next generation of cementless femoral stems were designed to address these complications and were successful in improving implant fixation and health-related quality of life (Rorabeck et al., 1994) and decreasing long-term complications in young and active patients (McLaughlin & Lee, 2016). Subsequently, many different designs of uncemented femoral stems (Khanuja et al., 2011) showed good to excellent long-term results (Teloken et al., 2002) with a low revision rate, high patient satisfaction (Parvizi et al., 2004), and high survival of over 90% at 10 to 17 years (Aldinger et al., 2009; Hailer et al., 2010; Thien et al., 2014).

Cementless THA is nowadays the leading surgical technique globally. In the United States (the American Joint Replacement Registry 2019 Annual Report), only 4.3% of all elective THA procedures utilized cemented femoral components. In the Nordic countries, Australia, England-Wales, the Netherlands, Romania, New Zealand, and Switzerland there is substantial variation from country to country as to how often uncemented fixation is used, ranging from 24% (Sweden) to 71% (Denmark) (Bunyozy et al., 2020). In the Scandinavian countries, the use of uncemented fixation has increased since 2010 (in Norway from 25% to 38%), in contrast to other countries that show decreases (in Finland from 71% to 49%) (Bunyozy et al., 2020). The contemporary trend is to use cemented THA and hybrid fixation (cemented femur) in patients older than 75 years old, because cementless femoral stem fixation seems to be associated with a higher early rate of revision in these patients (Tanzer et al., 2018; Bunyozy et al., 2020).

Currently, data from national implant registers (Table 1) are the main source of information on the rate of revision surgery for cementless and cemented hip prostheses in general practice. The registers also provide data on surgical complications (infection, dislocations) and patient-reported outcome measures (PROMs) (Rolfson et al., 2016).



**Table 1.** List of national implant registers.

American Academy of Orthopaedic Surgeons/American Joint Replacement Registry
Australian Orthopaedic Association National Joint Replacement Registry
Danish Hip Arthroplasty Register
Dutch Arthroplasty Register
Finnish Arthroplasty Register
National Joint Registry (United Kingdom)
New Zealand Orthopaedic Association Joint Registry
Norwegian Arthroplasty Registry
Swedish Hip Arthroplasty Register
Swiss National Joint Registry

### 2.1.1 Stability of the femoral stem

Initial stability of the femoral stem is of great importance for ingrowth of the bone into the implant and the long-term clinical success of cementless THAs (Casper et al., 2011; Demey et al., 2011; Gortchacow et al., 2012; Grant et al., 2017). However, many uncemented stems demonstrate a small amount of initial migration before they fix into the bone (Campbell et al., 2011; Ström et al., 2006; Ström et al., 2007). Excessive initial migration of the implants is a potential cause of early implant failure (van der Voort et al., 2015; Streit et al., 2016). Consequently, it is important to predict cases prone to excessive initial migration before cementless THA. Different factors including patient-related and surgery-related factors such as implant design, surgical technique, and stem to canal fill ratio may contribute to initial femoral stem migration (Weber et al., 2014; Grant et al., 2017).

### 2.1.2 Principle of osseointegration of femoral stem

Cementless THA incorporates with the host bone through a process called osseointegration (Morgano et al., 2017). Osseointegration is the phenomenon in which the host bone integrates an implant biologically by making a direct osseous interface without intervening fibrous tissue (Albrektsson et al., 1981; Bothe et al., 1940; Shah et al., 2019). Osseointegration creates permanent implant anchorage after the initial press-fit fixation achieved during the surgery (Tarala et al., 2013). When proper osseointegration occurs, the implant surface is covered by ongrown and ingrown new bone. Failure of osseointegration causes fibrous tissue at the bone-implant interface, which result in low strength and/or loosening of the implant (Mavrogenis et al., 2009). In an autopsy retrieval study of well-functioning uncemented femoral stems, a mean

of 35 percent of the surface of the implants had bone ingrowth (Engh et al., 1995). The osseointegration is known to be affected by several factors including biocompatibility of the implant, design and surface of the implant, surgical techniques, quality of the host bone, loading condition, and bone turnover.

For successful osseointegration, there are two critical factors: the close contact (Sandborn et al., 1988; Dalton et al., 1995) and the minimal amount of micromotion (Engh et al., 1992; Jasty et al., 1997) at the implant-bone interface. It is reported that periprosthetic micromotions up to 40  $\mu\text{m}$  lead to bone formation and osseointegration, whereas micromotions greater than 150  $\mu\text{m}$  may result in fibrous formation around the implant (Jasty et al., 1997). However, defining a certain threshold of stem micromotions for the success or failure of cementless THA remains in question.

Initial osseointegration usually takes four to twelve weeks after implantation but might continue progressing over several months and up to three years (Zweymuller et al., 1988). The strength of the osseointegration increases over time (Tarala et al., 2013). In the cementless femoral component, osseointegration can be assessed either from plain radiographs through Engh's classification (Engh et al., 1990) or more accurately using RSA (Ryd, 2006).

### 2.1.3 Role of stem design

Various femoral stem designs are utilized to maximize initial stability and to minimize the periprosthetic bone loss caused by stress-shielding (Khanuja et al., 2011). When cementless femoral stems initially came on to the market, they were classified as either straight or curved; similarly, they were divided as either fixing proximally on metaphysis or distally on diaphysis. However, nowadays different designs of cementless femoral stems have been developed which can be classified based on their contact site with implants and the cortical bone. The implant shape determines the cortical contact and initial stability. Porous surfaces are located in a place where the fixation is desired through ingrown new bone (Khanuja et al., 2011). The surface characteristics of the cementless femoral stem determine the pattern of new bone formation. Ingrowth occurs when the bone grows inside a porous surface, while ongrowth occurs when the bone grows onto a roughened surface (Khanuja et al., 2011).

Strain-adaptive bone resorption is an inevitable biological response around uncemented femoral stems (Kerner et al., 1999; Sumner, 2015; Yamako et al., 2017). Against expectations, it is difficult to avoid strain shielding by changing the implant geometry and material properties (Cilla et al., 2017). Indeed, custom-designed femoral stems have demonstrated periprosthetic bone loss (Grant et al., 2005; Nysted et al., 2011). The periprosthetic bone loss might detrimentally affect the longevity of the hip implant and increase the risk of periprosthetic fracture (Peitgen et al., 2018;

Riviere et al., 2018). It is important to recognize that evidence-based data on the causal association between strain-adaptive bone resorption and clinical complications which is still scanty. In fact, first-generation femoral stems with extensive coating have shown major periprosthetic bone loss but a low rate of periprosthetic fractures and late mechanical loosening (Grant & Nordsletten, 2004). The close association between periprosthetic bone loss and the increased risk of periprosthetic fractures has become evident in patients with femoral neck fractures treated by cementless THA (Sköldenberg et al., 2014).

#### 2.1.4 Complications of cementless THA in postmenopausal women

The current designs of the uncemented femoral stems show excellent overall results and success even in octogenarians (Keisu et al., 2001; Riley et al., 2016). However, there is a certain variation in the long-term survival rate of different implants. Intra-operative and postoperative periprosthetic femoral fractures have emerged as the main concern (Abdel et al., 2016; Ponzio et al., 2015; Streit et al., 2011; Thien et al., 2014; Watts et al., 2015).



**Figure 1.** Dorr classifications of type A, B, and C proximal femur in antero-posterior (left) and lateral (right) views (From: Nakaya et al., 2019 © Reprint with permission).

Female patients with low cortical indices showed a higher chance of stress shielding (Engh et al., 2003). There is a strong linear correlation between periprosthetic bone loss and the pre-existing bone mineral content of the femur (Kerner et al., 1999; Rahmy et al., 2004; Venesmaa et al., 2003). Clinically, women with low BMD are prone to early periprosthetic bone loss (Alm et al., 2009; Venesmaa et al., 2003). Female patients aged over 65–70 years are also at the highest risk for intra-operative and postoperative periprosthetic femoral fractures (Lindahl et al., 2007; Ponzio et al., 2015; Abdel et al., 2016).

Cortical-bone fragility is the main contributor to the pathogenesis of nonvertebral fragility fractures (Ahmed et al., 2015; Shigdel et al., 2015; Zebaze et al., 2010), and probably also in the pathogenesis of periprosthetic fractures. Female patients suffer from unfavorable changes of the cortical bone including endosteal trabeculation and increased intracortical porosity (Zebaze et al., 2010). This remodeling process leads to disproportionate changes in intraosseous dimensions of the femur, causing a gender issue in THA (Ahlborg et al., 2004; Casper et al., 2012). In the worst cases, the characteristics of a stovepipe femur with thinned cortices and a wide diaphyseal canal (Dorr type C) could be observed on the radiographs (Dorr et al., 1993) (Figure 1). Dorr type C of the femur morphology is frequently evident in postmenopausal women with osteoporosis (Mäkinen et al., 2007). Patients with femoral Dorr type C have a 5.2 times increased risk for postoperative periprosthetic fractures (Gromov et al., 2017).

## 2.2 Assessment of bone quality

Bone quality refers to several parameters that have an impact on the resistance of bone against fracture (Fyhrie 2005; Ascenzi et al., 2016). Bone densitometry using dual-energy x-ray absorptiometry (DXA), and measurement of cortical bone thickness with pulse-echo ultrasonometry are examples of clinical tools for indirect estimation of bone quality. The development of clinical methods for direct assessment of bone mechanical properties is still under progress (Allen et al., 2015).

### 2.2.1 Dual-energy x-ray absorptiometry

Dual-energy x-ray absorptiometry (DXA) is the standard established method for the measurement of bone density. From 1980s when DXA was commercially introduced until now, it has been the most widely used technique for osteoporosis diagnosis and fracture risk assessment (Genant et al., 1996; Blake & Fogelman, 2010). The method works by sending two low-dose x-ray beams that are absorbed differently by bones and soft tissues. The density profiles (x-ray attenuation) from these x-rays are used to calculate bone mineral content (g) and area (cm) is also assessed by calculating the number of pixels within the region of interest. Therefore, the areal BMD is reported by DXA as  $\text{g}/\text{cm}^2$ . DXA is usually utilized for the BMD measurement in the central and peripheral skeleton (hip, lumbar-spine, and distal radius). Recently, software algorithms have been applied to derive 3D models from hip DXA scans and compute volumetric trabecular and cortical bone BMDs (Winzenrieth et al., 2018). In addition, DXA is applied in vertebral fracture assessment (VFA) for detection of subclinical vertebral fractures with current measurements of vertebral BMD (McCloskey et al., 2008). DXA is the established method for quantifying the

extent of periprosthetic bone loss around the hip prostheses (Venesmaa et al., 2001; Bhandari et al., 2005; Alm et al., 2009; Knusten et al., 2014).

The precision of the DXA measurement is high (coefficient of variation from 1% to 2.5%) (Kim & Yang, 2014) and the radiation dose is low (about 10% of a normal chest x-ray) (Damilakis et al., 2010). Its accuracy (closeness of the measured BMD to the ash weight of the actual calcium content) is also reported to be between 85% to 90%. Nevertheless, DXA also has certain limitations. One of these limitations refers to the 2D nature of this imaging technique (Pezzuti et al., 2017) which results in the loss of information about the third dimension (depth of the bone) (Carter et al., 1992). This drawback makes the technique insensitive to the characteristic differences between varieties of populations. Another limitation of DXA is artifacts such as marrow fat (Kuiper et al., 1996), soft tissue (Bolotin, 1998), and degenerative diseases (Muraki et al., 2004; Salo et al., 2014) which might have an impact on the numerical results. In addition, two other disadvantages assigned to DXA are that is non-portable (Schousboe et al., 2017) and discrepancies exist between different manufactured devices (Carey et al., 2007). T-score thresholds are used to define different bone conditions based on DXA-measured BMD (Table 2).

**Table 2.** Classification of the bone status based on DXA-measured T-scores according to the WHO criteria.

Normal	T-score $\geq$ -1.0
Osteopenia	-2.5 < T-score < -1.0
Osteoporosis	T-score $\leq$ -2.5
Severe osteoporosis	T-score < -2.5 + fragility fracture

## 2.2.2 Pulse-echo ultrasonometry

The limitations and costs of DXA measurements (albeit modest), have limited the accessibility of the method in primary care centers (Schousboe et al., 2017). An ultrasound device has advantages when compared to DXA. It is portable, it has no ionizing radiation, and it is less expensive. Owing to these features, it seems to be a useful tool for pre-screening examinations for the identification of patients whose osteoporosis treatment decision could be made without the DXA examination (Schousboe et al., 2017).

Ultrasound techniques for screening and diagnosing osteoporosis had already been proposed in the 1980's with the introduction of the first quantitative ultrasound (QUS) (Langton et al., 1984). Later, several commercial devices based on through-transmission or axial-transmission were introduced (Damilakis et al., 2004; Nayak

et al., 2006). However, some of these devices did not exhibit a good correlation with central DXA-measured BMD (Massie et al., 1993; Young et al., 1993). As a limitation, the ultrasound methods are not feasible for evaluation of the treatment response to osteoporosis drugs (Firestein et al., 2012).

Pulse-echo ultrasonometry (PEUS) is a novel technique that was first introduced for the measurement of cortical bone thickness in osteoporotic patients (Karjalainen et al., 2008; Wear, 2003). Later, this technique was utilized for multi-site measurement of cortical bone thickness in the distal and proximal tibia and distal radius in combination with patient characteristic data (age, weight, and height), in the reconstruction of a parameter known as density index (DI), which is an estimate of the proximal femur BMD (Karjalainen et al., 2012). DI is highly correlated with total hip and femoral neck BMD (Karjalainen et al., 2012). This correlation was verified in a study population of 448 postmenopausal women (Karjalainen et al., 2016; Schousboe et al., 2017). In that study, the thresholds were also determined for the use of the device in clinical practice to pre-screen for hip osteoporosis with 90% sensitivity and 90% specificity which is in line with the recommendation by the UK National Osteoporosis (Blake et al., 2005) and the International Society for Clinical Densitometry (Hans et al., 2008; Krieg et al., 2008).

## 2.3 Radiostereometric analysis of the femoral stem migration

Radiostereometric analysis (RSA) which was developed in the 1970's, is a method for the three-dimensional (3D) migration measurement of orthopedic implants *in vivo* (Selvik, 1989). RSA is known as the most accurate and reliable method of implant migration measurement (Ryd 1992; Kärrholm et al., 1997). Due to its high accuracy and precision, RSA studies are powered with relatively few subjects (approximately 15 - 30 patients) (Kärrholm et al., 1994; Valstar et al., 2005; Derbyshire et al., 2009). Accordingly, new implants can be tested *in vivo* by limiting their exposure to as few patients as possible.

RSA is based on the simultaneous exposure of two x-ray beams and two recording media (e.g. film, cassettes, or digital detector) in conjunction with a calibration cage. Two radiographic arrangements are used for this set-up; uniplanar and biplanar. In the uniplanar setup, the x-ray recording media are placed next to each other while in the biplanar set-up, the x-ray recording media are positioned at a 90-degree angle to each other (Valstar et al., 2005). In THA implant migration measurement, a uniplanar set-up of RSA is used. In the uniplanar set-up, two x-ray tubes are angled approximately 20 degrees in relation to the floor and 40 degrees in relation to each other (Kärrholm et al., 1997). Subsequently, a calibration cage containing tantalum beads in well-defined, standard positions is placed on top of the

x-ray films which are located under the patient examination table. Using the markers on the calibration cage and tantalum bone markers implanted during the surgery, the original position and orientation of the RSA-marked implant are reconstructed by RSA computer software.

To measure the migration of an implant, radiostereometric radiographs are taken immediately after the surgery (within 5 days postoperatively according to the ISO standards; 16087:2013) and repeated at certain time-points. First postoperative radiographs are considered as baseline. The software calculates implant micromotion by assessing the 3D location of the implant in each time-point followed by the comparison of the current location and orientation of the implant with that of the baseline image.

RSA is not only applied for implant migration measurements. It has other applications such as implant wear particle migration (Callary et al., 2013), femoral head penetration (Bragdon et al., 2004), and monitoring fracture stability (Madanat et al., 2012; Finnilä et al., 2019).

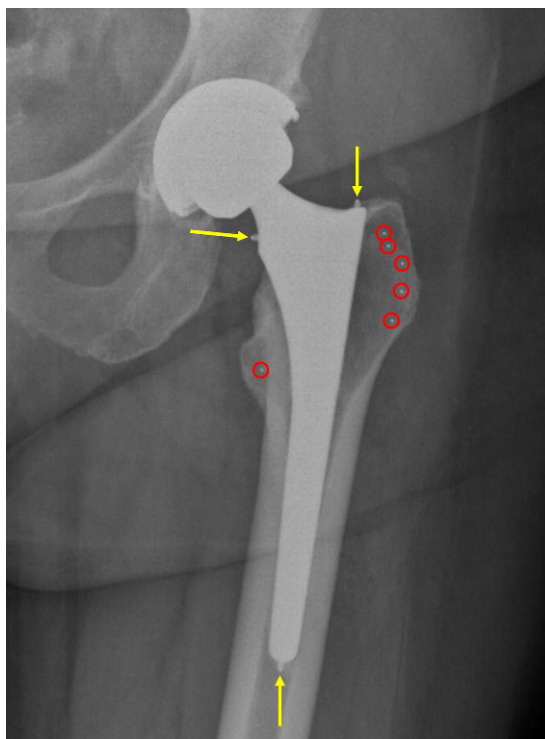
Einzel-Bild-Roentgen-Analyse (EBRA, University of Innsbruck, Austria) is another computerized measurement system method for measuring 2-dimensional (2D) migration of the femoral components from digitized plain radiographs. The method has been used in many studies to evaluate migration patterns of both implant components and for predicting cup and stem failure (Krismer et al., 1996, 1999; Friedl et al., 2009; Kutzner et al., 2016, 2020). However, the accuracy of this method is inferior to that of the RSA method due to the 2D nature of the EBRA-FCA measurement system.

### 2.3.1 Marker-based and model-based RSA

Conventional marker-based RSA, which is considered as the gold standard, requires attachment of tantalum markers in the bone (6 to 8 beads) and the use of custom-modified implants which are marked with at least three non-collinear tantalum beads in the locations demonstrated in Figure 2. Tantalum is an element with a high atomic number (73). Therefore, it is radiopaque and easy to identify on the radiographs. Indeed, this refractory metal has high biocompatibility (Levine et al., 2006). This element has been used as a bone marker for thousands of patients with no side effects (Kärrholm et al., 1997). In marker-based RSA the application of manufacturer-modified implants and assessment of the CE marking are costly in terms of time and money. In marker-based RSA the software calculates the micromotion of the center of gravity of the implant segment in relation to the bone segment as a function of the follow-up time.

Model-based RSA also requires surgical implantation of tantalum bone markers, however, there is no need for implant markers. Thus, model-based RSA makes

possible RSA studies of clinically used implants without modifications. The model-based RSA technique was developed to work without attaching markers to the implants. In the model-based RSA technique, the location of the implant is assessed by matching a 3D surface model to the actual radiographic projection of the implant (Kaptein et al., 2003, 2006, Prins et al., 2008, Valstar et al., 2001b). The virtual surface model of the implant components could be based on computer-aided design (CAD) (Kaptein et al., 2003; 2006; Prins et al., 2008), reverse-engineered implant models (Kaptein et al., 2003; Seehaus et al., 2013), or elementary geometric shapes (EGS) (Kaptein et al., 2006; Prins et al., 2008; Li et al., 2014). The RSA software calculates the exact 3D position of the implant by using the center of the femoral head and stem as reference points (Prins et al., 2008). The CAD model is then matched to the contour of the implant in the radiographs to reconstruct the position of the implant. The precision and accuracy of model-based RSA measurements should be evaluated before its application in a clinical trial (Kaptein et al., 2006; Valstar et al., 2005).



**Figure 2.** Illustration of an implant marked with beads for marker-based RSA. Three RSA beads are shown with yellow arrows and six tantalum bone beads are shown with red circles. (From: Aro et al., 2018 © Reprint with permission).



### 2.3.2 Accuracy and precision of RSA

The accuracy and precision of an RSA study depends on different factors, such as the radiographic technique, the software used for the analysis, and the position of the tantalum markers (Bragdon et al., 2004). Standardization of the clinical set-up for imaging is equally important (Lindgren et al., 2019; Mäkinen et al., 2004). Particularly, the precision of the model-based RSA is highly affected by stem design (Prins et al., 2008) and the quality of the CAD models used for the analysis (Seehaus et al., 2013). Consequently, due to great variation of the cementless femoral component designs (Khanuja et al., 2011) model-based RSA is sometimes reported as suffering from low precision (Kaptein et al., 2006). Regarding this issue, accuracy and precision validation are highly recommended before starting a model-based RSA trial (Kaptein et al., 2006; Valstar et al., 2005).

Accuracy and precision are two different terms that sometimes are used exchangeably in RSA studies. Accuracy demonstrates how close the measurement results are to ground truth, while precision refers to the closeness of the measurements when they are repeated. To evaluate the accuracy of an RSA system (including the implant, imaging technique and analytical software) phantom models are required. Phantoms make it possible to create accurate translations and rotations (ground truth) using highly accurate micromanipulators (Bragdon et al., 2004; Madanat et al., 2005; Önsten et al., 2001) which have substantially higher resolution than RSA and to compare the RSA-measured migration with the ground truth. The precision of the RSA system could be evaluated with phantom (pre-clinical) and with trial patients (clinical) by repeating the radiostereometric imaging (double examination) and calculating the differences between the repeated measurements. Based on the ISO 16087:2013 standard, the clinical precision should be assessed for each clinical study.

Accuracy of the RSA-measured micromotions is affected by the distribution of the tantalum beads within the rigid body, and their stability across the follow-up (Kärrholm, 1989). To calculate the micromotions properly, tantalum markers are required to be non-collinear and randomly and widely distributed over the segment. This should be examined for each radiograph using the calculation of the condition number (CN), which is an indicator of the markers distribution and a measure of how well the markers are scattered. A high CN might reflect the fact that the markers are positioned close to linear resulting in poor distribution, while a low CN indicates a wide enough spatial distribution. Condition numbers below 110 are considered very reliable and 150 is the upper CN limit according to RSA guidelines (Valstar et al., 2005).

The stability of the tantalum markers across the follow-up is also another important factor that might affect the accuracy of the RSA measurements. The mean error of rigid body fitting (ME) is the parameter which helps to examine the stability

of the tantalum markers by calculating the mean difference between the relative distances of markers in a rigid body in one examination compared to another examination (Valstar et al., 2005). The upper limit for ME is 0.35 mm according to RSA guidelines. ME and CN calculations constitute important quality control parameters that have to be confirmed before proceeding with the calculation of micromotions from follow-up examinations (Valstar et al., 2005).

## 2.4 Factors contributing to femoral stem migration

Ideally, uncemented femoral stems should not migrate at all (Kärrholm, 2012). However, studies of different population's age and gender showed that femoral stems subside to a certain extent, ranging from 0.7 mm to 1.7 mm, before the osseointegration (Campbell et al., 2011; Rutherford et al., 2019; Sköldenberg et al., 2011; Ström et al., 2007).

Based on the results of biomechanical testing with cadaver bones, two types of femoral component migrations are expected; the first is dynamic motion in response to loading cycle which usually happens during the first months after the surgery and, the second is irreversible movement over time (Schneider et al., 1989; Buhler et al., 1997). Pre-clinical in vitro tests have also shown that simulated stair climbing and muscle activity considerably affect the initial stability of uncemented femoral stems (Kassi et al., 2005). In vitro, uncemented femoral stems show a large variability in permanent motion before the stems had migrated into their final stable position (Ostbyhaug et al., 2010).

Investigating factors that contribute to femoral stem migration is of great importance. An EBRA-FCA study reported that stem excessive and continuous migration is directly correlated with long-term femoral component loosening and clinical failure (Streit et al., 2016). The limit of excessive migration remains unknown, but there are stems which have been seen to exhibit excessive subsidence (Baad-Hansen et al., 2011). Based on a meta-analysis of RSA studies (van der Voort et al., 2015), there are not sufficient published results to draw definite conclusions. It should be noted that RSA is not an irrefutable predictor of long-term stem success (Pijls & Nelissen, 2016). To expect RSA to fulfill such a role, a better understanding of the definite threshold values of migration for different stem designs is required (Frazer & Tanzer, 2020). In addition to the type of migration, including total migration or migration rate, the most relevant time point or period of measurement, the detection and interpretation of the outliers, and the appropriate sample size are other factors that need to be taken into account (Frazer & Tanzer, 2020). Nevertheless, continuous subsidence during a 6 to 12 month period after the operation could indicate an increased risk of future revision (Luites et al., 2006). In general, femoral stem migration after cementless THA in postmenopausal women is

poorly characterized in the literature. There might be patient-related and surgery-related co-factors dictating the magnitude of the initial stem subsidence and rotation.

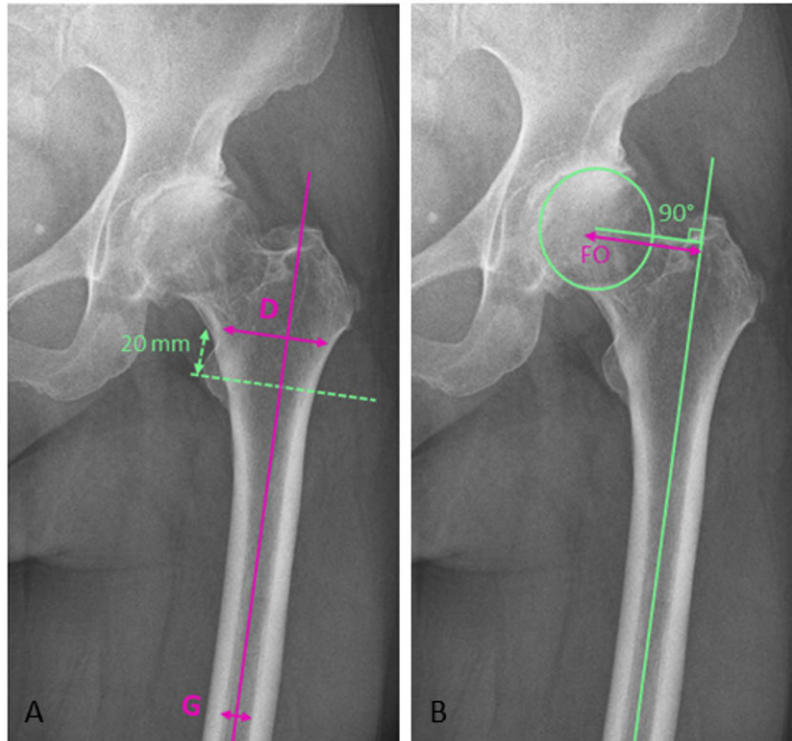
### 2.4.1 Patient-related factors

Femoral stem stability is sensitive to adequate bone stock and unaltered anatomy of the proximal femur (Grayson & Meneghini, 2018). The quality of the cortical bone is probably one of the most important factors contributing to stem initial migration in aging women. A considerable number of women with osteoarthritis of the hip suffer from primary or secondary hip osteoporosis (Glowacki et al., 2003; Mäkinen et al., 2007). It is already known that postmenopausal women with osteopenia and osteoporosis show increased femoral stem subsidence and rotation up to 3 months after cementless THA, while subjects with normal BMD demonstrate minimal stem subsidence (Aro et al., 2018; Aro et al., 2012). This association is not assumed to be related to the poor quality of intertrochanteric cancellous bone of the proximal femur (Moritz et al., 2011). Moreover, it is also known that most bone loss which occurs after 65 years is related to cortical and intracortical remodeling (Zebaze et al., 2010). These findings may suggest that the effect of postmenopausal bone loss on stem initial migration is related to endosteal trabeculation and increased intracortical porosity of the proximal femur in elderly women.

Canal flare index (CFI) may help to predict initial stem migration after cementless THA (Aro et al., 2012). CFI and Dorr classification are quantitative indicators of the femoral canal geometry. CFI is a quantitative measurement of geometrical changes of the proximal femur (Noble et al., 1988). It is defined as the ratio of D to G, where D is the metaphyseal width 20 mm proximal to the most prominent point of the lesser trochanter and G is the width of the intramedullary femoral isthmus (Figure 3-A). CFIs are classified either as stovepipe (< 3.0), normal (3.0 - 4.7), or champagne-fluted (> 4.7 - 6.5) (Noble et al., 1988). Dorr classification is also a quantitative evaluation of the proximal femur morphology from conventional radiographs (Dorr et al., 1993). Dorr system classifies the femurs into types A, B, and C; where type A refers to normally tapered shaped femur with thick cortices, type B designates a widened intramedullary canal diameter with thin cortices, and type C associates with complete lose of the tapered shape into a straight canal with thin cortices (Figure 1). Dorr type C has been reported as an independent risk factor for early periprosthetic fracture, following THA using a double tapered cementless stem (Gromov et al., 2017). Accordingly, considering bone morphology when planning for primary THA and using cemented femoral components in female patients with poor bone quality is highly recommended (Gromov et al., 2017).

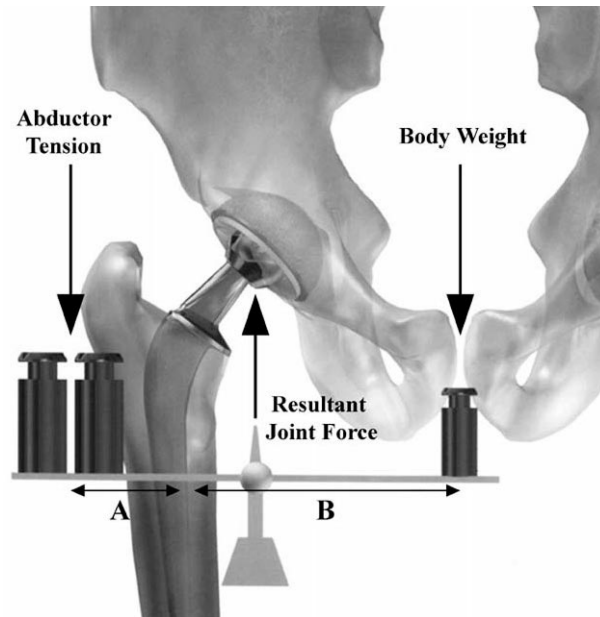
Presumably, physical characteristics such as body weight and height might also have an impact on stem migration. In an EBRA-FCA study, a weight of over 75 kg

and a height over 165 cm significantly influenced stem subsidence toward progressive migration (Stihsen et al., 2012). However, there is no RSA study showing such a correlation between the weight/ height and initial stem migration.



**Figure 3.** Illustration of the canal flare index and femoral offset measurements. Canal flare index (A) is calculated as the ratio of D to G, where D is the femoral canal width 20 mm above the most prominent point of the lesser trochanter, and G is the femoral isthmus width. Femoral offset (FO) was measured as the perpendicular distance from the center of femoral head rotation to the longitudinal axis of the femur.

In patients with THAs, femoral stems are under high physiological loads during walking and daily activities (GBergmann et al., 2001). Thus, the amount of physiological loading after surgery is a potential factor in promoting stem subsidence and rotation. The main load is applied to the stem from the anterosuperior (Figure 4) and the implemented force rises during stair-climbing (Davy et al., 1988; Kassi et al., 2005). This increased force might lead the stems, in particular cementless stems (Kassi et al., 2005), to migrate (Burke et al., 1991). However, immediate full weight-bearing after cementless THA seems to be safe and does not change the RSA-measured stem migration (Thien et al., 2007; Wolf, Mattsson, et al., 2010).



**Figure 4.** The hip joint has a fulcrum role in balancing the force of body weight with the force generated by the hip abductors (From: Charles et al., 2004 © Reprint with permission).

Based on the current recommendation (ISO 16087:2013), the baseline RSA measurements should be performed within 5 days postoperatively, preferably before weight-bearing. There are studies that have performed the baseline RSA imaging when the patients were still anesthetized. These studies demonstrated no migration of uncemented femoral stems (Ström et al., 2007) and acetabular cups (Wolf et al., 2010) during the first week after surgery. Comparison of the two weight-bearing regimens including unrestricted and partial weightbearing has also shown no impact on the initial migration pattern of the stem during the first postoperative week (Ström et al., 2007).

## 2.4.2 Surgery-related factors

Stem design seems to be an important surgery-related factor contributing to migration. Stem geometry, its surface properties, and its material all might affect the osseointegration and stability of the femoral stem (Khanuja et al., 2011). Geometry seems to be the most critical feature of the stem influencing its initial migration. Even small modifications of cementless hip stems might affect its 3D migration pattern (Weber et al., 2014).

The proper reconstruction of anatomical parameters of the hip joint is critical for stem stability and successful THA surgery (Mahmood et al., 2016), particularly, for

soft tissue balancing (Charles et al., 2004) and avoiding limb lengthening (Flecher et al., 2016). The femoral offset (FO) is one of the parameters that need to be restored. FO is assessed before the surgery (Amirouche et al., 2016) (Figure 3-B). The offset of the implanted prosthesis (neck-shaft angle) is the main determinant of the femoral offset (Charles et al., 2004). Accordingly, implant offset might be a surgery-related parameter influencing stem initial migration.

Fit and fill ratio parameters of cementless stems are other crucial parameters influencing femoral component stability and clinical outcomes (Ambrosio et al., 2020; Dorr et al., 1997; Dujardin et al., 1996; C. A. Engh et al., 1990; Laine et al., 2001; Naidu et al., 1996). A number of parameters including femoral stem design, the cross-sectional area of the stem, proximal geometry of the femoral canal, and surgical technique influence the degree of the stem to canal fill ratio (Haraguchi et al., 2001). The fill ratio in the metaphyseal region is reported as a factor decreasing torsional micromotions (Callaghan et al., 1992) and improving bone ingrowth (Cameron et al., 1973). Large gaps between the cortical bone and the femoral component's surface result in reduce bone ingrowth and lower mechanical attachment strength of the implant (Dalton et al., 1995). Custom-designed stems with an optimal proximal fit and fill may provide the best initial stability for rotation (Ostbyhaug et al., 2010) but clinically no improvement in long-term stability was found from using a customized stem design (Nysted et al., 2014). An EBRA-FCA study also reported that stems which provided a poor fit and fill into the bone with a lack of cortical contact resulted in significantly higher odds of migration compare to those with a tight fit (Stihsen et al., 2012). Nevertheless, there is a lack of data to confirm such an association between poor fit and fill ratio and femoral stem migration using the RSA measurement system.

## 2.5 Bisphosphonates and denosumab in joint arthroplasty

Bisphosphonates and denosumab are two important antiresorptive drugs approved for the treatment of osteoporosis (Baron et al., 2011). The mechanism of action of these two treatments is different (Baron et al., 2011). Bisphosphonates have a high affinity with bone and they inhibit osteoclastic bone resorption (Kennel & Drake, 2009). They inhibit osteoclast activity and thereby reduce bone resorption. The activation of osteoclasts is a necessary mechanism in bone and mineral homeostasis (Baron et al., 2011). This process involves two main tasks; the removal of mineralized bone by osteoclasts through resorption (Schaffler, 2003), and the formation and mineralization of new bone matrix created by osteoblastic activity (Bruzzaniti & Baron, 2006; Martin et al., 2009). After menopause and in osteoporosis patients, the amount of removed bone during resorption by osteoclasts

surpasses that replaced during bone formation by osteoblasts, resulting in a net loss of bone mass, and increased skeletal fragility and fracture risk (Russell et al., 2001). The administration of bisphosphonates can correct this imbalance between bone resorption and bone formation. Of the currently available bisphosphonates, etidronate and clodronate are non-Nitrogen (N)-containing-bisphosphonates, whose antiresorptive potency is at the lower end of the scale, whereas pamidronate, alendronate, risedronate, ibandronate, and zoledronic acid are N-containing-bisphosphonates which demonstrate antiresorptive potencies 100 to 10,000 times to that of etidronate (Russell et al., 1999). The changes in bone resorption and bone formation can be clinically monitored using serum marker measurements (Bone et al., 2011).

Denosumab is the first biologic therapy approved for postmenopausal osteoporosis (Cummings et al., 2009). It is an antibody that binds and inhibits osteoclasts (Lewiecki, 2018). Denosumab increases BMD in osteoporotic patients (McClung et al., 2017) and decreases fracture risk (Cummings et al., 2009). Denosumab can decrease intracortical porosity and increase the volume and strengthen parameters of both cortical and trabecular bone (already after 12 months with 60 mg of denosumab injection every 6 months) in the osteoporotic proximal femur of postmenopausal women (Genant et al., 2013; Zebaze et al., 2016). In a head-to-head comparison, denosumab resulted in higher BMD gains compare to oral bisphosphonates therapy (Brown et al., 2014).

Bisphosphonate users have been associated with a decreased risk of requiring hip arthroplasty revisions (Prieto-Alhambra et al., 2011; Khatod et al., 2015; Teng et al., 2015). However, there is still a lack of evidence on the clinical benefit of pharmaceutical interventions in the prevention of periprosthetic fractures, which emerge as a concern when using cementless THA (Abdel et al., 2016).

### 2.5.1 Prevention of periprosthetic bone loss

Periprosthetic bone loss is mediated by osteoclast activation in the vicinity of the stem. Periprosthetic bone loss is acutely due to the surgical trauma and chronically due to the stress shielding, which is mainly a consequence of the mismatch in elasticity modulus between the prosthesis and the periprosthetic bone (Kerner et al., 1999; Sumner, 2015; Yamako et al., 2017). According to a meta-analysis of six randomized controlled trials, antiresorptive bisphosphonate treatment can be effective in maintaining the periprosthetic BMD (Bhandari et al., 2005). However, these studies did not include the analysis of clinically relevant outcomes (functional outcomes, revision rates, and quality of life). Therefore, it was concluded that the evidence regarding the beneficial effects of bisphosphonates should be interpreted with caution (Bhandari et al., 2005). In recent years, randomized clinical trials have

confirmed the efficacy of postoperative bisphosphonates (in particular, zoledronic acid and risedronate) in the prevention of periprosthetic bone loss but the clinical follow-ups (range 4 to 10 years) did not reveal clear benefits in clinical outcome measurements (Aro et al., 2018; Muren et al., 2015; Sköldenberg et al., 2011).

## 2.5.2 Prevention of implant migration

In pre-clinical studies, zoledronic acid enhanced bone ingrowth into porous tantalum implants as a potential method for the improvement of implant stability (Bobynd et al., 2005; Bobynd et al., 2009). In contrast, a randomized RSA clinical trial showed no effects of zoledronic acid on femoral stem migration (Aro et al., 2018). Furthermore, in a clinical trial, zoledronic acid has been shown to reduce the EBRA-measured migration of acetabular components in patients with THA-treated for avascular necrosis of the femoral head (Friedl et al., 2009). However, bisphosphonate did not show a significant impact on the stem (Friedl et al., 2009) and cup migrations (Wilkinson et al., 2005) measured by the EBRA method. In a randomized clinical trial, oral risedronate did not reduce femoral stem migration measured by the EBRA method (Sköldenberg et al., 2011).

## 2.6 Assessment of functional recovery

Following THA, it is clinically crucial to restore the walking capacity and to get patient's functional as quickly and efficiently as possible. There are several parameters that can help to assess the functional recovery of patients after THA. These parameters include gait analysis, monitoring the walking activity of the patients, and patient-related outcome measures.

### 2.6.1 Gait analysis

Gait analysis can provide invaluable information on the functional recovery of THA patients (Queen et al., 2011). Several THA studies have assessed gait changes before and after the surgery (McCrary et al., 2001; Mont et al., 2007; Meneghini et al., 2008) and reported an increased range of motion and improved gait after the operation (Queen et al., 2011). Walking speed is a reliable and sensitive measure appropriate for assessing and monitoring functional status and overall health in a wide range of populations including THA patients. Restoration of the normal walking speed is one of the aims of THA surgery which could be examined using gait analysis. Previous research has demonstrated that higher walking speeds or more postoperative improvement in walking speeds are associated with better clinical



outcomes or more improvement in clinical outcomes (Boardman et al., 2000; Behery & Foucher, 2014; Foucher 2016).

## 2.6.2 Walking activity

Monitoring the walking activity could provide decent information on the functional recovery of the patients after THA (Schmalzried et al., 1998). In addition, the amount of walking activity might affect the final amount of stem migration. Accordingly, it is important to monitor the walking activity of the patients after THA. Recently, a study on the mobility recovery of THA patients in the early postoperative period showed a clear trend towards increased activity over time (Toogood et al., 2016). This research suggested that such monitoring may allow for the early identification of the patients with slow mobility recovery (Toogood et al., 2016). However, up to now, little attention has been paid to this issue and there has been no detailed investigation on the impact of the walking activity on the uncemented femoral stem migrations. The pedometer is an inexpensive investigative tool with many potential applications, which can be utilized for the assessment of walking activity after THA (Schmalzried et al., 1998).

## 2.6.3 Patient-related outcome measures

Several patient-related outcome measures (PROMs) including Harris hip score (HHS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and Short Form-36 (SF-36) are utilized in monitoring THA patients (Fairbank & Pynsent, 2000; Gjeilo et al., 2007; Soohoo et al., 2007; Singh et al., 2016). It is reported that both absolute HHS postoperative scores and HHS score postoperative changes are predictors of revision risk after primary THA (Singh et al., 2016). WOMAC and several components of the SF-36 have also shown a similar level of responsiveness in THA patients (Soohoo et al., 2007).

## 3 Aims

The general aim of this thesis was to investigate the impact of patient-related and surgery-related factors on femoral stem migration after cementless THA in postmenopausal women. Such knowledge can help to avoid the use of cementless THA in subjects prone to excessive stem subsidence or rotation. The specific aims of each study were as follow:

- I. To verify the accuracy and clinical precision of the model-based RSA for the migration measurement of a cementless tapered-wedge femoral stem using a phantom.
- II. To evaluate the effect of an antiresorptive medication, denosumab, on the bone mineral density changes of the proximal femur and femoral stem migration after cementless THA in postmenopausal women.
- III. To examine the contribution of patient- and surgery-related factors on the magnitude of initial femoral stem migration in cementless THA of postmenopausal women.
- IV. To examine if pulse-echo ultrasonometry of distal-radius cortical bone thickness can predict femoral stem subsidence in cementless THA of postmenopausal women.

## 4 Hypotheses

The general hypothesis of this thesis was that implant migration after cementless THA in postmenopausal women with low systemic BMD is not a random event. Most likely, there are various patient-related and surgery-related contributory factors dictating the magnitude of initial femoral stem migration in this major subgroup of THA patients. The specific hypotheses of each study were as follow:

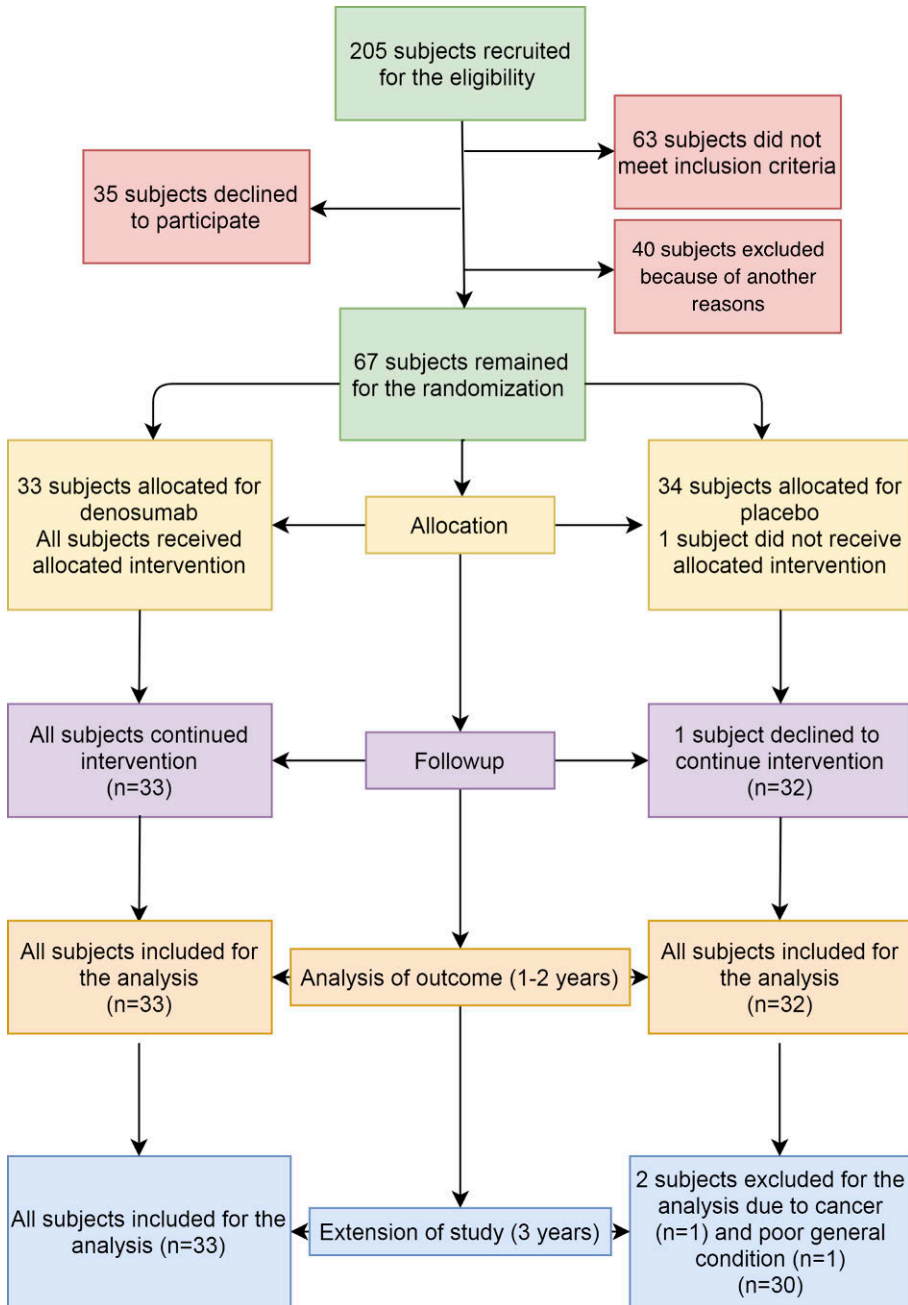
- I.** The accuracy of the model-based RSA for the three-dimensional measurement of stem translation and rotation is equivalent to that of marker-based RSA. The clinical precision of the model-based RSA is at an appropriate level that could replace marker-based RSA in the clinical trials of cementless tapered-wedge femoral stems.
- II.** Denosumab therapy started before cementless THR in postmenopausal women can have a double impact by decreasing periprosthetic bone loss and thereby reducing the amount of initial femoral stem migration.
- III.** In addition to low systemic BMD, other covariates, such as the amount of physiological loading, likely dictate the magnitude of initial femoral stem subsidence and rotation.
- IV.** Preoperative pulse-echo ultrasonometry of the distal radius is able to identify subjects who are at risk to femoral stem subsidence due to impaired bone quality.

## 5 Patients and study design

This thesis is based on the data analysis of a randomized clinical trial (RCT) (ClinicalTrials.gov NCT01926158). It was a single-center, randomized, double-blinded, placebo-control trial. Sixty-seven postmenopausal women aged between 60 to 85 years old were randomly assigned to receive subcutaneous injection of denosumab 60 mg or placebo 4 weeks before and 22 weeks after cementless THA and monitored for 48 weeks after the surgery (Figure 5). The trial included only female patients because postmenopausal women are prone to low BMD compared to age-matched men and the main targets of the denosumab treatment (periprosthetic bone loss and stem migration) are a detrimental consequence of low BMD.

The inclusion criteria was incapacitating primary hip osteoarthritis and Dorr A-type or B-type femur morphology. Exclusion criteria include severe osteoporosis (hip or lumbar spine T-score  $< -4.0$ ), Dorr C-type femur morphology, history of previous surgery of the index hip, evidence of secondary osteoporosis, rheumatoid arthritis or any other inflammatory arthritis, hepatic disease, vitamin D deficiency, disorders of parathyroid function, uncontrolled hyperthyroidism or hypothyroidism, history of malignancy (except basal cell carcinoma of the skin) within the last 5 years, severe asthma or chronic obstructive pulmonary disease, ever having used oral or intravenous bisphosphonates, use of other drugs that affect bone metabolism, Paget's disease, alcohol abuse, or mental, neurological, or other conditions that may affect the ability to perform functional or clinical assessments required by the protocol.

The **primary hypothesis** for this trial was that denosumab compared with placebo is effective in preventing periprosthetic bone loss in Gruen zone 7 of the proximal femur as measured by DXA at 48 weeks. The **secondary hypothesis** was that denosumab compared with placebo is effective in the enhancement of bone bonding (osseointegration) of cementless hip prostheses, as measured by RSA. This treatment effect is clinically highly meaningful because immediate stability and fast biologic osseointegration are the key goals of cementless THAs. Accordingly, the **primary endpoint** was the percent change from baseline in periprosthetic BMD of Gruen zone 7 of the proximal femur by 48 weeks. The **secondary endpoint** was the change from baseline in three-dimensional translational ( $\mu\text{m}$ ) and rotatory (degrees) migration of the femoral stems at 48 weeks.

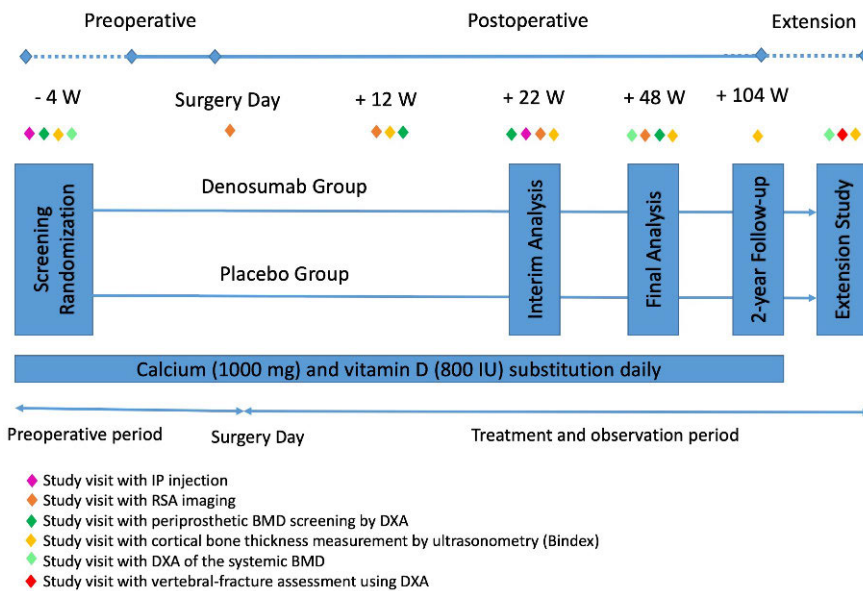


**Figure 5.** A flowchart of recruitment, randomization, and follow-ups in the RCT

The mean (95% CI) percentage change of periprosthetic BMD of the proximal femur in Gruen zone 7 from baseline to 48 weeks in the placebo group was expected to be about -21% (95% CI -17 to -26) (Alm et al., 2009). Denosumab was expected to

cause at least a 50% reduction of periprosthetic bone loss compared to the placebo. This reduction was considered as a clinically meaningful change resembling the difference of periprosthetic BMD (zone 7) between women with normal or low BMD (Alm et al., 2009). The minimum clinically relevant change of periprosthetic BMD is still unknown, for example, in the prevention of periprosthetic fractures. With a power of 90% ( $\alpha=0.05$ ) and a standard deviation of 7%, it was calculated that 28 patients were required in each group in order to detect the expected difference. A total of 68 patients (34 patients per category) were planned to be recruited in this trail.

The study was extended for a period of at least 2 years after the last dose of denosumab (the median after the surgery is 3 years) to investigate if discontinuation of denosumab might result in reduced BMD (as an adverse event [AE]) to the pretreatment levels (Bone et al., 2011; Cummings et al., 2018). The study design of the RCT is illustrated in Figure 6.



**Figure 6.** Study design and assessments during each visit.

The RCT was conducted according to the ethical principles of the Declaration of Helsinki. The Ethics Committee of the Hospital District of South-West Finland (decisions 105/2012 and 484/2017) and Finnish Medicines Agency (decision 183/06.00.00/2012, EudraCT 2011-000628-14) approved the RCT and all study participants provided written informed consent before enrollment.

## 6 Materials and Methods

For investigating the effect of patient-related and surgery-related factors on stem initial migration, the study covered preoperative baseline data (Table 3) including demographics and subjective data including physical activities, questionnaires (patient-reported outcome measures), radiological evaluation of the proximal femur and basic laboratory test. The accuracy of the model-based RSA, was assessed using a phantom experiment. For the accuracy and clinical precision measurement of the model-based RSA system, high-quality CADs of the combined stem-head models were utilized. Radiological outcome measures including RSA for the measurement of implant migration, fit and fill analysis for the assessment of stem to canal fill ratio, DXA imaging for the periprosthetic bone loss measurement and vertebral-fracture assessment, and pulse-echo ultrasonometry for the measurement of cortical bone thickness, were performed. The clinical outcome was assessed by evaluating the functional recovery of the patients, patient satisfaction assessment and hip-specific outcome scores.

**Table 3.** Patients characteristics and their values for outcome measures at baseline.

Parameters	Value
Age at consent (years) mean $\pm$ SD range	69.1 $\pm$ 5.5 60 – 84
BMI ( $kg/m^2$ ), mean $\pm$ SD	28.0 $\pm$ 4.5
ASA Class I-II (no. [%]) Class III (no. [%])	39 (60) 26 (40)
History of low-energy fractures (no. [%]) Yes No	17 (26.2) 48 (73.8)
25-hydroxyvitamin D (nmol/l), mean $\pm$ SD	95.8 $\pm$ 28.5
Total hip BMD ( $g/cm^2$ ), mean $\pm$ SD	0.92 $\pm$ 0.15
Femoral neck BMD ( $g/cm^2$ ), mean $\pm$ SD	0.83 $\pm$ 0.14
Lumbar spine BMD ( $g/cm^2$ ), mean $\pm$ SD	1.13 $\pm$ 0.20
Distal radius BMD ( $g/cm^2$ ), mean $\pm$ SD	0.65 $\pm$ 0.07
BMD diagnosis (no. [%]) <sup>a</sup> Normal BMD (T-score $\geq$ -1.0) Osteopenia (-2.5 < T-score < -1.0) Osteoporosis (T-score $\leq$ -2.5)	31 (48) 32 (49) 2 (3)
Femur cortical thickness (mm), mean $\pm$ SD	9.4 $\pm$ 1.6
Canal flare index, mean $\pm$ SD	3.8 $\pm$ 0.7
Size of the femoral stem, median (range)	3 (1 – 6)
Femoral offset (mm) Preoperative, mean $\pm$ SD Postoperative, mean $\pm$ SD	38.0 $\pm$ 4.6 37.6 $\pm$ 3.3
Stem-to-canal fill ratio <sup>b</sup> Proximal stem (%), mean $\pm$ SD Middle stem (%), mean $\pm$ SD Distal stem (%), mean $\pm$ SD	97.8 $\pm$ 2.4 85.8 $\pm$ 8.4 84.6 $\pm$ 8.9
Harris hip score, mean $\pm$ SD	48.4 $\pm$ 14.5
WOMAC score, mean $\pm$ SD	47.7 $\pm$ 15.7
Rand-36 score Physical component, mean $\pm$ SD Mental component, mean $\pm$ SD	33.1 $\pm$ 17.2 54.3 $\pm$ 18.5
Walking speed (m/s), mean $\pm$ SD	0.91 $\pm$ 0.26
Walking activity <sup>c</sup> (steps/day), mean $\pm$ SD	3080 $\pm$ 1920
Operation time (minutes), mean $\pm$ SD	81.9 $\pm$ 9.9
Blood loss during surgery (ml), mean $\pm$ SD	360 $\pm$ 150

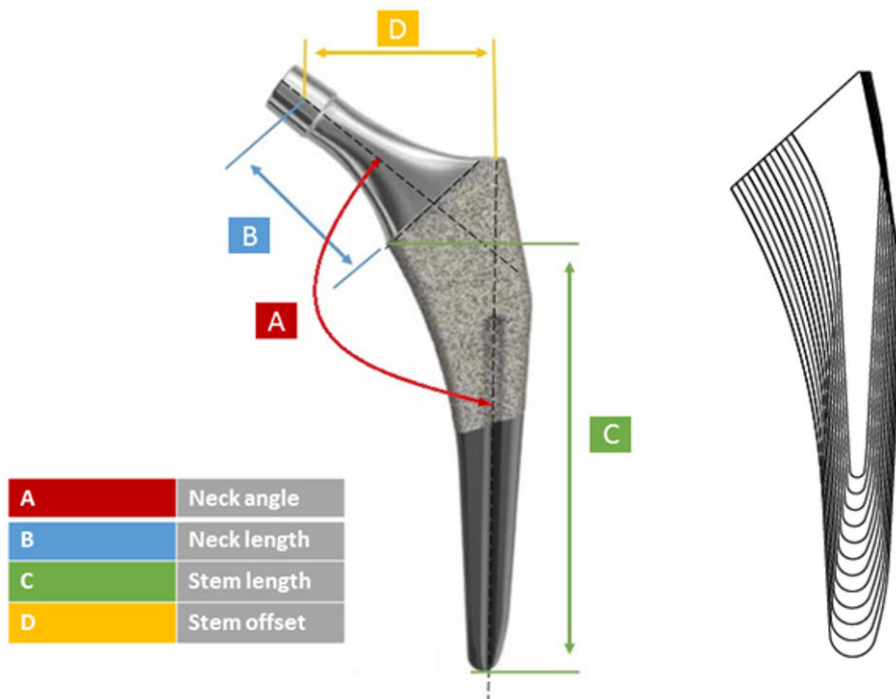
BMI = body mass index; ASA = Physical Status Classification of the American Society of Anesthesiologists; BMD = bone mineral density; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index,

<sup>a</sup>Based on T-score of the lumbar spine and the hip. <sup>b</sup>The ratio of the stem width over the femoral canal width 10 mm above the lesser trochanter (proximal), 60 mm below the lesser trochanter (middle), and 25 mm above the stem tip (distal). <sup>c</sup>Pedometer-measured activity during a 7-day period before surgery.



## 6.1 Accolade II hip implant

All the RCT patients received the cementless double-tapered parallel-sided morphometric-wedge femoral stem, Accolade II® (Stryker Orthopaedics, Mahwah, NJ, USA) with a metallic head and a porous-coated acetabular cup with a polyethylene liner. The proximal region of the stem is hydroxyapatite (HA) coated over a titanium plasma spray substrate. The morphometric wedge (an evolution of the tapered wedge) is characterized by its variable, size-specific medial curvature. The stem has 12 different sizes and two cervical-diaphyseal angles; a standard offset of  $132^\circ$  and a high offset of  $127^\circ$  (Figure 7). Accolade II has a custom-design which is known as SOMA (Stryker orthopedic modeling and analysis) technology. SOMA is a set of tools that utilizes a comprehensive database of computed tomography (CT) scans and associate 3D bone models, allowing the user to assess differences in bone morphology, bone density, and implant fit for research and development (Faizan et al., 2015). The design of the Accolade II is based on 556 CT scans of cadaveric left femora. The femora belong to a diverse group of individuals based on gender (57% male, 43% female), age groups (mean 63 years), and ethnicities (69% Caucasian, 16% Asian and 14% unknown) (Wuestemann et al., 2011).

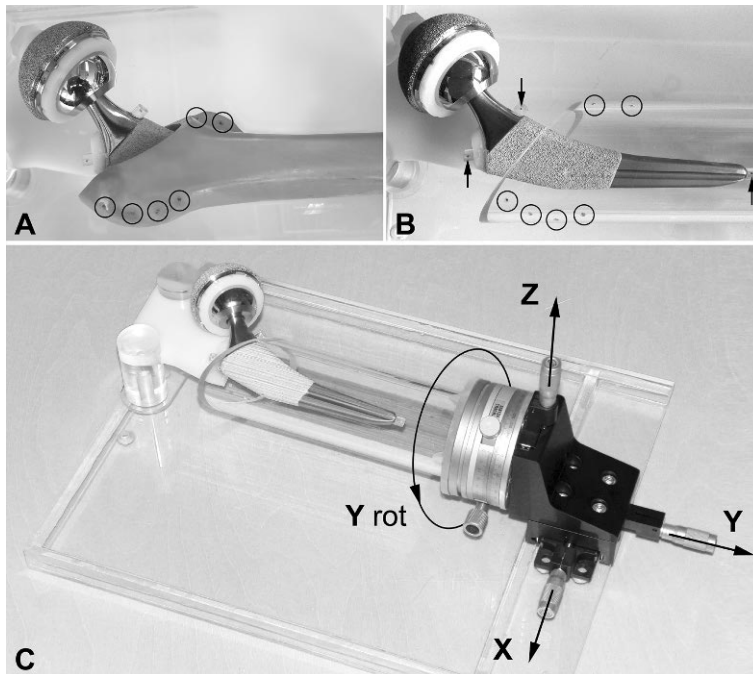


**Figure 7.** Demonstration of the Accolade II hip implant specifications (left) and its size-specific medial curvature feature (right). Modified from Stryker accolade II surgical technique guidebook.

Mechanical test of this implant proved that its design facilitates initial press-fit stability and load transmission in the proximal region of the femur (Faizan et al., 2015). The size-specific medial curvature feature of this stem intended to fit a broad range of bone sizes and shapes (Figure 7) (Issa et al., 2014). Compared to the first-generation design of this implant, the newer stem is approximately 15 mm shorter, the proximal to distal relationship changed and it has a distal lateral relief (Issa et al., 2014).

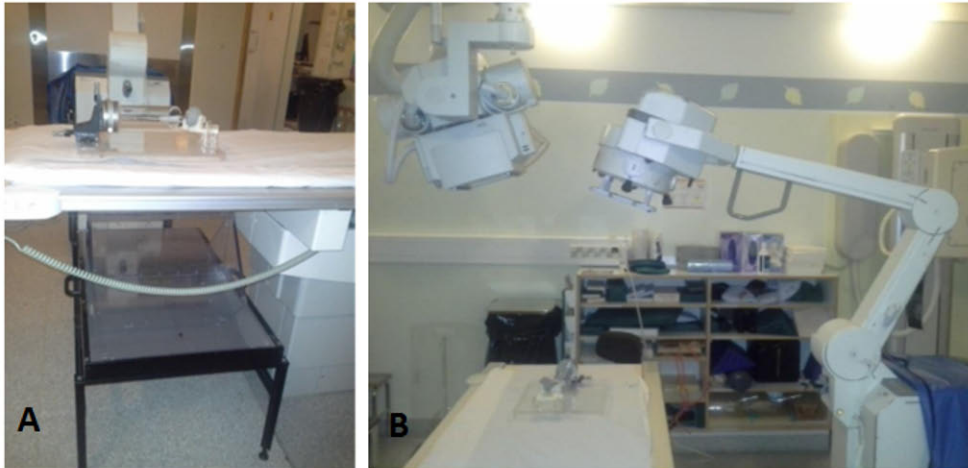
## 6.2 Preclinical phantom experiment

A physical phantom model consisting of the Accolade II hip implant and a plastic model of the right human proximal femur (model 2021, Sawbone AG, Karlhof, Switzerland) was constructed. Six tantalum beads with a diameter of 1.0 mm (RSA BioMedical Innovations AB, Umeå, Sweden), were attached to the plastic bone in the same locations as in the clinical practice (Figure 8-A). The positions of the markers were selected so that they would not be obscured by the metallic implant. The stem of the implant was also RSA-marked with three tantalum markers: one in the shoulder, one in the collar and one halfway along the stem (Figure 8-B). The femoral head of the plastic bone was cut off and the spongy part of the plastic bone was rimmed in order to allow the insertion of the femoral stem. A size 6 Accolade II stem (#6721-0635, Stryker Inc) with a neck angle of  $127^\circ$  was inserted into the medullary canal of the plastic bone and a size 36 mm metallic head (LFIT anatomic CoCr, #6260-5-136) was attached to the stem. A titanium alloy cup with the polyethylene liner (Tritanium®, Stryker Inc.) was firmly fixed to the platform and attached to the stem in the proper anatomical position of  $45^\circ$  of abduction and  $10^\circ$  of anteversion. The implant-bone construct was attached to the high-precision x, y, and z-axis translation (M-460A-XYZ, Newport Corp., Irvine, CA, USA) and rotation (M-UTR80, Newport Corp) stages. The translation stage was instrumented with three Vernier micrometers (model SM 13, Newport Corp) and the micrometers were attached to a plexiglass base. This experimental set-up allowed highly controlled translations along the three axes and rotation around the longitudinal axis (Figure 8-C). Due to technical difficulties with the motion of the implant inside the plastic bone, the bone was replaced with a  $\varnothing$  80 mm plexiglass tube to achieve an unrestricted movement of the implant. The positions of the markers in the proximal side of the tube were kept as close as possible to the positions of the markers in the plastic bone as well as in the clinical practice (Figure 8-B).



**Figure 8.** The original phantom model including a total hip prosthesis and a plastic model of the human proximal femur consisted of six tantalum RSA bone-markers. (B) The femur model was replaced by a plastic tube with tantalum markers (black circles) to achieve unrestricted motion of the stem. (B) For marker-based RSA, three implant markers (shown by black arrows) were attached by plastic studs with a configuration similar to that of the clinical RSA-marked stems. (C) The implant construct was fixed to a base plate and the plastic tube was distally attached to an x, y, z translation stage, and a y rotation stage using micrometers (black arrows) to create a controlled simulation of stem micromotions in relation to the plastic tube.

For the imaging of the phantom, a uniplanar set-up was used where the film plates were placed side by side of each other. A uniplanar calibration cage (Cage 43, RSA BioMedical Innovations AB, Umeå, Sweden), shown in Figure 9-A, was placed under the examination table with a fixed height. The calibration cage contained a number of tantalum beads (1.0 mm) which were fixed in well-defined positions in order to allow the construction of a 3D coordinate system. Two x-ray tubes were utilized; one x-ray unit was ceiling mounted (Philips Optimus 50; Philips Medical Systems DMC GmbH, Hamburg, Germany) and the other was a portable x-ray unit (Siemens Mobilett Plus; Siemens-Elementa AB, Solna, Sweden). The position of the X-ray tubes was accurately set so that the x-ray beams crossed each other at the site of the hip implant. The film-focus distance was set at 165 cm and the angle between the x-ray tubes at 40° (Figure 9-B).



**Figure 9.** (A) Demonstrating the uniplanar set-up that was utilized for the RSA imaging of the implant. (B) One fixed and one portable x-ray tube were positioned so that x-ray beams crossed each other at the site of the hip implant. The film-focus distance was set at 165 cm and the angle between the x-ray tubes at 40°.

The implant in the plexiglass was aligned to the global coordinate system. The radiograph with the alignment of the implant with the coordinate system was used as the reference examination. Based on the recommendations, a standard position was maintained for the phantom in all radiographs in order to achieve a higher precision. For motioned imaging of the phantom, the implant was moved in different directions (translation along x, y, and z-axis and rotation around y-axis). These micromotions were achieved in one axis at a time by turning one of the micrometers to a predefined value while the other micrometers were set to zero.

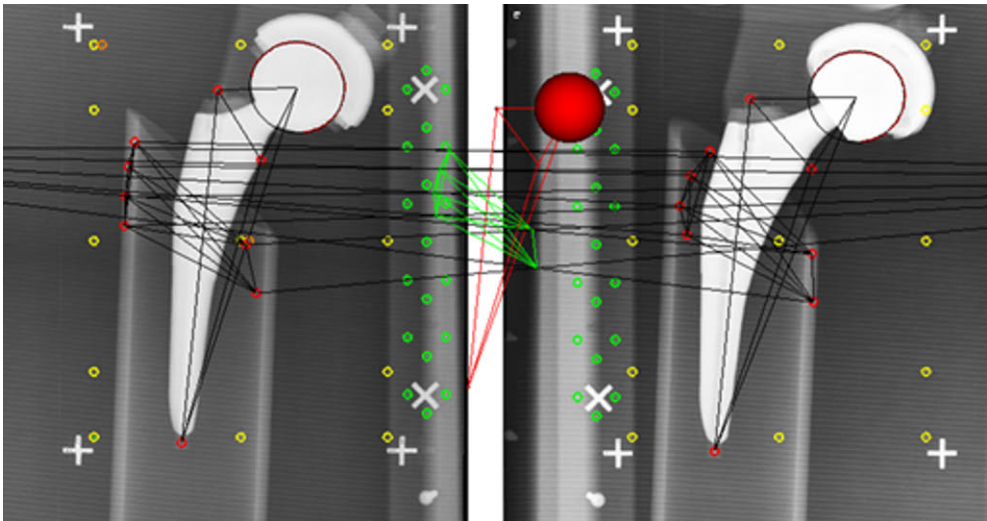
To measure the micromotion of the phantom two RSA software were utilized. These software calculated the 3D position of each marker followed by a positioning of the group of markers which construct a 3D rigid body segment. A rigid body is a system of mass points created in a way that the distance between all the pairs of points stand fixed even during motion. In the mathematic system, a rigid body could be described by a point matrix. As the distance between points is fixed, at least 6 elements are needed in order to recognize the exact position of a rigid body; these are known as a 6 degree of freedom.

The accuracy and precision of the Marker-based RSA were determined by using UmRSA (RSA BioMedical Innovations AB, Umeå, Sweden, version 6.0) software. RSA imaging of the phantom was repeated twenty times for different experimental set-ups (micromotions).

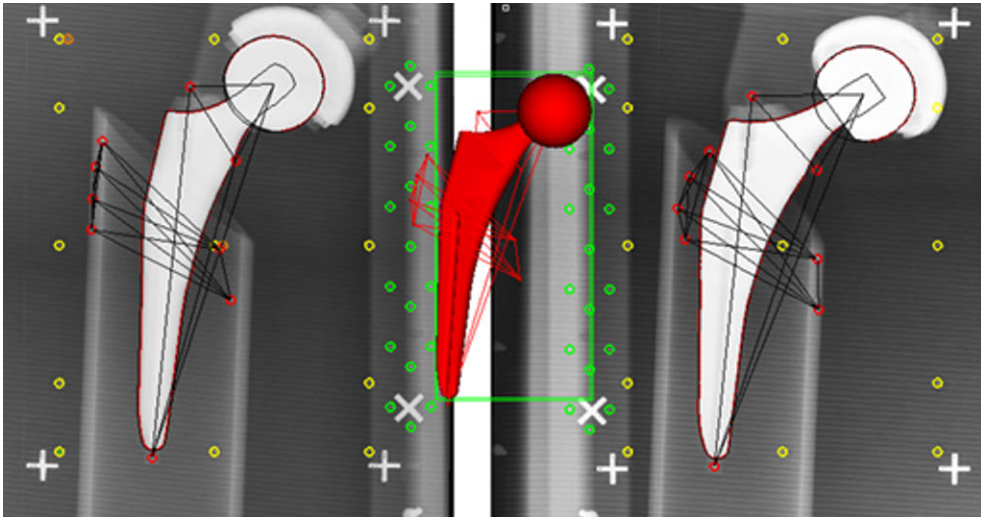
### 6.2.1 Marker-based and model-based RSA of the phantom

In marker-based RSA, the software calculated the motion of the stem (first rigid body) against the proximal femur (second rigid body) with the help of the coordinate system (Bottner et al., 2005). In this way, relative displacements between two segments (bone and implant) can be calculated from sequential pairs of radiographs (Figure 10). Three tantalum markers and the head of the implant are used as landmarks to calculate the migration of the implant. For comparison, the images were also marker-based analyzed with the model-based RSA software application (Medis specials, Leiden, The Netherlands, version 3.34).

In model-based RSA, a virtual 3D surface model of the implant is projected in each image pair. This model is then matched to the actual model of the implant which is made by an edge detection algorithm. The initial 3D surface model is then rotated and translated by the pose estimation algorithm until the best match between the actual and virtual model happens. In this way, the micromotion of the implant could be determined (Seehaus et al., 2013; Valstar et al., 2001) (Figure 11). The CAD models utilized in this study were combination CAD models of the stem and head (Prins et al., 2008). The CAD models of the implant's stem and head were provided by Stryker Europe Inc. They were converted to the MB RSA format by Leiden Biomechanics and Imaging Group (Dept. of Orthopaedic Surgery, Leiden University Medical Center, Leiden, Netherlands). In both measurements, the metallic head of the implant served as an additional large marker.



**Figure 10.** Demonstration of the femoral stem migration measurement using the marker-based RSA. The software calculates the relative motion of the femoral stem against the proximal femur using the coordinate system created by bone and stem markers.



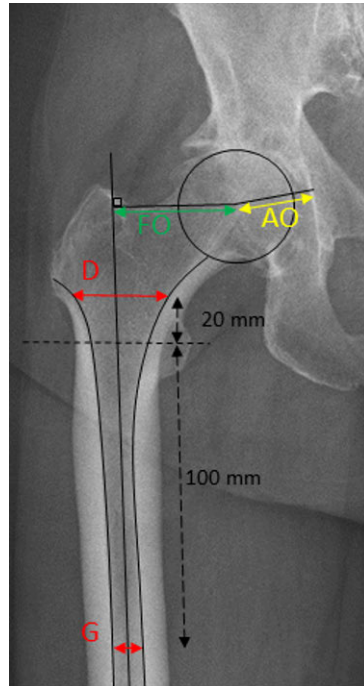
**Figure 11.** Demonstration of the femoral stem migration measurement using the model-based RSA. The software calculates the virtual 3D combined stem-head surface model of the implant. The model is matched to the actual model of the implant which is made by an edge detection algorithm in each image pair. The initial 3D surface model is then rotated and translated by the pose estimation algorithm until the best match between the actual and virtual model happens and the migration of the stem is calculated.

## 6.3 Evaluation of the patient-related factors

Preoperative demographics and functional activity of the enrolled subjects, plus their postoperative activity was monitored in order to discover clinically important factors for preoperative prediction of stem migration in postmenopausal women planned to have cementless THA.

### 6.3.1 Canal flare index and femoral offset

Canal flare index was measured from preoperative anteroposterior digital radiographs of the operated hips using computerized methods (Rhinoceros software, version 3.0SR5b, Robert McNeel & Associates, Seattle, USA). The CFI was calculated as the ratio of D to G (Noble et al., 1995), where D is the metaphyseal width 20 mm proximal to the most prominent point of the lesser trochanter, and a modified G, defined as the width of the intramedullary femoral isthmus 100 mm distal to the lesser trochanter (Figure 12).



**Figure 12.** Canal flare index was measured as the ratio of D to G. Femoral offset (FO) was measured as the perpendicular distance from the center of femoral head rotation to the longitudinal axis of the femur. The acetabular offset (AO) was also measured as the distance from the center of the femoral head to a line perpendicular to the teardrop. The Global offset was calculated as the sum of FO and AO.

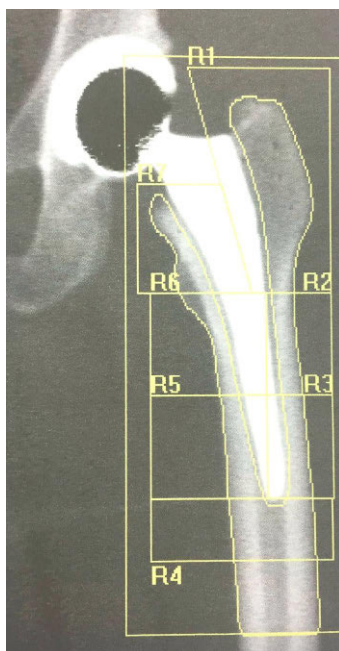
The femoral offset (FO) was assessed by measuring the perpendicular distance from the center of femoral head rotation to the longitudinal axis of the femur (Mahmood et al., 2016). The acetabular offset (AO) was also measured as the distance from the center of the femoral head to a line perpendicular to teardrop (vertical trans-teardrop line) (Flecher et al., 2016). The Global offset (GO) was calculated as the sum of FO and AO (Figure 12).

Cortical bone thickness at the level of 15 mm below the lesser trochanter was also measured from anteroposterior digital radiographs of the operated hips medial-lateral cortex preoperatively with the same computerized method (Rhinceros software, version 3.0SR5b, Robert McNeel & Associates, Seattle, USA).

### 6.3.2 DXA and pulse-echo ultrasonometry

Systemic and local BMD ( $\text{g}/\text{cm}^2$ ) were measured using DXA (Hologic Discovery A, Software 13.4.2, Hologic Inc., Marlborough, MA, USA). Systemic BMD was assessed before the surgery, at 48 weeks postoperative, and during the extension

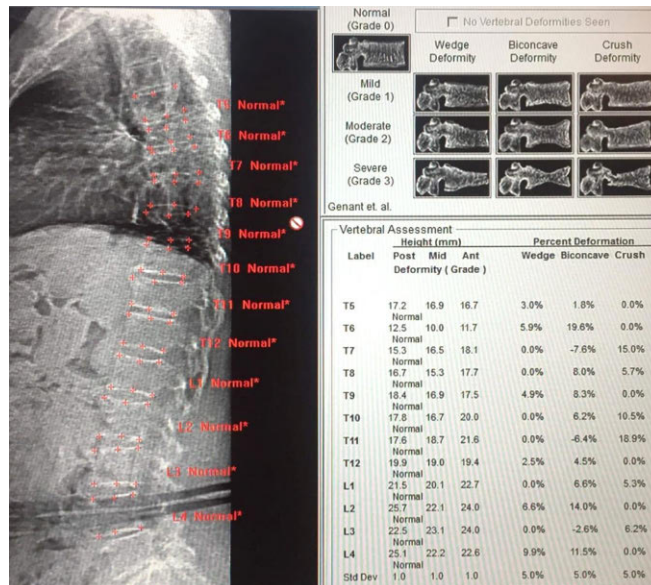
study period. The periprosthetic BMD was measured at 12, 22, and 48 weeks after the surgery (Figure 13). The same DXA machine was utilized for subjects at all time-points. DXA measurements were performed according to the manufacturer's guidelines at three anatomical sites: lumbar-spine (from L1 to L4), left and right femur, and distal-radius of the non-dominant hand. The BMD was measured in the three mentioned anatomic locations because hip osteoarthritis can be associated with a higher femoral neck BMD (Glowacki et al., 2010) and BMD measurements with the purpose of systemic osteoporosis diagnosis should be performed at sites distant from the joints affected by osteoarthritis (Lingard et al., 2010). Patients were classified into normal and low BMD groups based on the lowest T-score of the hip and the lumbar-spine. The cut-off level of the DXA measurements was defined as a T-score between -2.5 to -1.5 for osteopenia and a T-score of -2.5 or below for osteoporosis (Table 2, page 21).



**Figure 13.** Illustrating of seven Gruen zones in DXA periprosthetic evaluation.

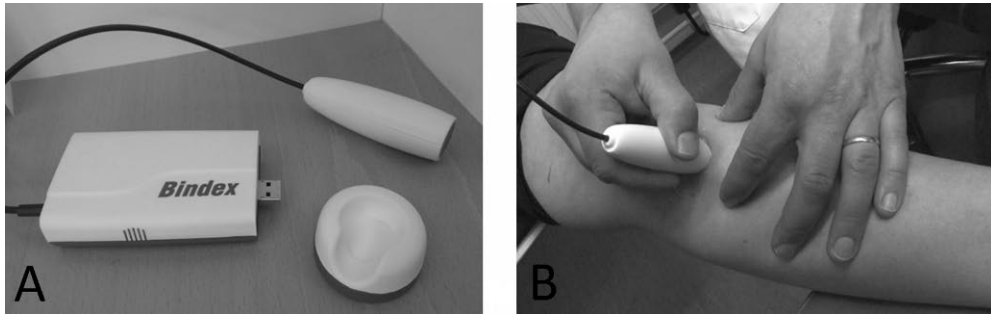
In the extension period of the study, VFA was examined using DXA (McCloskey et al., 2008) and Genant's classification of vertebral fractures (Genant et al., 1993) was also applied. The classification was based on the measurements of reductions in anterior, middle, and posterior heights of the vertebral body and the classification for deformities of shape (wedge, biconcave, crush) (Figure 14).





**Figure 14.** Demonstration of the vertebral-fracture assessment using DXA. Genant's classification was performed based on the measurements of reductions in anterior, middle, and posterior heights of the vertebral body and the classification for shape deformities.

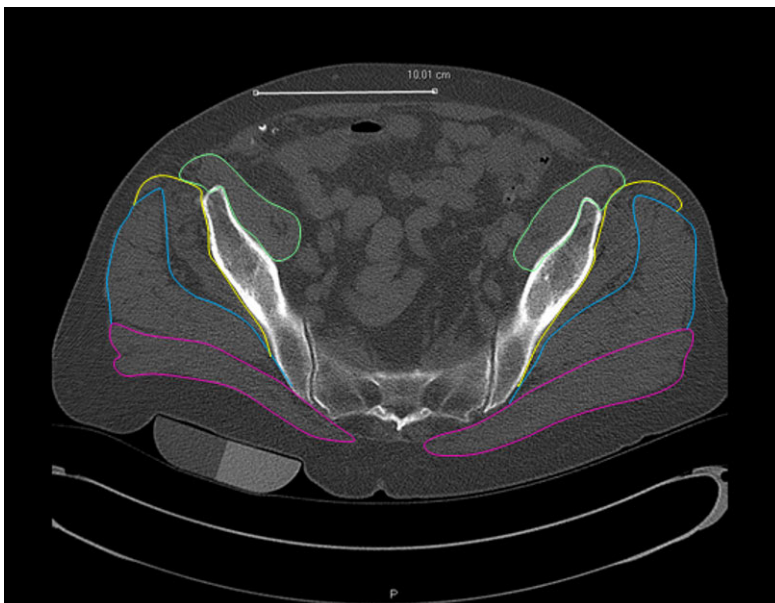
Bone ultrasonometry was performed using a Bindex device (Bone Index Finland Ltd, Kuopio, Finland) (Figure 15). Preoperatively, the RCT patients underwent multi-site pulse-echo ultrasonometry of the apparent cortical-bone thickness on predetermined sites according to the recommended technique (Karjalainen et al., 2018; Schousboe et al., 2017). These sites were localized using distance measurements from the anatomic landmarks including the distal radius at onethird of the distance from the radial styloid process to the proximal radial head, and the proximal and distal tibia at one-third and two-thirds the distance from the knee joint space to the medial malleolus, respectively. The measurements were performed by one of the two study physiotherapists. The examiners were blind to the DXA results. Five successful repeated measurements in each location were taken and averaged. After completion of the measurement protocol for each subject, the device calculated the density index (DI-  $\text{g}/\text{m}^2$ ) by combining the thickness measured values with patient characteristics including age, weight, and height. The intraobserver and interobserver variations, presented as a coefficient of variation (CV) of the measurement of density index, were analyzed using triplicate measurements of the 3 anatomic locations in an uninterrupted sequence in 45 patients. The test-retest variability was 4.3% (95% CI, 3.5-5.1) for the triplicate measurements, and CVs of the 2 examiners were 3.9% and 4.7%.



**Figure 15.** (A) Bindex device including USB pulser unit and transducer are demonstrated. (B) An example of the apparent cortical bone thickness measurement at the proximal tibia is shown. (From: Karjalainen et al., 2016 © Reprint with permission).

### 6.3.3 Computed tomography of cross-sectional muscle size

A preoperative cross-sectional area of the gluteal muscles was measured using computed tomography (CT) images. The optimal geometric level of all CT images was determined by means of bony landmarks (Rasch et al., 2009). In this level, the cross-sectional areas of the gluteus maximus, gluteus medius, gluteus minimus, and iliopsoas muscles were measured for both left and right sides (Figure 16). All the image analyses were performed by ImageJ software (version 1.50i).



**Figure 16.** Measurement of the cross-sectional gluteal muscle from CT images; gluteus maximus (pink), gluteus medius (blue), gluteus minimus (yellow), and iliopsoas (green).

### 6.3.4 Walking activity monitoring using pedometer and gait analysis

The functional capacity of the enrolled subjects was evaluated at baseline, before surgery, and repeatedly after surgery up to 48 weeks using the gait analysis system (RehaWatch, Hasomed GmbH, Germany) (Schwesig et al., 2011). Patients were asked to walk with a self-selected comfortable walking speed along a 10-meter walkway (RehaWatch®, Hasomed GmbH, Germany) (Foucher, 2016). Several gait-obtained parameters including walking speed (m/s), stride length (normalized to height), and stride time (% cycle) were recorded.

To assess the physical activity of the patients, their daily walking activity was recorded pre and postoperative. Accumulated walking steps were counted daily using digital pedometers. A pedometer is a reliable tool for the assessment of the walking ability of THA patients (Schmalzried et al., 1998). Subjects were asked to wear a pedometer from the time as they got up in the morning and until they went to bed at night. Each patient recorded the number of steps per day as counted by the pedometer for periods of 7 days that were representative of their usual activity. The median value of the number of steps measured each day of the 7 days was calculated and applied as a measure of walking activity.

### 6.3.5 Patient-related outcome measures

Five standard patients reported outcome measures (HHS, WOMAC, SF-36, BPI, and Oswestry low-back pain) were applied to assess the patients' opinion about their hip preoperatively and their subjective recovery from the surgery postoperatively. These PROMs have been considered to be necessary for global assessment of total arthroplasty outcomes in individual patients.

Harris hip score (HHS) (Harris, 1969) is a physician assessment of localized pain and physical functioning. It ranges from 0 to 100 (100 indicates the best possible outcome) based on the degree of pain, function, and range of motion in THA patients (Söderman et al., 2001).

Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a disease-specific PROM tool widely used in clinical trials of hip and knee osteoarthritis patients (McConnell et al., 2001). The questionnaire includes 24 questions on three subscales: five assessing pain, two assessing stiffness and 17 assessing physical function. Each item was scored as follows: 0 (none), 1 (mild), 2 (moderate), 3 (severe) and 4 (extreme). Item scores were summed to produce a WOMAC total score (possible 0-96) with higher scores indicating poorer health.

The short form-36 (SF-36) is the most widely used health-related quality-of-life measure in research (Laucis et al., 2015) and a variety of clinical populations including THA patients (Lieberman et al., 1997; Soohoo et al., 2007). Scores are

based on responses to individual questions in which subjects rate 36 items on a 5-point Likert scale. Items are grouped into 4 subscales (physical functioning, role physical, bodily pain, and general health) that are combined into a physical component summary and into 4 subscales (vitality, social functioning, role emotional and mental health) that were combined into a mental component summary. The summed scores were transformed into a 0-100 scale, following a designated scoring algorithm, with the higher scores reflecting better quality of life.

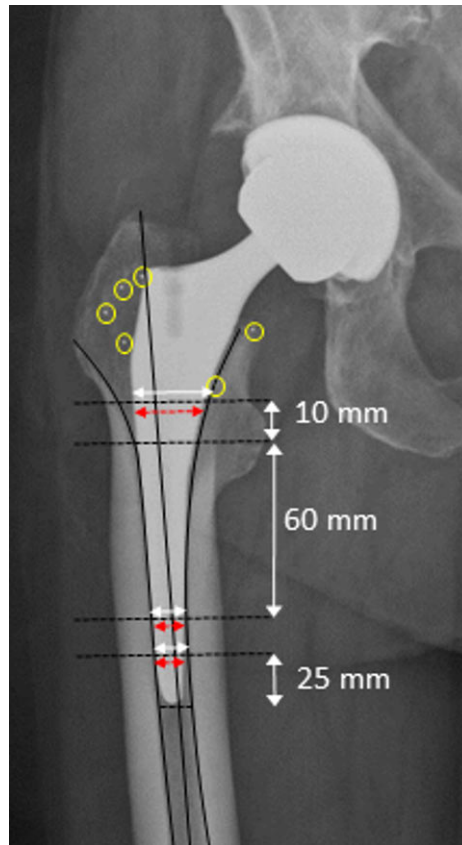
Brief pain inventory (BPI) is a questionnaire developed to assess the severity of pain and the impact of pain on daily function. Using BPI-Short Form, subjects were asked to rate their pain severity in a four-item questionnaire and the interference of pain with daily activities in a seven-item questionnaire. The mean score (range 0 to 10) for pain severity and the mean score (range 0 to 10) for the interference of pain with daily activities were recorded.

In the extension period of the study, the patients were asked to complete an Oswestry low-back pain questionnaire which is an important tool for the assessment of patient's permanent functional disability (Fairbank & Pynsent, 2000). The Oswestry low-back pain questionnaire is considered to be the gold standard as a low back functional outcome tool (Fairbank & Pynsent, 2000). The scores for all questions answered were summed to obtain the index (range 0 to 100), with low scores (0 to 20) indicating no or minimal disability.

## 6.4 Evaluation of surgery-related factors

### 6.4.1 Stem-to-canal fill and fit analysis

Fit and fill measurements were performed on the anteroposterior digital radiographs using computerized methods (Figure 17) (Rhinoceros software, version 3.0SR5b, Robert McNeel & Associates, Seattle, USA). Stem fit was measured as the gaps between the stem and cortical bone in three anatomic locations; 1) 10 mm above the lesser trochanter (medial-proximal section), 2) 60 mm below the lesser trochanter (medial- and lateral-middle section) and 3) 25 mm above the tip of the stem (medial- and lateral-distal section) (Issa et al., 2014). The overall stem-to-canal fill ratio was also calculated as the ratio of the width of the stem over the width of the femoral canal in the three defined locations (Issa et al., 2014). The lateral gap in the proximal section of the stem was not taken into account for the fit and fill analysis. The reason was that Accolade II is not designed for being in contact with cortical bone laterally in the proximal section. Femoral offset, acetabular offset and global offset were also measured postoperatively (within 3 days after surgery) from AP radiographs.



**Figure 17.** Stem to canal fill ratio measurements in the proximal (10 mm above the lesser trochanter), middle (60 mm below the lesser trochanter), and distal (25 mm above the prosthesis distal tip) section of the femoral stem. Implanted RSA bone markers are shown with yellow circles.

## 6.5 Data analysis and statistical methods

A number of statistical analyses were utilized in the studies of this thesis. Statistical methods were chosen according to each study question. Continuous data were tested for normal distribution (using Kolmogorov-Smirnov test) and equal variance (using Levene's test) before performing statistical analyses. Data that meet the assumptions of normality and homogeneity of variance were analyzed using a parametric test otherwise equivalent nonparametric tests were utilized. Statistical significance was set as a p-value less than 0.05. All the statistical analyses were performed using SAS System version 9.4 (SAS Institute, Cary, NC, USA) and/or IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA).

## 6.5.1 Study related data analysis

### Study I

The accuracy of the RSA systems (Marker-based and model-based) was calculated as  $t \times SD / \sqrt{2}$ , where  $t$  was the critical value of the two-tailed 95% t-distribution with eight degrees of freedom and  $SD$  was the standard deviation of the differences between the RSA-measured micromotions and the actual micrometer-created movements (Derbyshire et al., 2009).

The clinical precision of model-based RSA system was determined using double examinations of trial patients. The clinical precision was calculated as  $t \times SD$ , where  $t$  is the critical value of the two-tailed 95% t-distribution with 23 degrees of freedom (24 double examinations) and  $SD$  is the standard deviation of the differences between the double examinations (Derbyshire et al., 2009).

For the direct comparison of the established technique (marker-based RSA) and model-based RSA, we performed Bland–Altman plots with 95% limits of agreement (mean difference  $\pm 1.96 \times SD$ ). Using Bland-Altman plots the degree of agreement between two RSA measurement methods was assessed. The difference between the two paired measurements was plotted against the mean of the two measurements.

### Study II

The primary (percentage change in bone loss) and secondary (implant migration) endpoints measured at 48 weeks after the surgery, were analyzed using linear mixed-effects models for repeated measures. The same approach was also utilized for the intergroup comparison of the variables at different time points including 12, 22, and 48 weeks postoperatively. The primary and secondary aims of the study were investigated while data were adjusted for covariates of interest, including age, BMI, preoperative hip and spine BMDs, CFI, stem size, and stem to canal fill ratio.

### Study III

The two trial groups (denosumab and placebo-treated subjects) did not differ in stem migration (study II). Accordingly, the groups were combined for the analyses applied in study III. Nevertheless, the treatment groups were considered as a controlling factor in the statistical analyses of study III.

To identify significant contributing factors to stem initial migration, analysis of covariance (ANCOVA) was utilized. The randomized treatment groups of the original RCT (study II) and outliers were considered as explanatory variables in all the analyses. Moreover, one of the following explanatory factors was also added to

the models. These factors include: age, body mass index (BMI), preoperative fitness classified according to the American Society of Anesthesiologists (ASA class), serum 25(OH)D-vitamin level, total hip BMD, femoral neck BMD, distal radius BMD, canal flare index, femoral stem size, stem-to-canal fill ratio, femoral cortical bone thickness, normal or high-offset model of the femoral stem, femoral and global offset, gluteus muscle size, preoperative Harris hip score and WOMAC score, preoperative and postoperative (at 3 months) walking speed, and walking activity.

To further investigate the effect of walking activity on femoral stem initial migration, the cohort was divided into two groups based on the median value of daily walking activity (2600 steps/day) measured 3 months after surgery. The two groups (subjects with walking activity  $<$  or  $\geq$  2600 steps/day) were compared in relation to stem subsidence and rotation using an independent-sample two-tailed t-test.

## Study IV

ROC curves data were utilized to obtain cutoff values, corresponding to the maximum sum of sensitivity and specificity in discrimination of stem subsidence more or less than 2 mm. The threshold of 2 mm was the corresponding median value of the cohort and the standard threshold defined as subsidence for Accolade II stem. (Grant et al., 2017). ROC curves were created by plotting the true positive rate (sensitivity) against the false positive rate (1 - specificity). The accuracy of the classification of subjects to groups with less or more than 2 mm subsidence was estimated using the area under the curve (AUC).

### 6.5.2 Issue of outliers and missing data

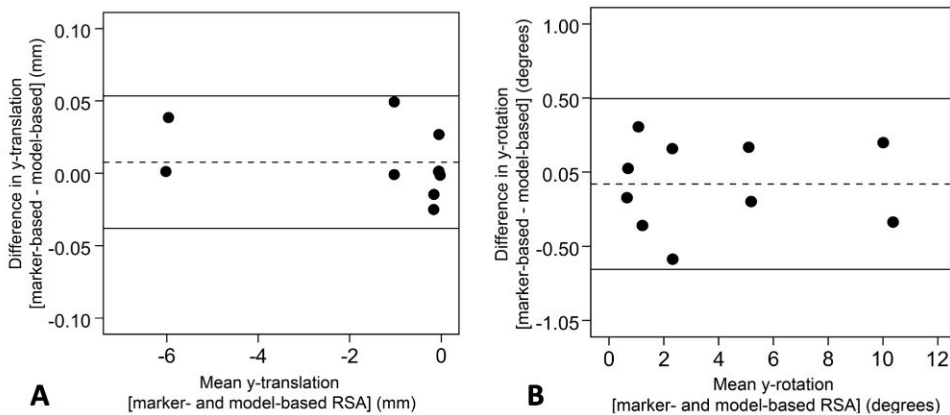
The original study (study II) of the RCT was conducted based on the intention-to-treat principle without any exclusions or exploration of outliers. However, outliers with excessive stem subsidence and/ or rotation were considered in the analysis of study III and IV. Reporting RSA results in a universal way including identification and interpretation of the outliers can improve the predictive potential of RSA values (de Vries et al., 2014) and allow a more reliable comparison of the THA outcomes using this technique.

The outliers were detected as  $X_i \geq Q3 + (1.5 \times IQR)$  and  $X_i \leq Q1 - (1.5 \times IQR)$ , where Q1 and Q3 represent the first and third quartile limits, respectively, and the interquartile range (IQR) represents the difference between Q1 and the Q3 limit. After the exclusion of outliers from the data, the subsidence and rotation data showed normal distributions.

# 7 Result

## 7.1 Accuracy and precision of model-based RSA

The accuracy of the model-based RSA was 30  $\mu\text{m}$  for the measurement of stem subsidence (translation along y-axis) and 0.39 degrees for the measurement of stem rotation (around the y-axis). The corresponding accuracies of the marker-based RSA were 60  $\mu\text{m}$  for the measurement of stem subsidence and 0.18 degrees for the measurement of stem rotation. Bland–Altman plots, applied to assess the degree of agreement between the model-based and marker-based RSA, showed no systematic difference between the two measurements (the bias) (Figure 18).



**Figure 18.** Bland–Altman plots for the comparison of model-based and marker-based RSA in the measurement of micromanipulator-induced stem translation (A) and rotation (B) along and around the y-axis in the phantom model are shown. The y-axis shows the difference between the model-based and marker-based RSA measurements which was calculated for each increment of micromovements. The x-axis demonstrates the mean of the two measurements. The two methods showed good global agreement for the measurement of both y-axis translation and rotation (B). The dashed line represents the mean of the differences, which was close to zero in each comparison, suggesting that model-based RSA measurements were not biased. The two solid lines represent the 95% limits of agreement.

Based on the least precise axis (rotation around the y-axis) and assuming a difference of 0.4 degrees in stem rotation between the two groups, the calculated number of patients required for a randomized model-based RSA trial was 13 per group.



Based on double examinations of trial patients, the clinical precision of the model-based RSA was 110  $\mu\text{m}$  for the measurement of stem subsidence and 1.04 degrees for the measurement of stem rotation.

## 7.2 Efficiency of denosumab intervention in cementless THA

### 7.2.1 Intervention and clinical outcome

Sixty-five (97%) randomized subjects out of 67 received the allocated treatment and completed the 2-year trial. There were no dropouts in the denosumab-treated group (n=33) and two dropouts in the placebo-treated group (n=34).

All subjects recovered from the surgery without major surgical complications. None of the subjects experienced periprosthetic infection, postoperative dislocation, or a periprosthetic fracture. No revision surgery was performed. At two years, all of the stems were radiographically classified as stable and osseointegrated according to the fixation and stability score.

The denosumab and placebo groups showed no statistical differences in walking speed and walking activity. Preoperatively, 71% of the subjects had a walking speed below the critical level of 1.1 m/s. The walking speed improved by 0.25 m/s (95% CI 0.17–0.33) in the denosumab group and by 0.23 m/s (95% CI 0.12–0.34) in the placebo group during the first postoperative year.

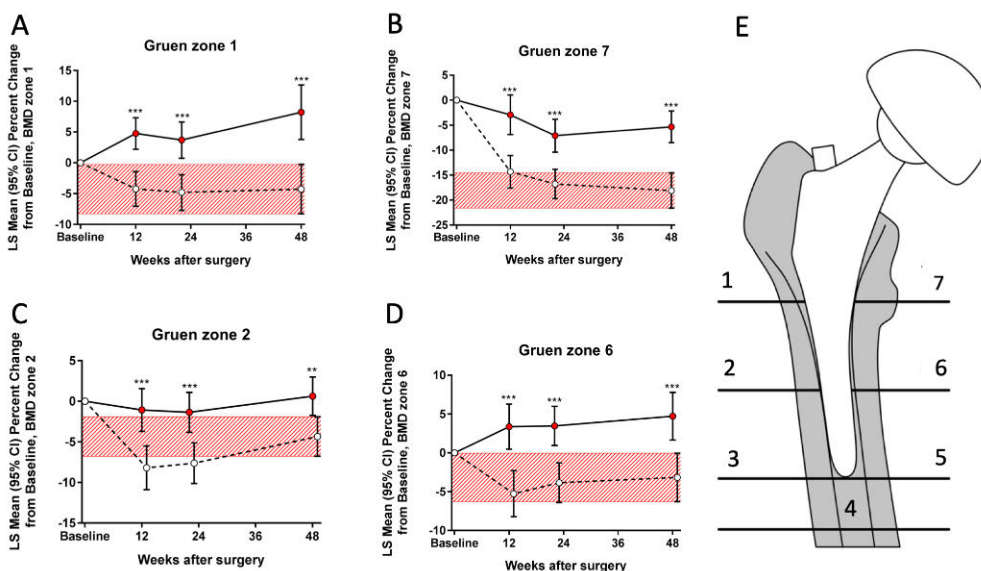
All mean values of PROMs improved compared with the preoperative values and there were no statistical differences between the two groups. Within three months, 61% of denosumab-treated subjects and 56% of the placebo-treated subjects achieved the minimum clinically important difference of HHS ( $\geq 18$  points). Correspondingly, 61% of denosumab-treated subjects and 59% of the placebo-treated subjects achieved the minimum clinically important difference in the WOMAC total score ( $\geq 25$  points) within three months.

The incidence of adverse events (AE) and serious adverse events (SAEs) was balanced in the two groups. No event showed a causal relationship to denosumab. No event was adjudicated as osteonecrosis of the jaw, atypical femur fracture, or a clinical vertebral fracture. The most common AE was low-back pain. After discontinuation of denosumab, there were no intergroup differences in severity of low-back pain and/or interference of low-back pain with daily activities. Postoperative magnetic resonance imaging (MRI) performed in 13 denosumab-treated and 11 placebo-treated subjects with radiating low-back pain, revealed relative lumbar spine canal stenosis or severe lumbar disc degeneration. Based on vertebral fracture assessment performed during the off-treatment period, seven subjects of both groups had one or more ( $\geq 2$ ) deformed vertebra. Grade 2 vertebral deformity (moderate crush or wedge) was found in six subjects of both groups.

## 7.2.2 Periprosthetic bone loss

Denosumab significantly decreased bone loss in the medial calcar (zone 7) and maintained or even increased periprosthetic BMD above the baseline in the clinically relevant regions of the proximal femur, namely in zone 1, 2 and 6 (Figure 19). As the reference, the placebo-treated subjects showed periprosthetic bone loss in all these zones (Figure 19). The intergroup differences of periprosthetic BMD were significant throughout the proximal zones (zones 1-2 and zones 6-7) and in the entire periprosthetic region (zones 1-7 combined) by the end of the first postoperative year. Concurrently, denosumab-treated subjects showed a significant increase in the contralateral total hip BMD and the lumbar spine BMD but not in the distal radius BMD.

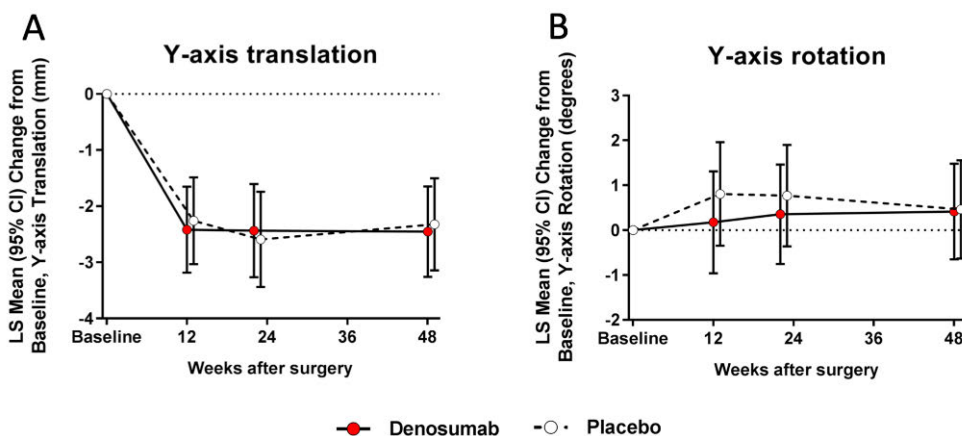
After discontinuation of denosumab, the periprosthetic BMDs of the denosumab group approached the levels of the placebo group by 3 year point. BMDs of the contralateral hip and the lumbar spine also decreased in response to discontinuation of denosumab, but the mean values remained at the upper CI levels of the placebo group at 3 years.



**Figure 19.** Least-square (LS) mean changes from baseline of the periprosthetic bone mineral density (and 95% CI) in Gruen zones 1 + 2 (the greater trochanter region) (A and C) and Gruen zones 6 + 7 (the calcar and the lesser trochanter region) (B and D). The whole Gruen zones are demonstrated in figure E (Modified from: Alm et al., 2009). The red-hatched zones demonstrate the 95% CI of the placebo group at 48 weeks. Results are based on the linear mixed-effects model for repeated measures including intergroup comparison at each time point (\*\*\*)  $p < 0.001$ .

### 7.2.3 Initial femoral stem migration

There were no significant differences between the two groups (denosumab and placebo) in the stem translation (subsidence) and rotation along and around the Y-axis (Figure 20). In both groups, stem translation and rotation occurred mainly during the first 12 weeks. Furthermore, denosumab had no effect on stem translations along and rotations around the other axes compared to the placebo group. The intergroup differences remained insignificant even after adjustments for age, BMI, local BMD, systemic T-score, canal flare index, stem size, and stem-to-canal fill ratio.



**Figure 20.** Least square mean (LS) changes from baseline (and 95% CI) of the stem translation along the y-axis (A) and rotation around y-axis (B). Results are based on the linear mixed-effects model for repeated measures including intergroup comparison at each time point.

## 7.3 Factors contributing to initial femoral stem migration

Since the treatment response to denosumab was not associated with any reduction of initial stem migration, further analyses were focused on discovering the underlying factors related to stem migration. This was possible because the original trial protocol was designed to account for different potential confounding factors that might affect the initial femoral stem migration.

### 7.3.1 Demographics and surgical variables

In the reanalysis of the trial data, the ANCOVA analysis (controlled for outliers and treatment group of the RCT) revealed that none of the preoperative patient-related and surgery-related variables had a significant effect on stem subsidence (Table 4). Three factors showed a trend ( $p < 0.1$ ) toward an impact on stem subsidence. These factors include total hip BMD ( $p = 0.075$ ), canal flare index ( $p = 0.097$ ), and ASA ( $p = 0.090$ ). However, when these three factors were included into a single model, none of them showed a significant effect on stem subsidence. For the femoral stem rotation, total hip BMD ( $p = 0.027$ ) and femoral neck BMD ( $p = 0.011$ ) showed significant impact (Table 4).

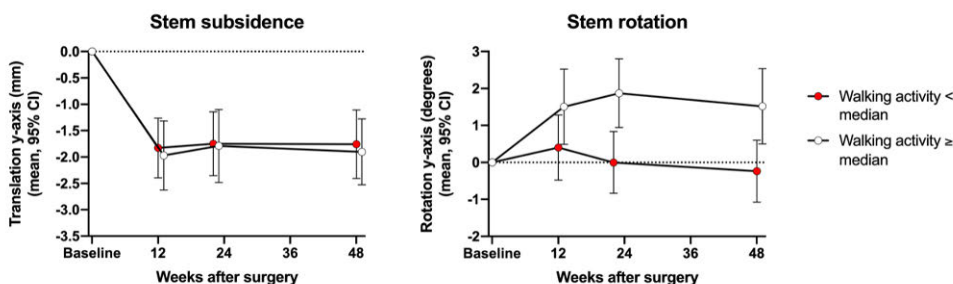
**Table 4.** Summary of ANCOVA results for the patient's baseline characteristics and femoral stem migration along and around y-axis.

Parameters	Translation ( $F_{df}$ ) $P$ value	Rotation ( $F_{df}$ ) $P$ value
Age (years)	(0.86 <sub>1</sub> ) 0.359	(0.34 <sub>1</sub> ) 0.564
BMI ( $kg/m^2$ )	(1.50 <sub>1</sub> ) 0.225	(1.12 <sub>1</sub> ) 0.294
D-vitamin ( $nmol/l$ )	(1.20 <sub>1</sub> ) 0.278	(2.70 <sub>1</sub> ) 0.106
Total hip BMD ( $g/cm^2$ )	(3.29 <sub>1</sub> ) 0.075	(5.17 <sub>1</sub> ) 0.027*
Femoral neck BMD ( $g/cm^2$ )	(1.99 <sub>1</sub> ) 0.164	(6.95 <sub>1</sub> ) 0.011*
Lumbar spine BMD ( $g/cm^2$ )	(0.08 <sub>1</sub> ) 0.782	(0.21 <sub>1</sub> ) 0.651
Distal radius BMD ( $g/cm^2$ )	(2.22 <sub>1</sub> ) 0.141	(1.42 <sub>1</sub> ) 0.238
Lowest T-score	(1.49 <sub>1</sub> ) 0.227	(1.97 <sub>1</sub> ) 0.166
Femur cortical bone thickness ( $mm$ )	(0.00 <sub>1</sub> ) 0.967	(1.13 <sub>1</sub> ) 0.292
Canal flare index	(2.84 <sub>1</sub> ) 0.097	(0.18 <sub>1</sub> ) 0.676
Size of the femoral stem	(0.47 <sub>5</sub> ) 0.798	(0.95 <sub>5</sub> ) 0.454
Offset of the femoral stem (Normal/high)	(1.69 <sub>1</sub> ) 0.199	(0.22 <sub>1</sub> ) 0.642
Stem-to-canal fill ratio (Middle stem)	(2.05 <sub>1</sub> ) 0.158	(0.16 <sub>1</sub> ) 0.693
Femoral offset ( $mm$ )	(0.31 <sub>1</sub> ) 0.578	(0.22 <sub>1</sub> ) 0.638
Global offset ( $mm$ )	(0.66 <sub>1</sub> ) 0.420	(0.16 <sub>1</sub> ) 0.692
Harris hip score	(0.27 <sub>1</sub> ) 0.604	(0.14 <sub>1</sub> ) 0.714
ASA score	(2.51 <sub>2</sub> ) 0.090	(0.15 <sub>2</sub> ) 0.864
Gluteus muscle size ( $mm^2$ )	(0.41 <sub>1</sub> ) 0.527	(0.15 <sub>1</sub> ) 0.698
Walking speed ( $m/s$ )	(0.70 <sub>1</sub> ) 0.405	(0.01 <sub>1</sub> ) 0.931
Walking activity ( $steps/day$ )	(0.18 <sub>1</sub> ) 0.676	(1.39 <sub>1</sub> ) 0.243

F = F-ratio adjusted for the covariates. df = Degrees of freedom. \*  $P$  value  $< 0.05$ .

### 7.3.2 Postoperative walking activity

Postoperative walking activity was associated with the amount and direction of the stem rotation (Figure 21). Subjects who had higher walking activity (equal or above the cohort median of 2600 steps/day measured at 3 months postoperatively) showed internal rotation (retroversion). The mean difference compared to the baseline position was 1.52 degrees (95% CI 0.50 to 2.53). However, subjects with walking activity below the median maintained the original position around the y-axis. The mean difference compared to the baseline position for this group was -0.24 degrees (95% CI -1.08 to 0.60). The relationship between the direction of stem rotation and the level of walking activity was evident in the cohorts with and without outliers. There was a positive correlation between walking activity and spontaneous walking speed (Pearson correlation  $r = 0.350$ ,  $p = 0.012$ ). At 3 months, walking speed was 0.94 m/s (95% CI 0.83 to 1.03) in subjects with a walking activity of  $< 2600$  steps/day and 1.06 m/s (95% CI 0.98 to 1.13) in subjects with a walking activity of  $\geq 2600$  steps/day.



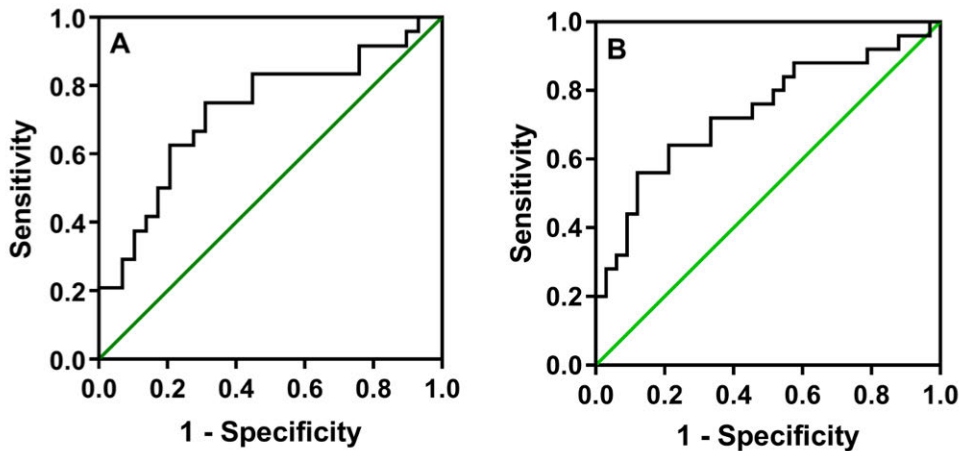
**Figure 21.** Impact of walking activity (categorized by median value) on the femoral stem subsidence and rotation. Values are means and bars show 95% CIs. Outliers were excluded for the analysis. Subsidence is marked by the negative sign of distal-proximal translation along the y-axis. Internal rotation (retroversion) is marked as positive and external rotation (anteversion) negative.

## 7.4 Pulse-echo ultrasonometry in prediction of stem migration

Stem migration is almost an inevitable event in women with decreased systemic BMD. However, osteoarthritic hip might alter the real value of femoral neck BMD by a higher value. Consequently, this counterfeit BMD fails to predict stem subsidence. Accordingly, the distal radius is an optional site for the evaluation of systemic BMD in patients with hip osteoarthritis. ROC curve analysis of the pulse-echo ultrasonometry of the radius cortical bone thickness showed that a cut off value of 2.33 mm can discriminate subjects with stem subsidence below or above the 2

mm (the median of the cohort subsidence) (Figure 22-A). This cut-off value resulted in an AUC of 0.73 (95% CI 0.584 to 0.867;  $p = 0.005$ ).

As a reference analysis, the ROC curve of the distal radius BMD (measured by DXA) resulted in a cutoff value of 0.668  $\text{g}/\text{cm}^2$  for discriminating between stem subsidence of below and above the 2 mm (Figure 22-B). The AUC value was 0.74 (95% CI 0.603 to 0.871;  $p = 0.002$ ). However, total hip BMD of the operated hip failed to discriminate between acceptable and unacceptable femoral stem subsidence. The AUC value was 0.588 (95% CI 0.435 to 0.741) ( $p = 0.26$ ).



**Figure 22.** ROC curve analysis of the radius cortical bone thickness (A) and distal radius BMD (B) for the assessment of cut off values able to discriminate subjects with femoral stem subsidence higher or lower than the cohort median value of 2 mm. Cortical bone thickness was obtained using pulse-echo ultrasonometry, and radius BMD was obtained using DXA.

## 8 Discussion

### 8.1 Model-based RSA for the measurement of femoral stem migrations

Our phantom experiment on the assessment of model-based RSA accuracy demonstrated that model-based RSA can yield comparable accuracy to that of the marker-based RSA if particular considerations are taken into accounts. These considerations include the application of high-quality (Kaptein et al., 2006; Seehaus et al., 2013) combined stem-head CAD models (Prins et al., 2008), standard radiographic setup, accurate patients positioning (Gascoyne et al., 2014; Mäkinen et al., 2004), and enough and accurate configuration of bone markers (Ryd et al., 2000; Madanat et al., 2005). Our model-based accuracy was close to that of our marker-based accuracy and those marker-based accuracies (from 0.01 to 0.5 mm and 0.02 to 1.15 degrees [Kärrholm, 1989; Selvik, 1989; Valstar et al., 2002; Önsten et al., 2001]) and model-based accuracies (from 0.14 to 0.22 mm and 0.1 to 0.52 degrees [Kaptein et al., 2006; Seehaus et al., 2013; Valstar et al., 2001]) observed in previous phantom studies. However, the head-to-head comparison of the accuracy values reported in different studies is not legitimate. Unlike the clear definition of the accuracy (Derbyshire et al., 2009), researchers reported different terms (such as the mean and standard deviation and/or confidence interval of the difference between applied and measured micromotions) as the accuracy.

It is important to clarify the difference between accuracy and precision in order to avoid the misselection of these two terms. Accuracy demonstrates how close the measurement results are to the ground truth, while precision refers to the closeness of the measurements when they are repeated. An accuracy assessment is only viable using phantom and simulation of the micromotions using micrometers. Since the accuracy of the model-based RSA depends on the shape of the stem, it is essential to evaluate the accuracy before using model-based RSA as an alternative to marker-based-RSA. Measurement of the precision using phantom models (in vitro precision) (Prins et al., 2008) neither guarantees high accuracy of the measurements nor similar clinical precision. As is reported by Prins et al., (2008), the clinical precision for the translation along the y-axis was much lower than that of the phantom even in combined head-stem model-based RSA (phantom precision of 0.06 mm vs clinical

precision of 0.19 mm for Mallory/Head stem and phantom precision of 0.02 mm vs clinical precision of 0.07 for Stanmore stem). It is clear that maintaining a fixed and standard positioning for the double examination is more challenging with patients (clinical) compare to the phantom.

Our study showed a lower accuracy for the model-based RSA (compared to marker-based RSA) for rotation around the y-axis. This inferior accuracy is assumed to be due to the nature of the model-based RSA. Application of model-based RSA for the assessment of femoral stem migration is reported to suffer from lack of precision due to the unfavorable geometry of the femoral stem (in particular tapered round stems), and inaccuracies and low quality of the CAD models (Kaptein et al., 2006). It is already known that the accuracy of the rotation around the axis of symmetry of axially symmetric objects does not change the contour of the projected image to as large as degree as motion about non-symmetric axes (Seehaus et al., 2013).

The clinical precision of our model-based RSA was in line with those reported by previous research for the translation (0.07 to 0.25 mm) and rotation (0.20 to 3.12 degrees) (Prins et al., 2008; Li et al., 2014; Lindgren et al., 2019).

## 8.2 Efficacy of denosumab in cementless THA

The results of the study II indicated that denosumab increased the BMD in the greater and lesser trochanter along with the entire periprosthetic regions at week 48, as compared to the baseline measurements. This type of strong response was a novel finding. A recent study on the effect of denosumab in prevention of early periprosthetic bone loss after cementless THA confirmed our results (Nyström et al., 2020). In that study, the BMD in the denosumab group was 32% higher (compared to 12.8% in our study) in the Gruen zone 7 as compared to the placebo group after 12 months. The patient population of these two studies was different. Our study included only postmenopausal women while the other study only included young and middle-aged patients without osteoporosis, which are not the typical population for whom denosumab is indicated (Shao & Wu, 2020). The increase of periprosthetic BMD in our study was less compared to the other study in the Gruen zone 7 (-5.3% versus 3% compared with baseline) and in the entire periprosthetic region (5.5% versus 11% compared with the placebo). The reason behind this variance refers to the different responses between young and elderly patients (Shao & Wu, 2020) considering the fact that preoperative low BMD results in further periprosthetic bone loss (Kerner et al., 1999; Venesmaa et al., 2003).

In our trial, denosumab increased periprosthetic BMD above the baseline in the greater (zone 1) and lesser trochanteric regions (zone 6) and in the entire periprosthetic region. This type of strong response has not been observed in trials



with oral risedronate (Sköldenberg et al., 2011) or intravenous zoledronic acid (Aro et al., 2018). Concerning Gruen zone 7, the primary treatment responses of the oral risedronate, intravenous zoledronic acid, and alendronate in previous trials were similar to that of the denosumab in our trial. All these drugs decreased bone loss compared with a placebo at 6-12 months (Aro et al., 2018; Sköldenberg et al., 2011; Tapaninen et al., 2010; Venesmaa et al., 2001).

The long-term impact of antiresorptive therapies is different from the primary effect. In trials of zoledronic acid (5 years) (Aro et al., 2018) and risedronate (4 years) (Muren et al., 2015), there was a similar bone loss of about 20% in zone 1 and 7 in all patients. In the alendronate trial, (Tapaninen et al., 2010), there was 16% decrease in zone 1 and 28% decrease in zone 7 in the control group. Although the alendronate group showed less bone loss in these zones, the differences compared with the placebo group were not statistically significant (Tapaninen et al., 2010). Accordingly, it could be concluded that, although these drugs prevent periprosthetic bone loss postoperatively, a decrease in periprosthetic BMD accelerates when therapy is discontinued and no effect is seen at 4-5 years. In our trial, after discontinuation of denosumab, the periprosthetic BMDs of the denosumab group approached the levels of the placebo group after 3 years. Compared with baseline, periprosthetic BMD of the medial femoral neck (zone 7) was -12.6% in the denosumab group and -17.3% in the placebo group after 3 years. In fact, our extension study confirmed that the action of denosumab is reversible (Baron et al., 2011). The recent study by Nyström and coworkers also confirmed that the effect of denosumab in the prevention of periprosthetic BMD diminishes after discontinuation of treatment (Nyström et al., 2020).

When the efficacy of the bisphosphonates was compared between cemented and cementless THAs in a review paper, the treatment responses were higher in patients with uncemented stems (8.4% to 8.7% in zone 1 and 7.6% to 8.8% in zone 7) (Knusten et al., 2014). More specifically, cemented studies did not show any significant difference in BMD between patients in the control groups and the bisphosphonate treated group (Knusten et al., 2014). Interestingly, uncemented stems showed more bone loss proximally compared to cemented stems and the treatment was more effective in patients with an uncemented stem, except for Gruen zone 7 (Knusten et al., 2014). The reason for more periprosthetic bone resorption in uncemented stems might be that many uncemented implants are larger than cemented ones. These larger stems result in more stress shielding followed by higher bone loss (Knusten et al., 2014). However, there are controversial results in the literature suggesting that patients with a cemented implant experienced similar (Lin et al., 2012) or more (Dattani, 2007) bone loss. Nevertheless, as Knusten et al., (2014) mentions, accurate direct comparison of cemented and uncemented stems is limited by the stem design and material.

Although denosumab reduced periprosthetic bone resorption, it had no significant impact on the stem initial migration. This result accords with a previous RSA research on the effect of zoledronic acid on the initial migration of a double-tapered straight femoral stem in postmenopausal women (Aro et al., 2018). It is also in line with the other EBRA\_FCA research by Sköldenberg and colleagues who reported that weekly oral risedronate had no impact on the initial migration of a tapered stem in a mixed population of males and females with an average age of about 60 years (Sköldenberg et al., 2011). Accordingly, it could be concluded that the reduction of periprosthetic bone resorption achieved by antiresorptive treatment cannot improve the initial femoral stem stability after cementless THA. However, treatment with denosumab, if started at the proper time before the surgery, may improve the quality of cortical bone and thereby reduce initial femoral stem migration. In postmenopausal women, denosumab therapy can enhance the osteoporotic cortical bone of the proximal femur, but the treatment response takes time to develop (Genant et al., 2013). In our trial, denosumab was started 1 month preoperatively, which transpired to be too late for prevention of stem migration. If denosumab treatment had been started sufficiently early (approximately 6 or 12 months preoperatively), the cortical bone structure might have had time to respond and improve stem stability.

The most common AE in denosumab RCT was low-back pain both in denosumab-treated and placebo groups. After discontinuation of denosumab, the differences in severity of low-back pain and/or interference of low-back pain with daily activities were not significant between the two groups. The recent study by Nyström et al., (2020) also reported no differences in muscle and back pain AE between the denosumab and placebo groups.

### 8.3 Predictors of initial stem migration after cementless THA

Although some attempts have been made to investigate the predictors of initial migration of uncemented stems using RSA, there is still no RSA study examining a wide range of patient-related and surgery-related factors contributing to initial femoral stem migration. However, an EBRA-FCA study reported that a body weight of over 75 kg and a height of over 165 cm significantly influenced stem subsidence towards progressive migration (Stihsen et al., 2012). Interestingly, BMI > 30 kg/m<sup>2</sup> did not trigger progressive stem migration in this study (Stihsen et al., 2012). Previous research also investigated the initial migration pattern of Accolade stems (original and Accolade II). However, these studies (Grant et al., 2017; Jacobs & Christensen, 2009; White et al., 2012) are only based on the radiographic assessment and there is no accurate migration measurement system involved in these studies.

Jacobs and Christensen (2009) reported progressive subsidence of the original Accolade (TMZF<sup>®</sup>) stem from six weeks to one year postoperatively. This subsidence was seen significantly more often in men than women at one year ( $1.7\pm 2.0$  mm vs  $1.0\pm 1.4$  mm,  $p=0.03$ ). The investigators of this study report that it is unclear if the increased subsidence in men was related to patient-related factors of age, weight, and activity level or with specific implant characteristics (Jacobs & Christensen, 2009). White et al., (2012) also reported a high incidence of migration of Accolade stems with radiographic failure as a concern about the patient clinical function and long-term survivorship of this stem design. However, another study compared the radiographic assessment of the Accolade II stem with a traditional fit-and-fill femoral stem demonstrated greater axial stability and decreased subsidence of the Accolade II in patients with a higher BMI (Grant et al., 2017). One caution that should be mentioned is that the accuracy of the manual radiographic measurement technique utilized in these studies does not yield the accuracy of RSA. It is reported that when using RSA as the reference method, the accuracy of one of these radiographic measurement systems, Düsseldorf Migration Analysis – Femoral Component Analysis (DMA-FCA), was calculated to be 2.51 mm for subsidence and  $2.49^\circ$  for varus-valgus tilt (Schutz et al., 2005).

In addition to patient-related factors, surgery-related factors was shown to influence the stem stabilization into the femoral bone, especially in heavy patients in an EBRA-FCA based study (Stihsen et al., 2012). In that study, stems providing a poor fit and fill into the bone with a lack of cortical contact showed significantly higher odds of migration compare to those with a tight fit (Stihsen et al., 2012). Recently, a study on the Accolade II stem also showed that the distal canal fill might affect the outcome of THA using this stem design; inadequate metadiaphyseal fill of this stem resulted in increased subsidence and a risk of aseptic loosening (Warth et al., 2020). In that study, patients whose surgeon vigorously broached to maximizing the mediolateral stem dimension and confirmed final broach stability with a torsional test, showed significantly less subsidence ( $0.3$  vs  $1.3$  mm,  $P < .001$ ) at 1 month in contrast to patients whose surgeon did not do so (Warth et al., 2020). The mean canal fill of the patients with tight stems was 95% compared to 86% in the other group at a location 60 mm below the lesser trochanter (Warth et al., 2020). However, the subsidence was measured from the plain radiograph. Accordingly, there is a lack of evidence suggesting the association between poor fit and fill ratio and RSA-measured femoral stem migration.

Our analysis for the prediction of stem initial migration did not reveal any particular predictor for stem subsidence when the effect of outliers was taking into account for the statistical analysis. When the effect of outliers was not considered, there was a strong relationship between systemic low BMD and stem subsidence. In fact, outliers with excessive stem subsidence, rotation or both had a significantly

lower total hip BMD compared with non-outliers. In addition, in Study IV, the subjects with a stem subsidence of more than 2 mm had significantly ( $p = 0.007$ ) lower total hip BMD compared with those whose subsidence was less than 2 mm.

Walking activity during the first 3 months after the surgery had a significant impact on the amount and direction of stem rotation around the y-axis. It is already known that walking at a normal speed causes high contact forces and torsional moments in the femoral components of total hip prostheses (Bergmann et al., 2001; Bergmann et al., 2016; Heller et al., 2001). These studies with instrumented femoral stems have predicted that the torque around the stem axis may influence the initial torsional stability of cementless implants in the femur (Bergmann et al., 2016). Accordingly, it is not surprising that postoperative walking activity leads to femoral stem rotational migration. This finding suggests the significance of physical activity monitoring after the surgery in cementless THA research.

In this study, the subjects with walking activity equal to or above the cohort median exhibited limited internal rotation of the stem (mean 1.84 degrees compared to the baseline position). This was in line with the previous observations on the typical direction and degrees of rotation of different femoral stem designs including a double-wedged straight femoral stem (Symax) with 1.5 to 2 degrees (Aro et al., 2018), a tapered straight femoral stem (CLS) with 0.59 to 1.18 degrees (Ström et al., 2007), a double-tapered (Furlong HAC) with 0.80 degrees (Weber et al., 2014), and a parallel-sided stem (Furlong active) with 1.18 degrees (Weber et al., 2014).

The RCT subjects investigated in this thesis showed considerable stem subsidence (mean 1.5 mm, 95% CI 0.1 to 2.9) even in patients with normal BMD. This result was in contrast to earlier findings in which subjects with normal BMDs experienced minimum stem subsidence (0.5 mm - 0.7 mm) compared to osteopenia and osteoporosis subjects independent of the femoral stem design, including an anatomically designed stem (Aro et al., 2012) and a double-wedged straight femoral stem (Aro et al., 2018). The Accolade II stem which was implanted in the subjects of this trial was a redesign of a previous stem with the aim of metaphyseal cortical bone engage in the medial-lateral plane. Accolade II showed lower subsidence and retroversion in preclinical tests (Faizan et al., 2015) and improved proximal and distal engagement (stem fit and stem to canal fill ratio) in a clinical study (Issa et al., 2014). There are recommendations for the implantation of this stem in subjects with sufficient bone stock and unaltered femoral geometry (Grayson & Meneghini, 2018). To follow these recommendations, subjects with Dorr type C were excluded from the clinical trial of this thesis. However, the existence of sufficient bone stock (normal preoperative BMD) and unaltered femoral geometry (Dorr type A and B with canal flare index  $\geq 3.0$ ) did not guarantee stem initial stability. These results suggest that further considerations need to be taken into account for the implantation

of the current prosthesis in postmenopausal women who are prone to osteopenia and osteoporosis and demonstrate different geometries of the proximal femur.

Ideally, uncemented implants should not migrate at all, but many designs still do (Kärrholm, 2012). The time frame for acceptable initial migration depends on several factors such as the type of implant and the type of fixation (Kärrholm, 2012). The initial migration time frame is reported to be limited to the first 3 months (Weber et al. 2014, Salemyr et al., 2015) or 6 months (Campbell et al., 2011). However, a period of 1 year after the surgery seems to be the maximum time limit for migration of cementless stems to not result in fibrous fixation or loosening (Kärrholm, 2012). The migration of the stems in our RCT patients was so close from 3 to 5 months after the surgery. We utilized 5-month time-point data to ensure that all the stems were already stabilized.

## 8.4 Role of pulse-echo ultrasonometry in the prediction of stem subsidence

Pulse-echo ultrasonometry of the radius cortical bone thickness was able to discriminate postmenopausal women prone to early stem subsidence with moderate accuracy (0.73). As a control analysis, DXA-measured radius BMD was also effective (accuracy of 0.74) in discriminating subjects prone to stem subsidence. However, DXA-measured BMD of the operated hip failed to recognize subjects prone to subsidence. This finding supports the idea that distal radius is the optimal site for evaluation of the bone quality in postmenopausal women before cementless THA. The patients with osteoarthritis may show higher BMD in hip and lumbar-spine (Hart et al., 1994; Nevitt et al., 1995; Peel et al., 1995). This counterfeit BMD (from hip and/or lumbar-spine) may result in a misleading impression of BMD in osteoarthritis patients.

The accuracy of pulse-echo ultrasonometry for discrimination of subjects prone to initial stem subsidence was not perfect. The reason behind this moderate accuracy might be that stem initial subsidence is a complex issue and many potential confounding factors might have an impact on it. The quality of the cortical bone is only one of these factors. Accordingly, it is expected that the power of bone quality for the prediction of stem subsidence is limited.

Subjects with the low ultrasonometry-measured cortical bone thickness of the radius (less than the cut off value obtained by ROC analysis) had significantly lower canal fill ratios in the middle and distal stems and a tendency for a lower canal flare index. The reason for this inappropriate stem to canal fill ratio might be the thinning of the medial cortex of the femur. The lower canal flare index in these subjects is an indicator of the enlarged medullary canal and corroborates this hypothesis. Previously it was reported that the distal radius also undergoes similar structural

changes to that of the proximal femur in postmenopausal women (Ahlborg et al., 2004). Both these phenomena including thinning of the medial cortex of the femur and enlarged medullary canal (of the proximal femur and distal radius) are common in postmenopausal women (Ahlborg et al., 2004; Casper et al., 2012), suggesting the requirement of a screening protocol (such as DXA or pulse-echo ultrasonometry) of the distal radius before performing cementless THA in the postmenopausal women population.

## 8.5 Strengths, limitations, and future aspects

### Strengths

This thesis work includes strengths and limitations. One of the main strengths of this thesis is that it is based on the analyses of randomized clinical trial data. RCTs are known as one of the most reliable forms of scientific evidence due to their substantially lower spurious causality and bias. Another strength of this thesis work is the application of RSA to the measurement of femoral stem migration. RSA is the most accurate and precise technique for the measurement of stem migration. It also provides information for the surgeons to predict the longterm outcome of the THA. In addition, the monitoring of different patient's characteristics and analyzing a high number of patient-related and surgery-related factors make this thesis work strong. However, there are certain limitations in each sub-works of the thesis.

### Limitations

In the preclinical phantom study (study I), the accuracy of RSA for the rotation of the stem around the x and z-axis were not measured due to the technical complexity of simulating these micromotions. Additionally, the lack of simulated soft tissue in the phantom limited us when investigating the effect of soft tissue, if any, on the model-based RSA accuracy. Different configurations of the bone markers, the different qualities of the CAD models, as well as different stem designs were not examined. Accordingly, the impact of these factors on the model-based RSA accuracy remains unknown. Consequently, caution should be applied before generalizing the results of the model-based RSA accuracy in this study.

In the denosumab sub-work of the thesis (Study II), the start of the denosumab treatment (1-month preoperatively) was quite late with the result that the denosumab did not have enough time to effectively improve the cortical bone structure.

In the prediction of stem initial migration sub-work (Study III), a power analysis was not performed for the purpose of this sub-work, but instead for the original RCT (Study II). Accordingly, the number of subjects with specific conditions including

osteopenia and osteoporosis, overweight or obese, Dorr type of B and C, a CFI of lower than 3 (stovepipe) and greater than 4.7 (Champagne flute), and the number of subjects receiving stems with high offset (neck angle of  $132^\circ$ ) was limited. Furthermore, the results of this sub-work are based on the examination of only one femoral stem design implanted in the specific subgroup (postmenopausal women) of THA patients. Therefore, the generalizability of the results is legitimate only under certain conditions.

In the fourth sub-work of the thesis (Study IV), the limited group size and restricted inclusion criteria of the original RCT disempowered the study as regards generalizing the results to different THA patients with a variety of characteristics as well as different stem designs.

### Future aspects

The addition of simulated soft tissue and an examination of different configurations of the bone markers, as well as the different quality of the CAD models together with different stem designs would reveal the correct information about the factors which might have a detrimental effect on the accuracy of the model-based RSA. Further investigations about the effectiveness of antiresorptive therapies such as denosumab for the reduction of stem initial migration in THA patients is recommended. It is hypothesized that if the treatment starts between 6 to 12 months before the surgery, denosumab might have enough time to effectively improve the structure of the periprosthetic cortical bone. Nevertheless, it is clinically challenging to motivate a symptomatic patient to accept a delay of 6 to 12 months before the surgery. To reveal the factors contributing to the stem initial migration more precisely, it is suggested that balanced groups of patients with different conditions and characteristics and diverse stem designs should be taken into account. It would be appropriate to also examine the capacity of the pulse-echo ultrasonometry for the discrimination of patients prone to stem subsidence in such a population with a diversity of characteristics. However, the preoperative examination of the proximal femur using high-resolution CT imaging may demonstrate the real status of the cortical bone. The preoperative imaging of the proximal femur might be indicated and cost-effective in specific subgroups of patients such as postmenopausal women who are prone to stem subsidence after cementless THA. If CT imaging verifies the altered structure of the proximal femur, cemented THA might be a better choice.

# 9 Conclusion

The findings of this thesis suggest the following conclusions:

- I.** The application of model-based RSA with high quality combined stem-head CAD models and a sufficient number and an appropriate configuration of the bone markers seems to be an appropriate tool for clinical trials of cementless tapered-wedge femoral stems. The key message is that the accuracy of the model-based RSA should be verified for each stem design in a phantom experiment. The clinical precision of the model-based RSA is comparable to that of marker-based RSA suggesting the requirement of the same number of patients for the RCTs with marker-based and model-based RSA.
- II.** Denosumab therapy increased periprosthetic femoral BMD after cementless THA. However, this did not result in a reduction of the initial stem migration and the speed of functional recovery. Nevertheless, it is possible that with an optimized preoperative starting time for the denosumab treatment, THA patients might benefit from stem initial stability. However, prior to the application of denosumab therapy in THA patients, large clinical trials need to focus on the clinical relevance of the pharmacological intervention. Clinical trials of uncemented hip stems could be conducted in postmenopausal women with systemic osteopenia.
- III.** The migration of the implanted parallel-sided femoral stem in this thesis was associated with the amount of physiological loading directed by walking activity. This finding highlights the significance of physical activity monitoring immediately after the surgery in RSA research on cementless THA. The great impact of outliers on the statistical analysis emphasizes the significance of analyzing RSA data of THA patients with and without outliers.
- IV.** Preoperative pulse-echo ultrasonometry of the distal radius may help to identify postmenopausal women at high risk of stem subsidence. The accuracy of pulse-echo ultrasonometry of the distal radius was similar to that of the radius DXA in discriminating between  $< 2$  mm and  $\geq 2$  mm stem subsidence.



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