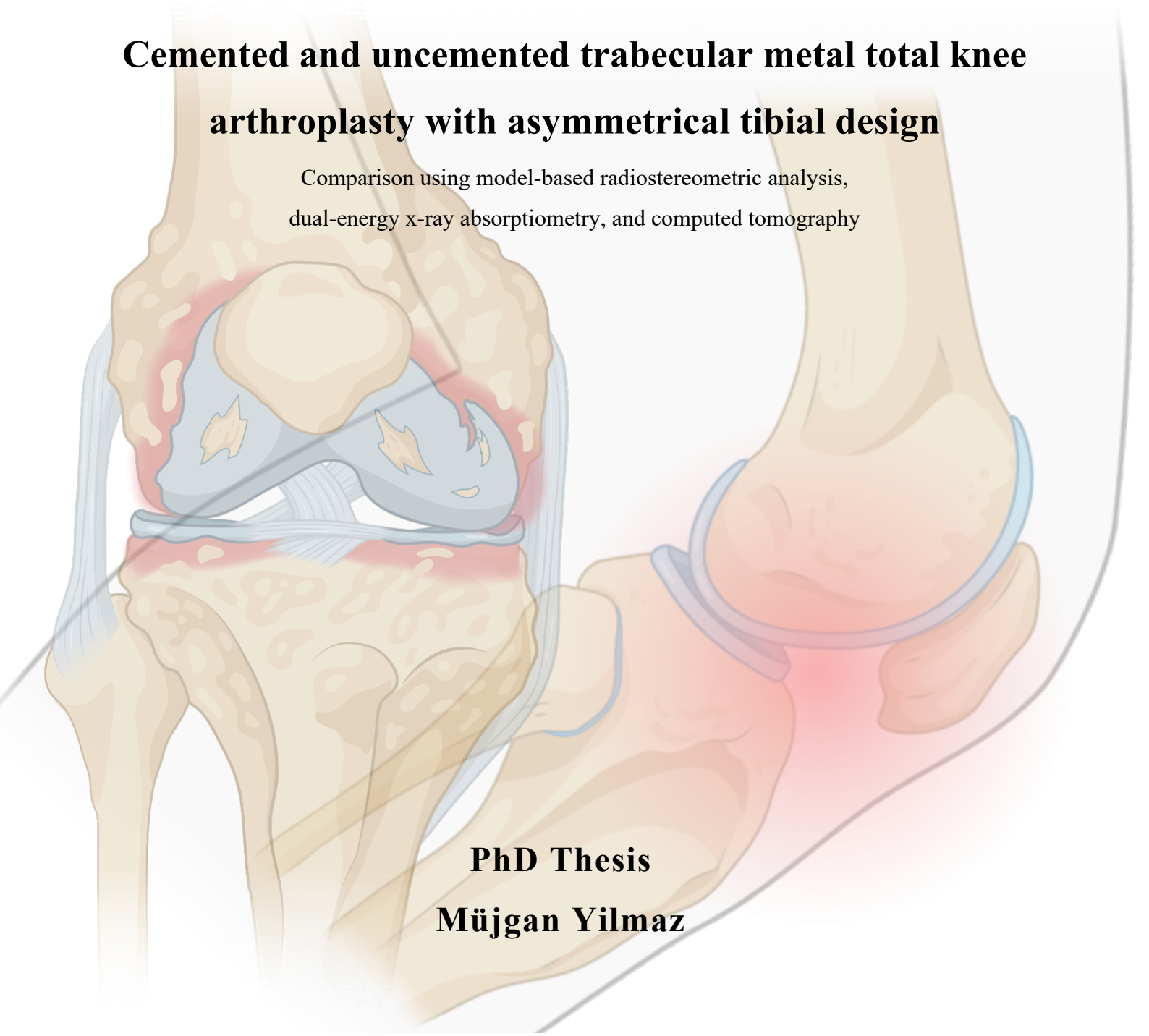
UNIVERSITY OF COPENHAGEN
FACULTY OF HEALTH AND MEDICAL SCIENCE

Cemented and uncemented trabecular metal total knee arthroplasty with asymmetrical tibial design

Comparison using model-based radiostereometric analysis,
dual-energy x-ray absorptiometry, and computed tomography



PhD Thesis

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Conflict of interest

The authors declare no conflict of interest.

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Preface and Acknowledgements

I am surrounded by the most amazing, family, friends, and colleagues, so this preface is very hard to write as everyone deserves to be mentioned because all of you have touched my life in such a good way – I am deeply thankful.

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Müjgan Yilmaz
January 2023

List of Papers

Study I

Bone remodeling and implant migration of uncemented femoral and cemented asymmetrical tibial components in total knee arthroplasty - DXA and RSA evaluation with 2-year follow-up.

Müjgan Yilmaz, Christina Enciso Holm, Thomas Lind, Gunnar Flivik, Anders Odgaard and Michael Mørk Petersen. Knee Surg Relat Res. 2021 Aug 17;33(1):25. doi: 10.1186/s43019-021-00111-5. PMID: 34404487.

Study II

Implant migration in cemented and uncemented knee arthroplasty with an asymmetrical tibial component. A randomized controlled trial with a 2-year model-based RSA follow-up.

Müjgan Yilmaz, Christina Enciso Holm, Thomas Lind, Gunnar Flivik, Anders Odgaard, and Michael Mørk Petersen (not submitted).

Study III

Adaptive bone remodeling after cemented and uncemented knee arthroplasty with an asymmetrical tibial component. Results from a randomized study using dual-energy X-ray absorptiometry.

Müjgan Yilmaz, Thomas Lind, Gunnar Flivik, Anders Odgaard, and Michael Mørk Petersen (not submitted).

Study IV

Influence of tibial component overhang and bone surface coverage on implant migration. Evaluation of a cemented asymmetrical tibial component using computed tomography and model-based RSA.

Müjgan Yilmaz, Albin Christtensson, Mette Lønstrup Harving, Thomas Lind, Anders Odgaard, Gunnar Flivik, and Michael Mørk Petersen (not submitted).

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Abbreviations

TKA:	Total Knee Arthroplasty
MBRSA	Model-based radiostereometric analysis
RSA:	Radiostereometric Analysis
OA:	Osteoarthritis
MTPM:	Maximal Total Point Motion
CT:	Computed tomography
SEMAR:	Single Energy Metal Artefact Reduction
CAD:	Computer-Aided Design
TM:	Trabecular metal
CR:	Cruciate retaining
MC:	Medial congruent
CN:	Condition number
ME:	Mean error
PE:	Precision error
95CI:	95% Confidence Interval
SE:	Sweden
DK:	Denmark
PACS:	Picture Archiving and Communication System
PE:	Precession error
ROI:	Region of Interest
CV:	Coefficient of Variation
BMD:	Bone Mineral Density

Dansk resumé

Igennem denne Ph.d.-afhandling evalueres de tre fikseringsformer, cementeret, ucementeret eller hybrid, af en nyere total knæalloplastik (TKA). Afhandlingen evaluerer implantaternes migration, den adaptive knogles remodulering i nær relation til implantatet samt tibia implantatets positionering på den underliggende knogle.

I dag er TKA en succesfuld behandling med en proteseoverlevelse på >90% efter 10 år. Trods høj proteseoverlevelse er patientstilfredsheden efter en TKA-operation, lavere end patienttilfredsheden sammenlignet med andre ortopædkirurgiske indgreb. Denne utilfredshed er fundet at være multifaktoriel. Dog findes 20% at være udløst af vedvarende postoperative smerter.
Årsagen til disse smerter er undersøgt uden at en klar ætiologi, er kortlagt. Protesens placering med tibia implantatet i en intern rotation eller femur implantatet med et større udhæng, menes at have en betydning for de postoperative smerter.
Den undersøgte protese blev ifølge producenten udviklet, med henblik på at minimere risikoen for fejlplacering. Det asymmetriske tibia implantat skulle optimere dækningen af tibia plateauet, samtidig med at det minimerer risikoen for at placere protesen i en indad rotation. Dermed burde andelen af patienter med vedvarende postoperative smerter teoretisk mindskes.

Før nye proteser introduceres til klinisk brug anbefales der, som beskrevet ved Malchau, en trinvis introduktion. RSA-studier er det første trin ved denne introduktionsanbefaling.

Denne afhandling præsenterer fire forskellige studier. Studie I er et fortløbende studie, som brugte MBRSA og DEXA til at undersøge migration af protesekomponenterne med hybrid fiksering til knoglen. I dette studie fandt vi acceptable migrationsværdier for femur implantatet samt marginalt forhøjede værdier for tibia implantatet.
Studie II var designet som et fortløbende lodtrækningsforsøg hvor migration af protesekomponenterne med fuld cementering, blev sammenlignet med fuld ucementeret og blev evalueret med MBRSA. Vi fandt ingen forskel i migration mellem fikseringsformerne af det tibiale implantat, hvorimod der var en forskel mellem fikseringsformerne af femur implantaterne omend

uden klinisk betydning. For begge fikseringsformer og både tibia og femur implantatet fandt vi acceptable migrations data.
Studie III brugte DEXA-scanninger til at undersøge knogletætheden omkring implantaterne i den cementerede og ucementerede version af protesen. Knogletæthedsmålingerne blev udført som et led i opfølgningen i lodtrækningsstudiet. Vi fandt det største fald i knogletætheden på forsiden af femur samt den midterste del af tibia. Yderligere fandt vi en forskel på knogletætheden mellem fikseringsformerne i femur, men ikke blandt tibia implantaterne.
Studie IV undersøgte positionering af tibia komponenten på knogleoverfladen vurderet udfra CT-skanninger. Vi fandt acceptable dæknings- og rotationsgrader.

TKA anvendt i denne afhandling vurderes udfra studierne, at have en lav risiko for aseptisk løsning uafhængigt af fikseringstypen. Derudover viser tibia implantatet gode resultater ved positionering i forhold til dækning og rotation. Længere opfølgning er dog nødvendig, for at kunne vurdere om det observerede fald i knogletæthed, vil komme til at have en klinisk relevant betydning.

English summary

This thesis aims to evaluate the relatively newly introduced TKA. The fully cemented, uncemented, and hybrid fixated implants were evaluated with MBRSA measurements to determine the risk of aseptic loosening, DEXA measurements to determine the adaptive bone remodeling close to the implants, and CT scans to estimate the positioning of the tibial implants.

TKA is today a very successful treatment with an implant survival of >90% after 10 years. Despite high implant survival TKA surgery tends to have a lower patient satisfaction when compared with other orthopedic procedures, with patient satisfaction of around 80%. The dissatisfaction is found to be multifactorial of which approximately 20% complain of persistent postoperative pain.
The main cause of persistent postoperative pain has been investigated but no clear etiology without conclusive evidence. However, the positioning of the tibial implant in an inward rotation or/and the femoral component with an overhang is considered to cause persistent postoperative pain.
The prosthesis was designed with the aim of minimizing the group of patients with persistent postoperative pain by optimizing the positioning of the tibial implant due to its asymmetrical design and also herby aiming for better coverage of the tibial plateau.

When introducing new orthopedic implants for clinical use a phased instruction as described by Malchau is recommended. Migration studies are the first step to assessing the risk of aseptic loosening.

Through this thesis, four different studies will be presented. Study I is a prospective study of the hybrid fixated TKA. We found acceptable values of migration for both the uncemented femoral implant as well as the cemented tibial implant although these were marginally higher. Study II was a randomized controlled trial comparing migration values of the fully cemented TKA components with the uncemented fixation. We did not find any significant difference between the two fixation types in the tibial implants. However, we did find a significant difference between the femoral implants although not reaching clinical relevance. For both the femoral and tibial implants and for both fixations types acceptable migration values were reported.

Study III evaluated the adaptive bone remodeling close to the implants. We found a decrease in BMD in the anterior femur and medial tibia regardless of fixation type and additionally a statistically significant difference for the femoral implants.
Study IV evaluated the coverage and rotation of the implants using CT-scans. Coverage and rotation values were found to be acceptable.

In conclusion, the studies in this thesis assessed the risk of aseptic loosening in the femoral and tibial implants regardless of fixation mode and found a low risk of aseptic loosening, why the implants can be used in clinical settings. Positioning of the implant regarding coverage and rotation was acceptable. Longer follow-up is recommended to evaluate if the observed decrease in BMD will have any clinical implications long-term.

Background

Aseptic loosening of the tibial component is still a major cause of revision in patients with total knee arthroplasty (TKA). This thesis evaluates migration and segmental motion measured with model-based radiostereometric analysis (MBRSA) in cemented, uncemented trabecular metal (TM), and hybrid (cemented tibia and uncemented femur implants) fixated TKA with an asymmetrical tibial design used in patients with severe osteoarthritis (OA). Furthermore, adaptive bone remodeling of the bone next to the TKA implants was evaluated with dual-energy X-ray absorptiometry (DEXA) and the positioning of the implants was measured with computed tomography (CT).

Anatomy of the knee

The knee joint consists of the femoral, tibial, patella, and fibular bone. It is a modified hinge joint with the main movement in flexion and extension but small movement in rotation can occur in flexed knees. The stability in the knee is achieved through the anterior and posterior cruciate ligaments that prevent anterior-posterior dislocation (figure 1). Additionally, the medial and lateral collateral ligaments prevent dislocation in a lateral and medial direction. The meniscus is a fibrocartilage tissue that absorbs shock. Inside the capsule surrounding the joint is a synovial fluid that prevents resistance during movements. The tibial plateau is asymmetrical with a smaller lateral circumference.

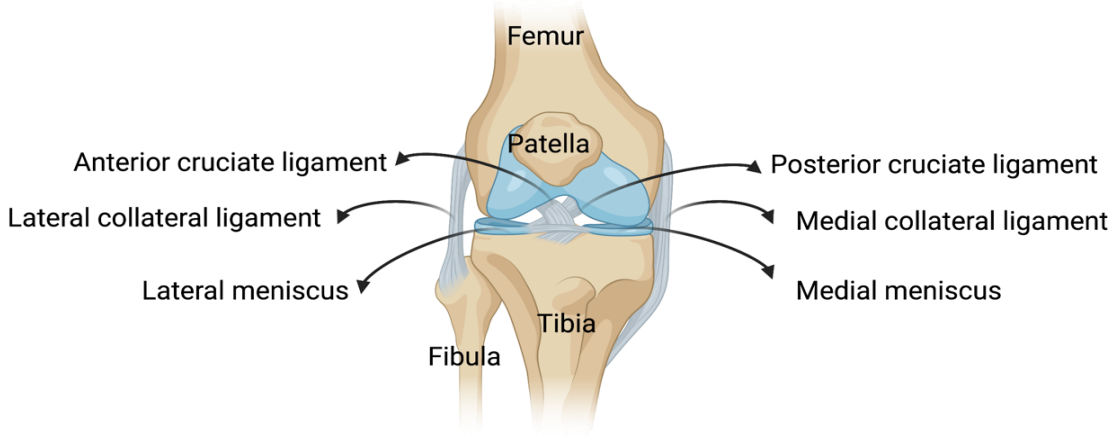

Figure 1: Anatomy of the knee joint. Created with Biorender.com, permission to publish was obtained.

Osteoarthritis (OA)

OA is a multifactorial and complex disease that commonly affects the knee joint [1, 2]. Initially, the metabolism of the tissue in the joint is affected. After a period of time, degeneration of the cartilage, formation of osteophytes, joint space narrowing, bone remodeling with sclerosing, and subchondral cyst formation can be detected (figure 2). This will lead to patients experiencing loss of joint function and pain [3]. Obesity [4] and previous trauma [5] increase the lifetime risk of symptomatic OA, whereas age and female gender are risk factors for knee OA [2].

In Europe, 29% of women and 16% of men ≥ 55 years have a radiologic sign of knee OA whereas 23% of women and 8 % of men ≥ 50 years have symptomatic knee OA [6]. It is estimated that 250 million people worldwide are affected by OA [6].

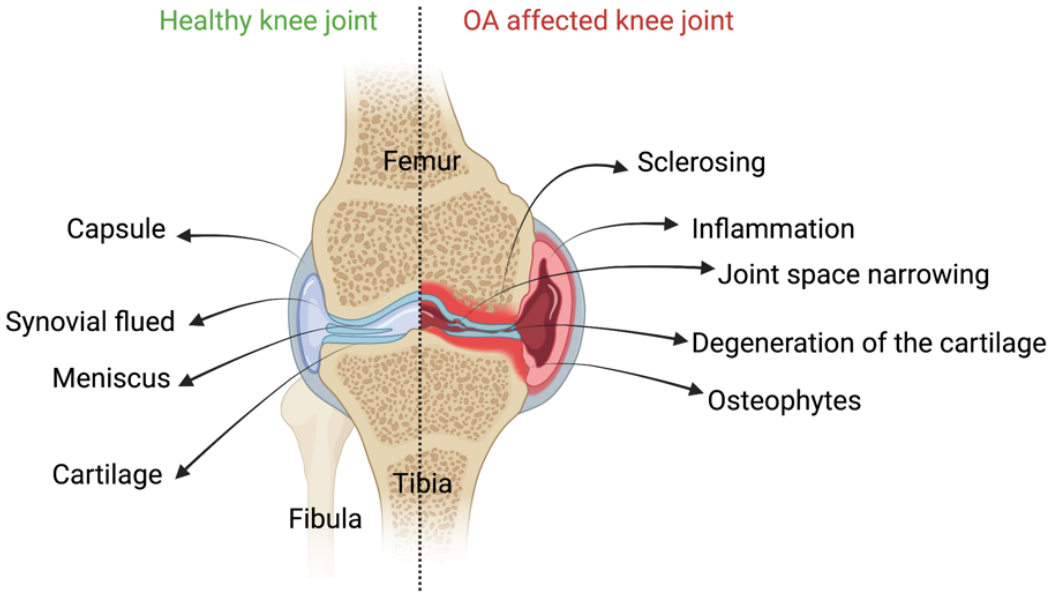

Figure 2: Image of a knee with healthy (left) and OA (right) sides. Created with Biorender.com, permission to publish was obtained.

Total knee arthroplasty (TKA)

Early attempts at knee replacement were carried out in the 1860s when a German surgeon named Themistocles Gluck restored a knee joint with a hinged prosthesis made of iron. The design of TKA as we know them today was inspired by Frank Gunston that made the first gliding TKA designed in 1968 with two separate femoral implants in metal, a lateral end medial part [7, 8].

The implants glided on polyethylene attached to the tibial plateau (figure 3) [8].

Since then, a great improvement in TKA designs has occurred and today different designs such as cruciate-retaining, ultra-congruent, posterior-stabilizing, and fixed or rotating platform prosthesis are used [7].

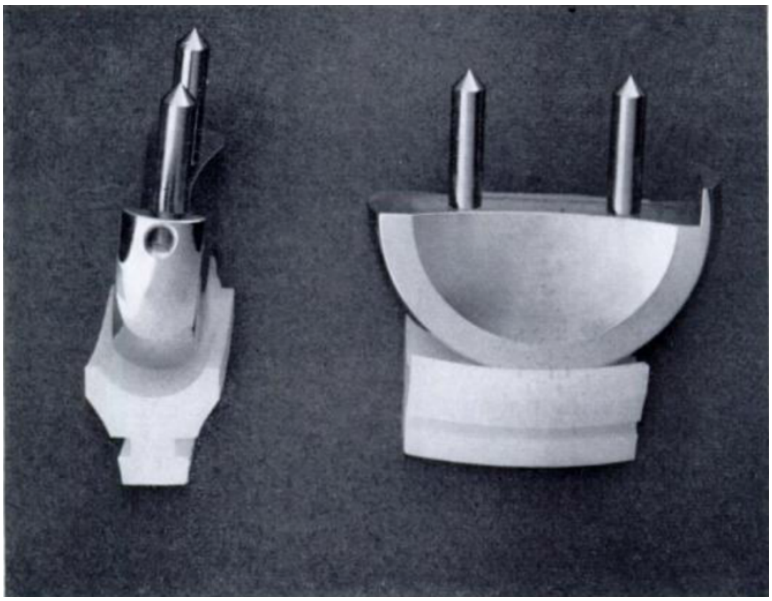

Figure 3: First gliding TKA [8], reprinted with permission from Copyright Clearance Centre.

TKA is a very successful treatment, with implant survival rates of >90% after 10 years according to registry studies [9, 10]. Despite the high implant survival rates, an 80% patient satisfaction rate has been reported, which is lower when compared with other orthopedic procedures [11-14]. A recent study similarly reported 82.5% satisfaction one year after TKA, however, the study suggested that patient satisfaction should at the earliest be evaluated 6 months postoperatively [15]. Multiple factors have been found to influence the experience of satisfaction such as postoperative complications [14], additional pain in other joints [16] and personality traits [17, 18]. Various causes have been demonstrated to cause dissatisfaction in patients of which persistent pain represents the majority [19] and is estimated in around 20% of the cases [20]. Although the reason for persistent pain in patients after TKA surgery is unknown. Factors related to the positioning of the implant, such as inward rotation of the tibial implant [21] and overhang of the femoral implant [22] have been suggested to cause postoperative persistent pain [23].

Persona® TKA was designed with the aim of minimizing postoperative pain. Due to the asymmetrical design of the tibial plateau, it is thought that the tibial implant will have a better fit and, in this way, it should minimize postoperative pain by preventing the implant from being placed in an inward rotation. The Persona® TKA consists of a regular femoral and an asymmetrical tibial implant of which both implants are accessible for cemented fixation or with a trabecular metal (TM) surface with high porosity enhancing bone ingrowth (figure 4).

Figure 4: Persona® total knee prosthesis. The tibial implants are pictured on the left side as well as the upper right picture. The femoral implant is pictured on the bottom right.

In general, the TKA components can be fixated to the bone by either cement or with the coating/surface of the implant which stimulates the bone growth into the implant (uncemented).
In Denmark, three main fixation types are commonly used of which the fully cemented is the most common (64.3%). Secondly, hybrid fixation (uncemented femur implant and cemented tibial implant) is used (26.5%) and lastly, uncemented fixation with different coating and surface design is used (9%) [24]. A previous study has demonstrated a slightly better implant survival of the cemented fixation when compared with uncemented fixation [25]. On the contrary, a register study from the Norwegian arthroplasty register indicated a better survival of the hybrid fixation when compared with the cemented fixation [26]. Nevertheless, more recent studies have indicated similar revision rates, implant survival, and functional outcomes when comparing cemented and uncemented fixation [27-30].

The prevalence of TKA in Denmark in the period 1997-2020 was 6,683 surgeries pr. year of which 11.5% required revision surgery [24]. Revision surgery can be caused by different complications of which aseptic loosing, instability and infections are the most common causes [24]. The etiology of aseptic loosing is believed to be a combined mechanism of different factors usually divided into host, genetic, surgical, or implant-related factors. A systematic review by Jeffrey et al. [31] did not find any host-related factor such as BMI above or under 30 as aseptic loosening correlating factors. Factors such as particles from excess wear are thought to be one of the main reasons for aseptic loosening in TKA [31].

Radiostereometric analysis (RSA)

RSA can be used to measure and evaluate the migration of the TKA implants and hereby identify the implants at risk of aseptic loosening.

The RSA setup was first introduced by Göran Selvik in 1972-1974, in Lund, Sweden with the purpose to evaluate the kinematics of the skeletal system [32].

By placing tantalum markers during surgery in the bone near the TKA implants small movements of the implants (migration) can be measured with a special setup and analyzed in a customized designed software program.

First, tantalum markers of size between 0.5-1.0 mm are attached to the bone segments (tibia and femur) around the prosthesis during surgery with a tantalum marker inserter.

To ensure reliable reference markers additional tantalum markers are located in a fixed position inside a plexiglass calibration cage (figure 5).

Hereby a three-dimensional reference as control or fiducial markers is created and used for further analyses.

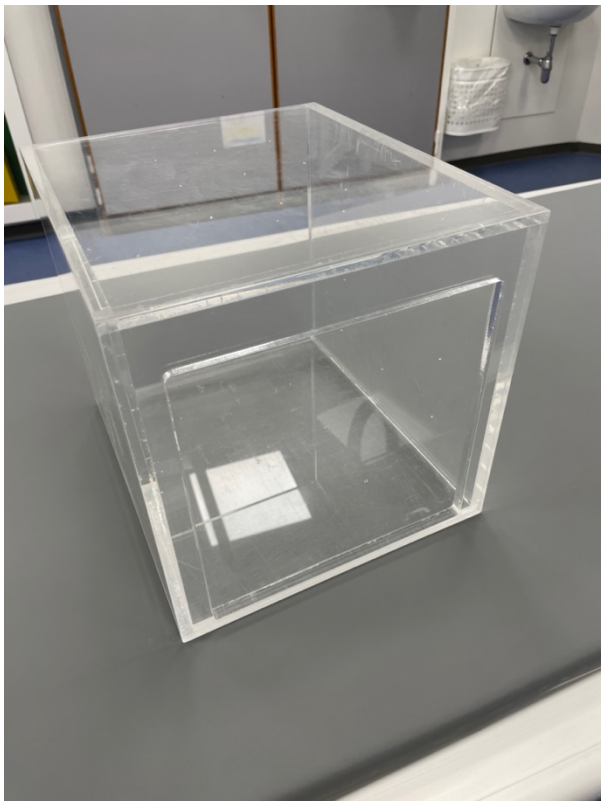

Figure 5: Plexiglass calibration cage.

In a bi-planner setup with two ceiling-fixed X-ray tubes perpendicular to each other and the patient in a supine position, simultaneous exposure can be performed and an anterior-posterior and a lateral view X-ray image can be obtained simultaneously (figure 6).

Figure 6: RSA equipment, patient supine, 2 perpendicular celling fixed X-ray tubes, calibration cage with the examined knee positioned inside the cage. Permission for publication from the patient is obtained.

The first postoperative images are used as the baseline for further follow-up.

During a 2-year follow-up period, RSA images are obtained with priorly determined intervals. The images are used to detect small movements of the implants around the body fixed axes. To obtain useable RSA images and to enable an evaluation of the migration a minimum of three non-collinear markers are needed in each bone segment. However, up to 9 markers are recommended as this will accommodate if some markers looseness or cannot be visualized due to overlap with the prosthesis on the X-rays.

The stability of the markers will influence the accuracy of the migration measurements. Due to this the mean error (ME) of the rigid body is measured and reported as this represents the stability of the markers. If affected, the accuracy of the measurements will be invalid.

The ME is a description of relative changes in the position of the tantalum markers and an acceptable value should be below 0.35 mm [33]. Additionally, the distribution of the tantalum markers can be evaluated by reporting the condition number (CN) and the CN is recommended to be less than 150 [34]. Both of these values should be reported with the RSA results.

Maximal Total Point of Motion (MTPM) represents the markers that have moved the most or the implants which moved most compared to a specific marker in a three-dimensional vector and does not have a direction.

Segmental motion

Translation and rotation along and around the X, Y, and Z axis have a direction as illustrated in figure 7. The calibration cage with standard tantalum markers allows the software system to create a coordinate system where position and orientation can be measured.

Translation along the X-axis indicates medial and lateral movement, where positive values are related to movement in a medial direction and negative values in a lateral direction. The Y-axis describes inferior/superior or cranial/caudal movement. Positive values are related to movement in a superior/cranial direction whereas movement in an inferior/caudal direction has negative values. Movements along the Z-axis are in an anterior and posterior direction, of which positive values indicate an anterior translation and negative values a posterior translation (figure 7).

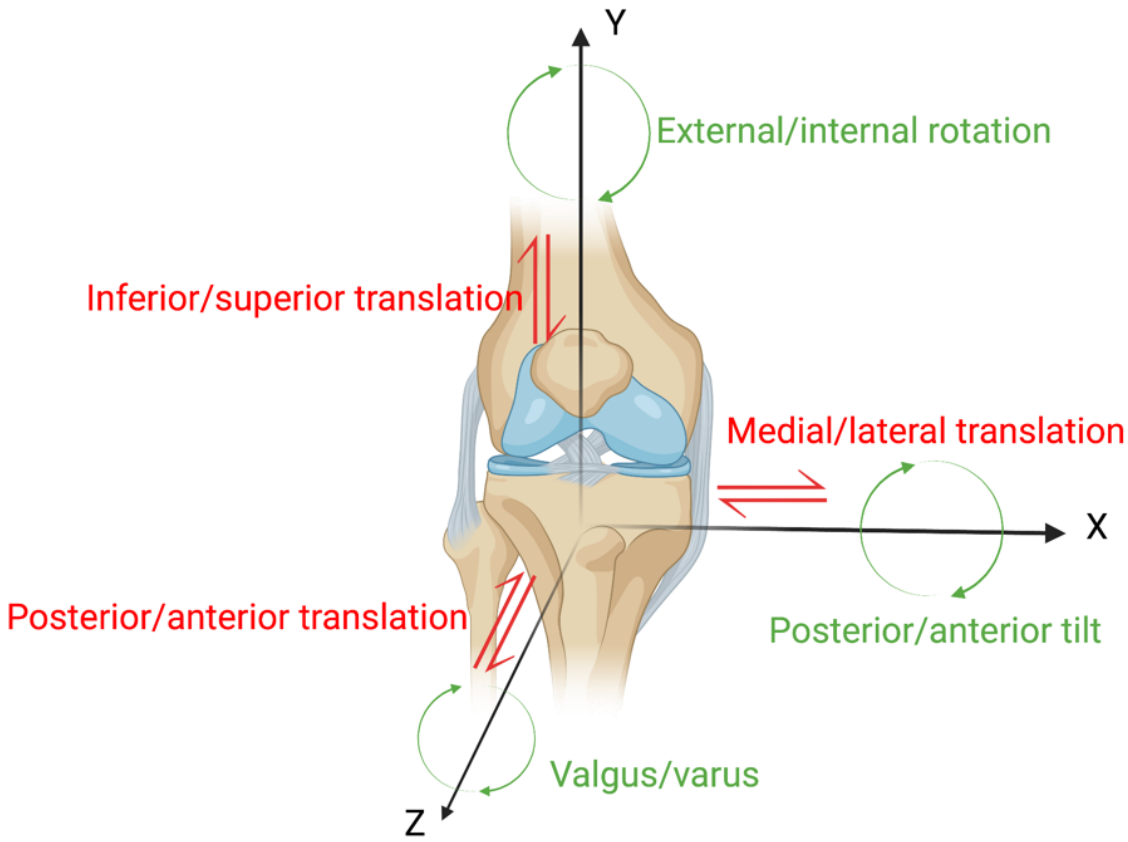

Figure 7: Migration direction visualized on an anatomical structure of the knee. Created with Biorender.com, permission to publish is obtained.

The rotational movement for the X-axis is flexion/extension or posterior/anterior tilt. The positive values on the X-axis indicate flexion/anterior tilt and negative values extension/posterior tilt. On the Y-axis internal and external rotation are measured of which the positive values indicate internal rotation and negative values external rotation. Rotation around the Z-axis can be either adduction/abduction or valgus/varus. The positive value indicates abduction/valgus for the tibial component in combination with adduction/varus for the femoral component in the same movement. Correspondingly, negative values indicate adduction/varus for the tibial component in combination with abduction/valgus of the femoral component in the same movement (figure 7).

The right extremity is recommended to be used for initial measurements of all axes and the measurements of the left extremity will have opposite sign values for the X and Z axes which should be taken into consideration in the following analyses.

Analyses

Conventional RSA requires that the tantalum markers are attached to the implants and additional CE approval due to changes in the prosthesis design may be needed. The model-based RSA (MBRSA) only uses tantalum markers that are attached to the bone. Migration and segmental motion can be calculated in specialized MBRSA software by using a computer-aided design (CAD) model of the implant [33] (figure 8). [35]

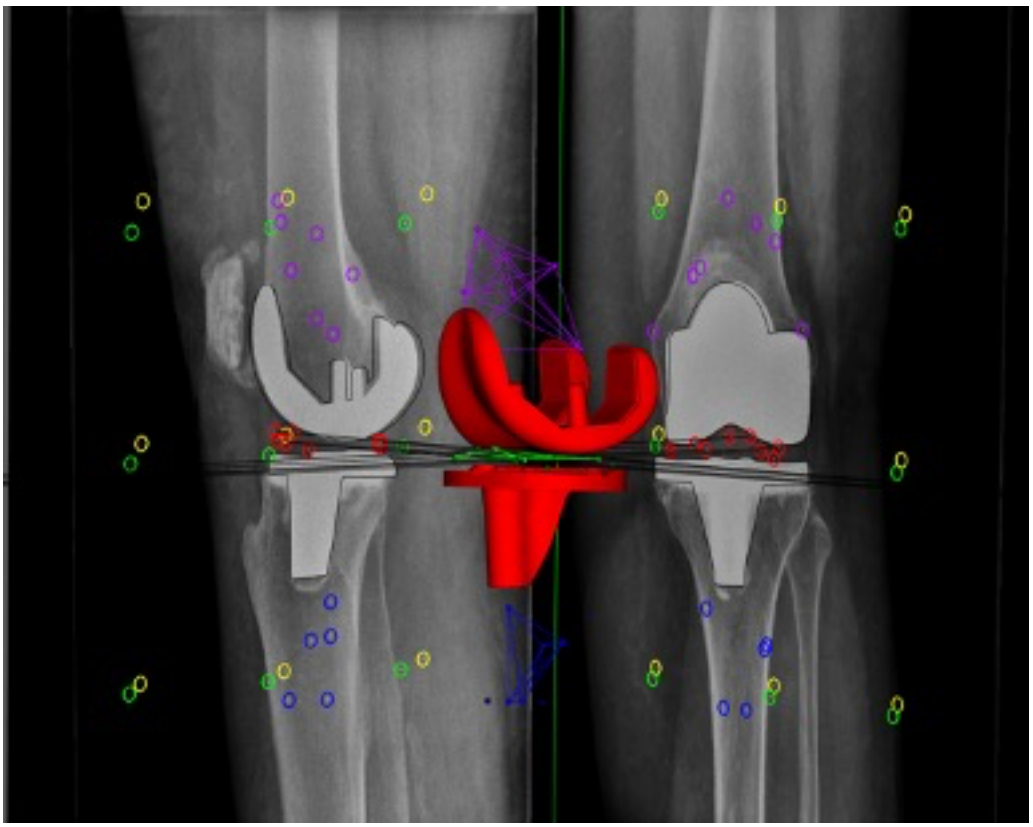

Figure 8: RSA X-ray measurements in MBRSA software, fiducial and control beads from the calibration cage marked with yellow and green, and the CAD model of the prosthesis in the center (red). From Yilmaz et al. [35] Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

RSA measurements are shown to be a reliable three-dimensional measurement system [32, 33] whereas MBRSA has been found to have acceptable precession error and can be used in RSA studies [36, 37]. RSA and MBRSA only require a small sample size to achieve sufficient data to demonstrate significant results [33]. New orthopedic implants can be evaluated with RSA/MBRSA as it requires a small sample size and follow-up through 2 years where migration can be estimated and those implants with high or continuous migration will be at risk of later aseptic loosening.

Therefore, RSA studies are recommended in the phased introduction of new orthopedic implants. Malchau et al [38] has defined a procedure where RSA examination takes place early in the phase.
RSA measurements are precise and with small sample sizes and short follow-up, the risk of aseptic loosening can be assessed [33, 39]. The precision of the RSA X-rays is calculated by performing a double examination. The first of two X-rays are performed as the regular RSA examination after which the patient is requested to stand up and walk around, thereafter repositioned and the second X-ray is performed. It is assumed that the implant has not moved between the two examinations.

Fixation types

RSA studies comparing different types of fixations (cemented vs uncemented) and different implant surfaces and coating have been performed on the tibial implant. Initial studies indicated a higher and continuous migration of the uncemented implants [40-42]. However, more recent studies evaluating uncemented TM tibial implants found almost the same level of migration as cemented implants and the same with initial high migration and stabilization within 6 months assessing the risk of aseptic loosening as low [43-48].
Previous studies comparing the fixation type of the femoral implant found no significant differences between the cemented and uncemented fixation [49-51]. Only a few RSA studies comparing the fixation type of the femoral implant have been conducted most likely due to the fact that marker-based RSA requires tantalum beads attached to the implants. To our knowledge no previous studies have in a randomized controlled trial investigated MBRSA results in femoral and asymmetrical tibial implants comparing cemented and uncemented fixation.

Dual-energy X-ray absorptiometry (DEXA)

Several studies have demonstrated a decrease in bone mineral density (BMD) initially after surgery of up to 44% in the anterior distal femur [35, 52-58] and up to 41% in the medial tibia [35, 59-62]. The decrease in BMD has been found to be multifactorial where factors such as surgical trauma, immobilization, stress-shielding, and foreign body reaction are considered to be significant contributors [63-66].

A decline in the BMD is clinically important because it has been proven to be associated with the breaking strength of the bone and is therefore considered to be a risk factor in periprosthetic fractures [67-72].

Patients with OA are considered to have higher preoperative BMD due to changes in the bone structure [73]. On the contrary, patients are considered to have a decrease in BMD postoperatively due to trauma from the surgery.

The decrease in the distal femoral part is mainly considered to be caused by stress shielding because the transmission of load from the patella is affected after TKA surgery which leads to a decrease in BMD [52, 54, 74-76].

Dual-Energy X-ray Absorptiometry (DEXA) is a technology based on X-ray and is most commonly used to assess the risk of osteoporosis by estimating the BMD.

A very small dose of ionizing radiation passes the body and is absorbed in the bones and to some extent the soft tissue. The amount of mineral content in bones will cause less ionizing radiation that will pass and be detected. By measuring the energy absorbed by bone after soft tissue absorption is removed, BMD may be calculated. BMD is calculated in g/cm^2 as it is an area density (figure 9).

Figure 9: DEXA scanner with the patient position for examination. Permission for publication from the patient is obtained.

Computed tomography (CT)

Computerized tomography (CT) can with the use of a spinning X-ray tube and a row of detectors arranged in a framework, measure the attenuations of X-rays caused by various body tissues. Through reconstruction procedures, the data from the multiple X-rays are used to create a variety of images.

The CT scan be used in patients with metallic implantation, and by using single energy metal artifact reduction (SEMAR) the bone near an orthopedic implant such as the TKA can be visualized and the images can be used for diagnostics and assessment.

CT scans were used to examine the tibial implant and bone coverage, as well as the rotational alignment of the asymmetrical tibial implant in study IV.

Aims

Overall aim

The overall aim of this thesis was to evaluate the Persona® (Zimmer Biomet) TKA with MBRSA, DEXA and CT-scans in fully cemented, fully uncemented, or hybrid fixation prosthesis components.

Specific aims

Study I: This study aimed for evaluating implant migration using MBRSA and adaptive bone remodeling using DEXA in patients with new cemented asymmetrical tibial and new uncemented femoral TKA implants throughout a 2-year follow-up period.

Study II: This study used a randomized controlled trial (RCT) design with a 2-year follow-up to assess the migration using MBRSA of a new uncemented asymmetrical tibial implant and uncemented femoral implant and compared it to the cemented version of the implants. Additionally, Oxford Knee Score (OKS) and Knee Society Score (KSS) were assessed as secondary functional outcomes.

Study III: The purpose of this study was in a 2-year follow-up RCT to assess the adaptive bone remodeling using DEXA of the bone around new TKA implants with an asymmetrical tibial implant and compare cemented and uncemented fixation.

Study IV: The objective of this study was to assess on postoperative CT scans the rotational alignment and coverage of the asymmetrical tibial component. The study also wanted to determine whether migration was impacted by the placement of the tibial component.

Hypotheses

Study I

This study did not have a specific hypothesis, but it was performed to check the implants according to a phased introduction and compare implant migration measured with MBRSA and adaptive bone remodeling pattern assessed by DEXA of the uncemented femoral and cemented asymmetrical tibial components of the new Persona® TKA system to already published results of other implants.

Study II

In the original study protocol, we hypothesized that the uncemented TM Persona® TKA tibial and femoral components will have the same migration patterns as the cemented Persona® TKA implants, measured with MBRSA and migration expressed as MTPM. However, the study was designed as a conventional superiority RSA trial, and the sample size was not calculated to answer the non-superiority research question.

Study III

Our hypothesis was that uncemented TM Persona® TKA will have a lower decrease in BMD assessed by DEXA compared to the cemented Persona® TKA.

Study IV

We hypothesized that the placement of the asymmetrical cemented and uncemented Persona® tibial implant will have superior coverage and rotational alignment compared to published results in the literature. Furthermore, we hypothesized that poor coverage and inward rotation were related to higher tibial implant migration.

Materials and methods

Study design and patient cohorts

Study I

Study I was performed as a prospective study design and included 33 patients. All patients were scheduled for TKA surgery due to OA at Gentofte Hospital, Department of Orthopedic surgery between March 21st to October 12th 2017. Two patients withdrew from the study; one did not get the allocated treatment (Ultra Curved insert was used instead of Cruciate Retaining), and one patient declined to participate in further follow-up. A total of 29 patients were included for follow-up (figure 10).

At the time of surgery, the mean age was 65 years (female/male=17/12) and the demographics are visualized in table 1.

Patients were identified after their first visit to the outpatient clinic where they were informed about the study and written information was provided. All patients had at least 48 hours for consideration before informed written consent was obtained, all according to the Helsinki declaration. All patients received a Persona® ((Zimmer Biomet, Warsaw, Indiana, USA) hybrid (uncemented TM femur and cemented tibia components) prosthesis with cruciate-retaining polyethylene insert and cemented all-polyethylene patella components. Surgeries were performed in accordance with the guidelines by two consultant orthopedic surgeons subspecialized in knee replacement surgery.

Patients were followed for 2 years with a DEXA (Norland XR-46 bone densitometer (Norland Corp, Fort Atkinson, WI, USA)), KSS, and OKS preoperative, and with DEXA and RSA (Arcoma Precision T3, Siemens, 0.7mmAI/75kV, filtration 1.5mm) measurements 1 week, 3 months, 6 months, 12 months, and 24 months postoperative. At 6 months, 12 months, and 24 months follow-up KSS and OKS were assessed.

No revision surgeries were performed during the 2-year follow-up.

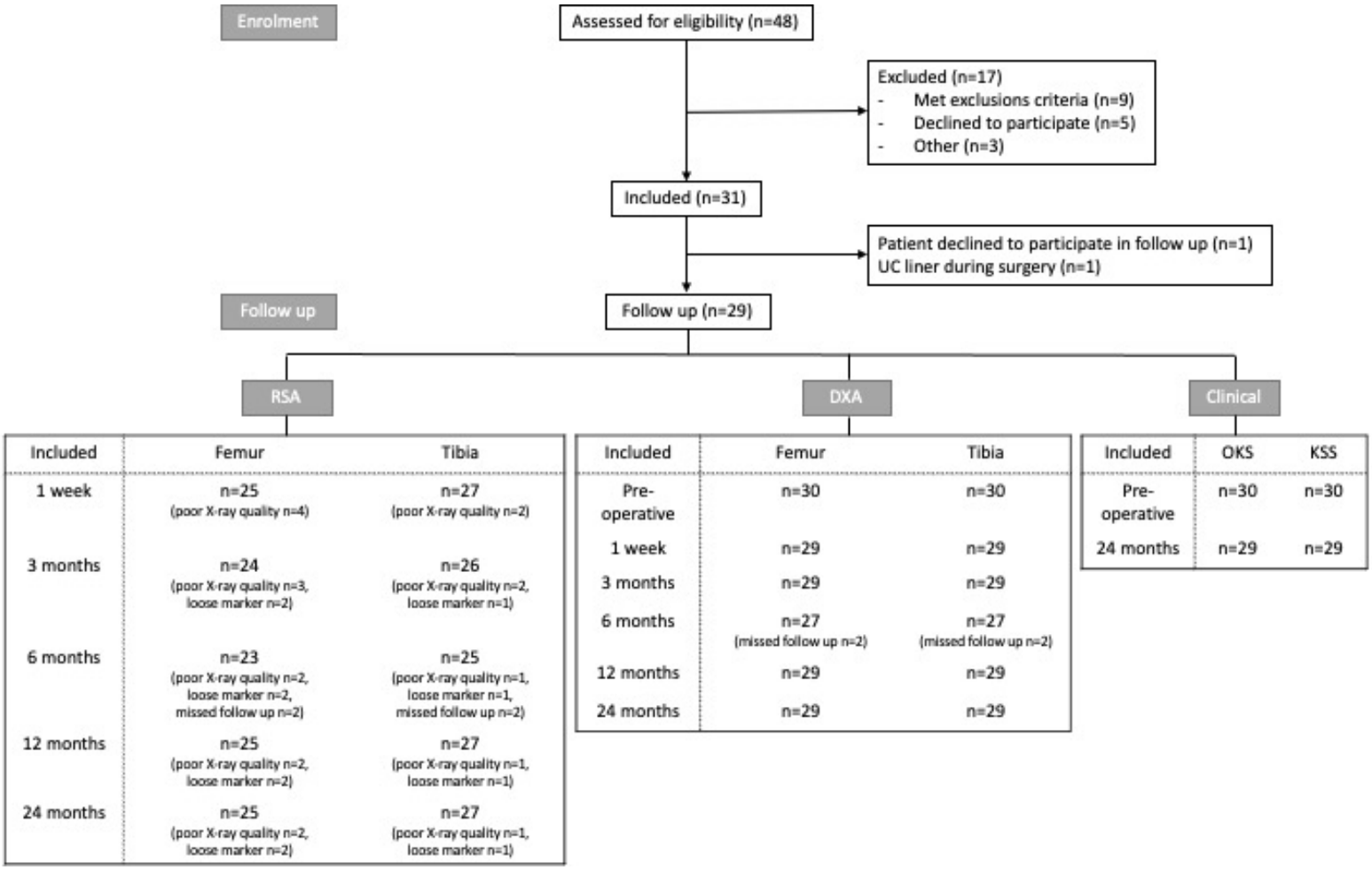

Figure 10: Enrolment study I, from Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

	All (n=29)	Female (n=17)	Male (n=12)
Mean age at surgery in years (range)	65.1 (52.8 – 70)	63.8 (52.8 – 70)	67.1 (53.3 – 69.7)
Weight in kg (range)	85.4 (58 – 120)	81.6 (58 – 114)	92 (75 – 120)
BMI (range)	29.2 (18.5 – 41.5)	29.1 (18.5 – 38)	30 (23.2 – 41.5)
Smoking			
Never:	15	9	6
Current:	4	2	2
Former:	10	6	4
Anesthesia			
General:	10	6	4
Spinal:	19	11	8
Polyethylene inserts in mean mm (range)	12 (10 – 16)	12 (10 – 14)	12 (10 – 16)
Patella size			
32:	7	6	1
35:	17	11	6
38:	5	-	5
Femur component size			
5:	2	1	1
6:	3	3	-
7:	5	4	1
8:	6	4	2
9:	6	5	1
10:	2	-	2
11:	5	-	5
***25 Standard and 4 narrow components**			
Tibia component size			
D:	5	5	-
E:	8	7	1
F:	7	5	2
G:	7	-	7
H:	2	-	2

Table 1: Overview of demography study I, from Yilmaz et al [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Study II-III

At Gentofte Hospital, Department of orthopedic surgery between September 2018 to October 2019 309 patients were eligible for this study of which 89 patients met the inclusion criteria for the randomized controlled trial (RCT) comparing cemented and uncemented fixation of Persona® TKA (figure 11).

Overall, 66 patients were randomized with 1:1 allocation, in blocks of 10, into group A (uncemented Trabecular Metal coated Persona® TKA, Zimmer Biomet, Warsaw, Indiana, USA) or group B (cemented Persona® TKA, Zimmer Biomet, Warsaw, Indiana, USA). The patella was resurfaced with a cemented Zimmer Biomet 3-Peg all-polyethylene patella component, and each patient got a cruciate-retaining polyethylene insert. The randomization sequence, in blocks of 10 was packed in separate sealed envelopes. The allocation to group A or B was drawn by an external person after anesthesia was given but before the surgery began.

Two patients were excluded after the randomization process because they did not get the assigned treatment, and one patient withdrew consent at the start of the study. A total of 63 (M/F = 22/41, mean age 62.4 years (range: 50.3-70.8 years)) patients were included in this study, and after 1 year, two more patients' follow-up appointments were prematurely interrupted due to revision and prosthesis changes, leaving 61 patients to complete the 2-year follow-up (table 2, figure 11).

Patients that participated in study III were a part of study II [77] (figure 12).

Patients were followed for 2 years with DEXA scans (Norland XR-46 bone densitometer (Norland Corp, Fort Atkinson, WI, USA)), at Rigshospitalet, Copenhagen, by an experienced research nurse in both study II and III. Additionally, patients were asked to complete questionnaires, and functional outcomes were assessed with KSS and OKS. Postoperatively patients were followed after 1 week, 3 months, 6 months, 12 months, and 24 months with DEXA and RSA (Arcoma Precision T3, Siemens, 0.7mmAI/75kV, filtration 1.5mm) measurements (at 12 months double examinations were performed) and questionaries and functional outcomes were assessed after 6 months, 12 months, and 24 months. Five revision surgeries were performed in 4 patients: 3 polyethylene inserts were changed, 2 due to instability and 1 due to infection, 2 patients had their prosthesis components revised between 1 and 2 years of follow-up, 1 due to infection, and 1 due to instability.

	Total (n=63)	***Female (n=41)***	***Male (n=22)***
Mean age at surgery (range)	62.4 (50.3 to 70.8)	62.1 (50.3 to 70.5)	62.8 (54.0 to 70.8)
BMI (range)	30.2 (21.6 to 46.1)	30.3 (21.6 to 43.7)	29.9 (23.5 to 46.1)
Smoking			
Never	31	20	11
Current	8	5	3
Former	24	16	8
ASA			
1	15	12	3
2	46	28	18
3	2	1	1
Anaesthesia			
General	27	17	10
Spinal	36	24	12
Surgery extremity			
Left	28	20	8
Right	35	21	14
Cemented	32	22	10
Uncemented	31	19	12
Prosthesis components			
Femoral size			
4	2	2	0
5	2	2	0
6	9	9	0
7	12	12	0
8	17	9	8
9	11	5	6
10	6	2	4
11	2	0	2
12	2	0	2
Standard	37	15	22
Narrow	26	26	0
Tibial size			
C	1	1	0
D	18	17	1
E	15	15	0
F	17	7	10
G	7	1	6
H	5	0	5
Insert	12 (10 to 18)	12 (10 to 18)	12 (10 to 14)
Patella	34 (29 to 41)	34 (29 to 41)	36 (32 to 41)

Table 2: Overview of demographics study II, manuscript study II [77].

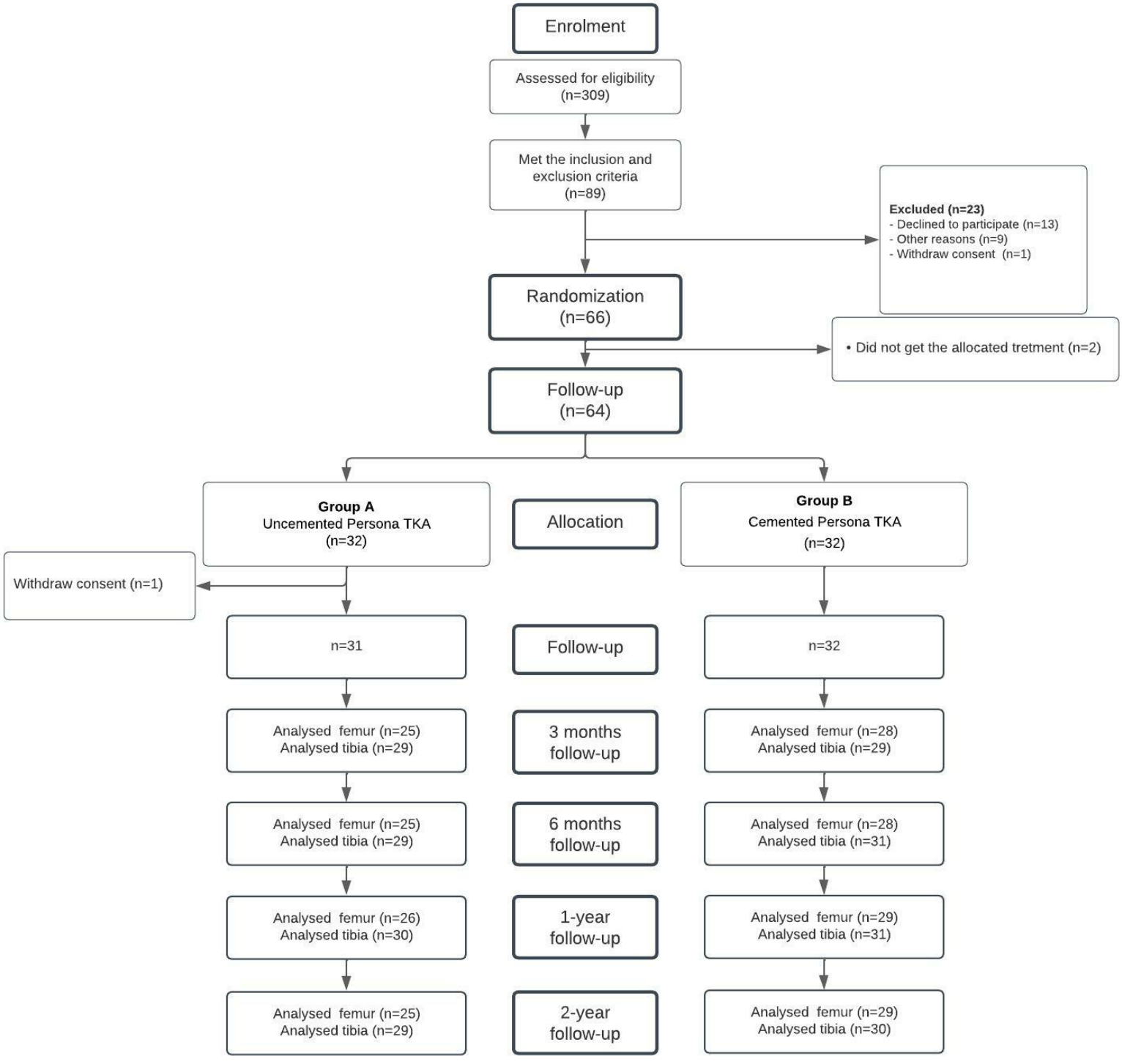

Figure 11: Enrolment study II, manuscript study II [77].

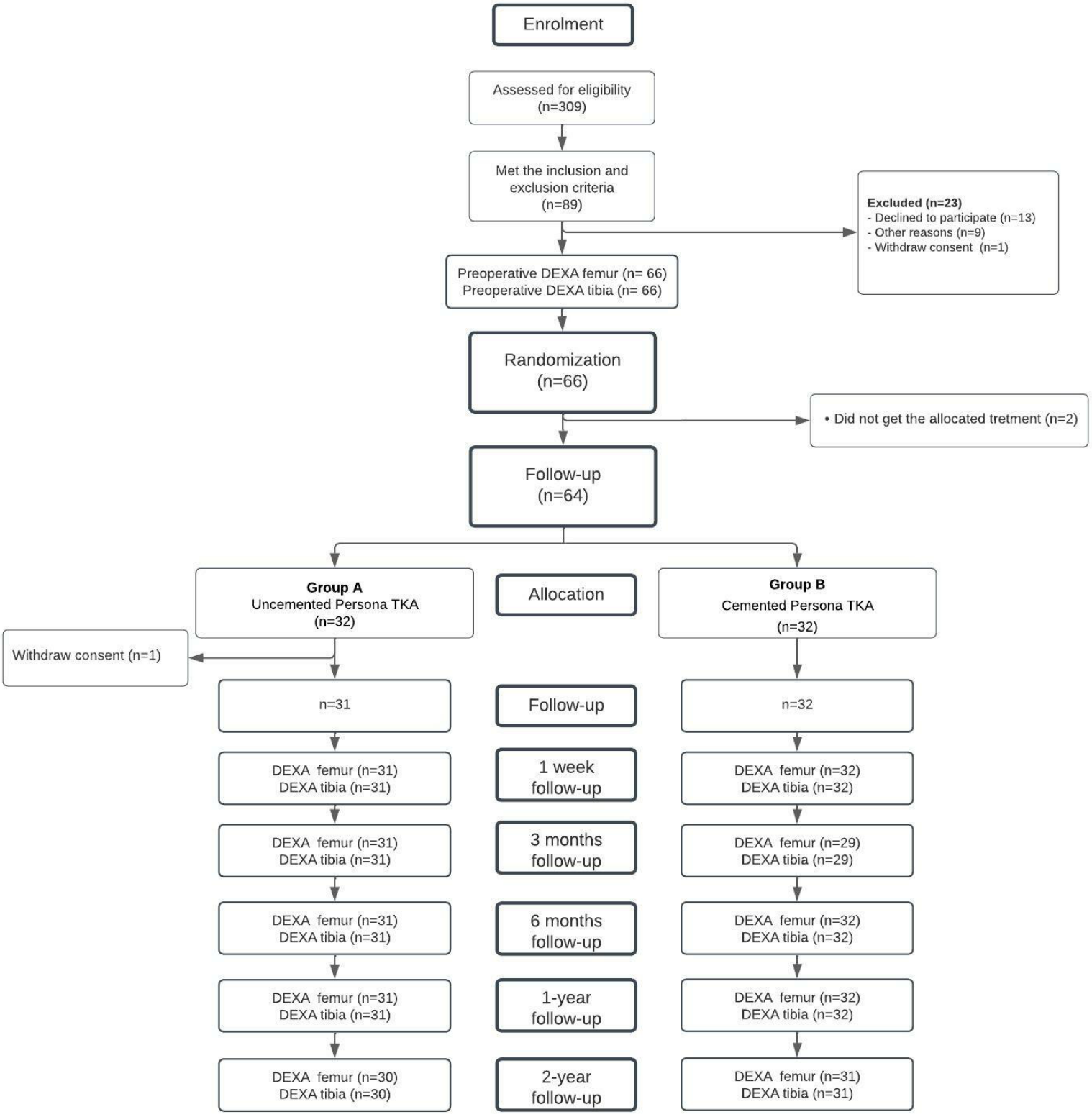

Figure 12: Enrolment study III, manuscript study III [78].

Study IV

Patients in study IV consist of the patients from the RCT study II and III carried out in Denmark (n=63) and patients from a Swedish (n=57) RCT comparing Persona® (Zimmer Biomet, Warsaw, Indiana, USA) prosthesis on their polyethylene insert, and the randomization was between cruciate-retaining or medial congruent inserts. The cohort in this study constituted of 126 patients (figure 13), all patients received a Persona® TKA due to OA, and their CT scans were performed 3 months postoperative.

The patients included in study IV originated from the RCT patient groups (study II and III) and additionally patients from a Swedish RCT comparing Persona® (Zimmer Biomet, Warsaw, Indiana, USA) prosthesis on their polyethylene insert, and the randomization was between cruciate-retaining or medial congruent inserts.

After randomization, 126 participants in total (DK=66 and SE=60) were eligible for the study. Patients are required to undergo a postoperative CT scan 3 months postoperative, as well as baseline and follow-up RSA measurements, in order to be eligible for enrollment. Patients who underwent revision surgery for the bone-anchored components were not eligible.

The study included a total of 111 individuals (DK n=59, SE n=52), of whom 29 patients from Denmark had uncemented tibial implants while the remaining 30 patients from Denmark and 52 patients from Sweden had cemented tibial components.

The patients average age was 65 years (SD 8, range: 51 to 86 years). Males made up 38% of the sample (n=42) while females made up 62%.

All patients received a Persona® TKA due to OA and their CT scans were performed 3 months postoperative.

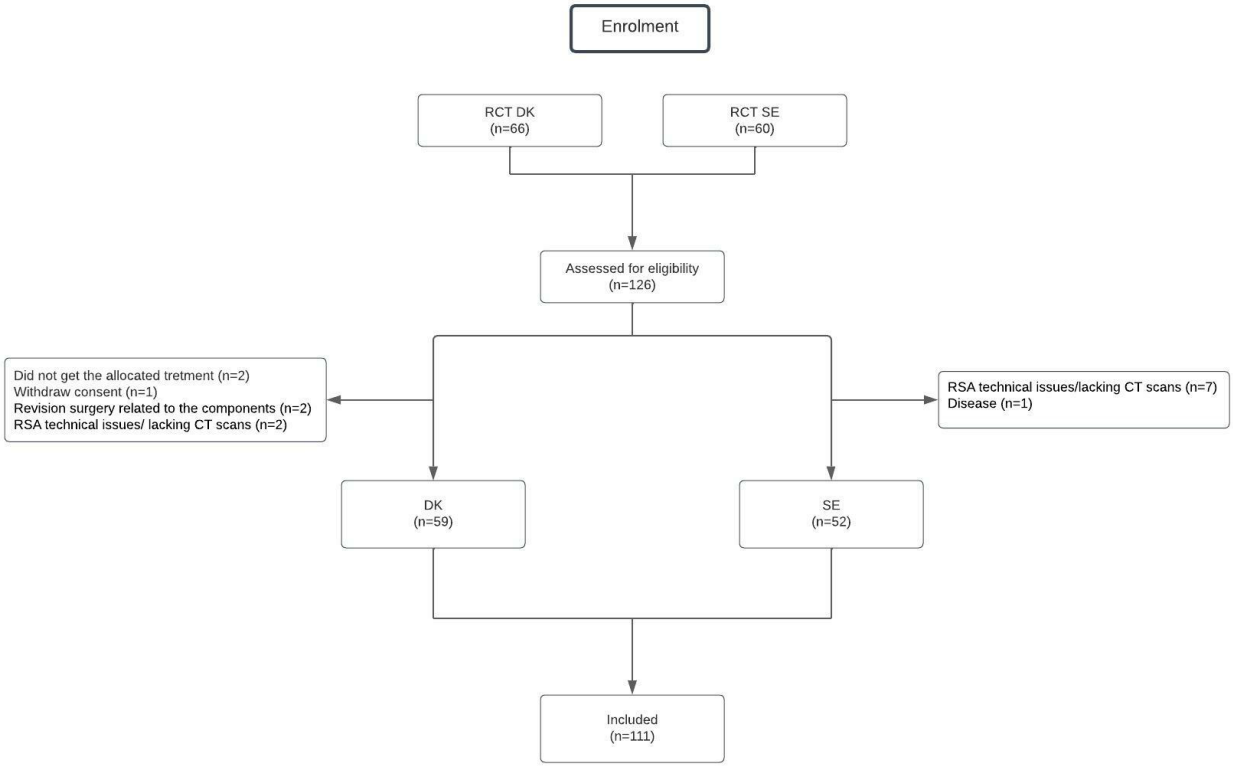

Figure 13: Enrolment study IV, manuscript study IV [79].

Inclusion criteria

Study I-III

- Patients scheduled for TKA due to OA at Gentofte Hospital, Department of orthopedic surgery.
- Age 40 to 70 both inclusive.
- Ability to give written informed consent.

Study IV

- Patients scheduled for TKA due to OA at Gentofte Hospital (Denmark) and Skane University Hospital, Lund (Sweden), Department of orthopedic surgery.
- Age:
    - Denmark: 40 to 70 both inclusive.
    - Sweden: 50 to 80 both inclusive.
- Ability to give written informed consent.
- Sweden:
    - ASA I-III and fit for elective surgery.
    - BMI between 18 to 35.

Exclusion criteria

Study I-III

- If TKA surgery with a standard cruciate retaining implant was not possible due to malalignment, deformity, or instability.
- Diseases affecting bone metabolism e.g., severe osteoporosis, Paget's disease, hyperparathyroidism, etc.
- Inability to understand the information.
- Inability to give informed consent for language or mental reasons.

Study IV

The cohort from Denmark had the same exclusion criteria as mentioned above.

Sweden:

- Previous medical history with joint diseases.

- Use of immunosuppressive medication in the last 5 years.
- Rheumatoid arthritis.
- Diseases affecting bone metabolism or severe osteoporosis.
- Personal or neuromuscular disorders.
- Previous intra-articular knee fractures and surgery with osteotomy.
- Patients with perioperative or postoperative complications with fractures.
- If TKA surgery with a standard cruciate retaining implant is not possible due to severe valgus deformity (> 15°) and/or contracted soft tissues, need augmentation, PCL deficiency.
- Postoperative infections.

Patients in study I-IV were secondarily excluded if the obtained images (RSA, DEXA, or CT), only for that image, were not suitable for analyses.

Implants

Study I-IV

Persona® (Zimmer Biomet, Warsaw, Indiana, USA) cruciate-retaining components with standard femoral and asymmetrical tibial components were used for all four studies. In study I all patients received an uncemented femoral component, cemented asymmetrical TM tibial implant, cruciate-retaining polyethylene insert, and cemented all-polyethylene patella component. In study II and III patients were randomized to receive either a fully cemented femoral and tibial implant or a fully uncemented TM femoral and asymmetrical tibial component. Study IV consisted of two different cohorts from a Danish and Swedish RCT study respectively. The Danish patients were the same as in study II and III whereas the Swedish patients were randomized to either receive a Persona® (Zimmer Biomet, Warsaw, Indiana, USA) cruciate-retaining component with standard femoral and asymmetrical tibial components with either cruciate-retaining or medial congruent insert, the patella was not resurfaced in this group. In studies, I, II, III, and IV (Danish cohort) Zimmer Biomet (Warsaw, Indiana, USA), Optipac® 40/60 vacuum mixing system cement was used and in study IV (Swedish cohort) vacuum-mixed bone cement (Palacos R+G, Heraeus, Hanau, Germany) was applied. The uncemented trabecular metal surface on the components is believed to enhance bone ingrowth by mimicking the cancellous bone structure and this component is press fitted whereas the cemented are positioned in cement.

Surgery

Study I-IV (Danish cohort)

All surgeries were performed at Gentofte Hospital, Department of orthopedic surgery, the section for elective knee and hip surgeries. At Gentofte Hospital, the department of orthopedic surgery around 1000 knee replacements are performed yearly. The surgeries took place from marts 2017 to October 2019 and were performed by experienced consultant orthopedic surgeons subspecialized in knee replacement surgery with at least 5 years of experience in the field. TKA surgery was performed according to guidelines from the company. The standard medial parapatellar approach for TKA was used for surgeries and the patients were in spinal or general anesthesia. Tantalum beads were placed during surgery (0.8 mm, Tilly Medical Products, Lund, Sweden) in the femoral and tibial bone near the prosthesis with a non-linear distribution with an inserter (Wennbergs Finsmark AB) by the assistant that was the same two persons throughout the studies. Preoperative 2g cloxacillin and postoperative 1g cloxacillin were administered twice, and the pain was managed with paracetamol and Morphine/Oxycodone, if necessary. Non-steroid anti-inflammatory drugs were not used. Cementation was performed by adding cement on to the bone and the implant surface after routine lavage was completed. All patients received local infiltrative medication at the end of surgery before leaving the surgery room. All patients received 10 mg of Rivaroxaban daily for 5 days postoperative. Mobilization started postoperatively the same day of the surgery or the day after depending on the time of surgery. Every patient received the same standardized physical treatment in the department and was afterward offered outpatient physical treatment locally after discharge.

Study IV (Swedish cohort)

Surgeries were performed at Skane University Hospital in Lund, Sweden in the period September 2017 to August 2018 by 3 experienced arthroplasty surgeons with a minimum of 10 Persona® TKA experiences before surgeries for the RCT were performed. Prior to surgery templating on a long and regular knee, X-ray images were performed in the Picture Archiving and Communication System (PACS). Perioperative 6-9 tantalum beads with a diameter of 0.8 mm were positioned in the femur and tibia around the components. All surgeries were performed in accordance with the guidelines from the company.

No patella surfacing was performed, and cementation was done with vacuum-mixed bone cement applied on both the implants and the bone prior to positioning of the implants. Local infiltrative analgesia was applied before the suture.

Preoperative 1 dose and postoperative 2 doses of flucloxacillin were administrated within the first 8 hours and low-molecular-weight heparin was administrated as thromboprophylaxis.

RSA

Study I, II, and IV (Danish cohort)

Tantalum markers placed during surgery were used for the postoperative RSA analyses. The baseline measurements were in study I performed with a mean of 7.8 days postoperative, range (6–13 days), and in study II to IV (Danish cohort) 7 days (range: 4-16 days) postoperative. All RSA examinations were performed at Rigshospitalet, Copenhagen, Denmark by the principal investigator.

Patients were placed in a supine position with the surgical limb placed in the calibration cage (Calibration cage 21; Tilly Medical Products, Lund, Sweden) which was premarked with tantalum beads. Two sealing fixed X-ray tubes perpendicular to each other (Arcoma Precision T3, Siemens, 0.7mmAI/75kV, filtration 1.5mm), with the intensity of 50kV and 25mAs and resolution of 10 pixels per mm, and 100 cm to the calibration cage, two X-ray images, anterior-posterior and lateral were taken simultaneously (figure 5).

RSA examinations were performed after 1 week (baseline), 3 months, 6 months, 12 months, and 24 months postoperatively. Double examinations were performed at the 12 months follow-up examination to evaluate precession. The patients were requested to stand up between the two measurements, and walk around and after 5 min the patients were repositioned in the above-mentioned position and new images were taken.

RSA images were saved in Digital Imaging and Communications in Medicine (DICOM) format in Picture Archiving and Communication System (PACS).

The RSA images were analyzed in Biomechanics and RSA-laboratory, department of orthopedic surgery at Skane university hospital in Lund Sweden. MBRSA was used for further analyses (Model-based RSA 4.1, 2003-2014 RSAcore Department of orthopedics Leiden University Medical Centre) of migration expressed as MTPM and rotational and translational segmental motion around the X, Y, and Z axis.

CN and ME were calculated by the software, and limits were set in accordance with the guideline [33] to 150 and 35 mm respectively.

Study IV (Swedish cohort)

The RSA setup as described above was also used in the Swedish RCT from which we included patients in study IV.

The above-mentioned RSA constellation also applies to the Swedish part of the cohort only with some minor differences. The RSA baseline measurements were performed on the first postoperative day after weight bearing but before mobilization and further follow-up was performed after 3 months, 12 months, and 24 months. CN was set at below 120 and ME below 35.

DEXA

Study I and III

The follow-up with DEXA scans was coordinated with RSA measurements to accommodate the patient. Therefore, DEXA scans were performed postoperative and at 1 week, 3 months, 6 months, 12 months, and 24 months. At 12 months follow-up double examinations were performed to estimate the precision error of the measurements, the patient was requested to stand up between two examinations, walk around, and repositioned again after 5 min.

All the DEXA scans were performed at Rigshospitalet, Copenhagen, Denmark at the department of orthopedic surgery by an experienced research nurse. A Norland XR-46 bone densitometer (Norland Corp, Fort Atkinson, WI, USA), with a scan speed of 45 mm/s and a pixel size of 0.5x0.5 mm was used in all patients. The software allows one to adjust the threshold for metal exclusion and therefore the bone close to the prosthesis component can be analyzed. Before the first DEXA scan of the day the scanner was calibrated.

Patients were positioned in a supine position, with a block underneath the feet and the surgical limb in a small internal rotation to avoid overlay of the tibial and fibular bone. In this position, the proximal tibia was first scanned to create an overview. Subsequently, the images were corrected and the actual examination was performed. The ankles were scanned on both sides in the same position.

To obtain images of the distal femur the patient was positioned on the surgical limb site, and the knee was placed in a small flexion. An overview scanning was performed, and images were corrected and

then the actual examination was performed (figure 9 illustrates the DEXA scan and positioning of a patient).

Images were analyzed by dividing the distal femur and proximal tibia in region of interest (ROI). The distal femur was divided into three ROIs. ROI I (anterior) and ROI II (posterior) were created by a line vertical from the pegs and a crossing line from the anterior apex of the femoral component. ROI III was the bone segment 2 cm above ROI I and ROI II and named ROI III (proximal) (figure 14).

Similarly, the proximal tibia was divided into three ROIs. ROI I (medial) and ROI II (lateral) were divided with a vertical line in the middle of the tibial component and 4 cm distal or for the cemented prosthesis at the end of the peg the vertical line stops and underneath this a ROI III consisting of a bone segment 2 cm distal (figure 15). All BMD measurements were measured in g/cm^2.

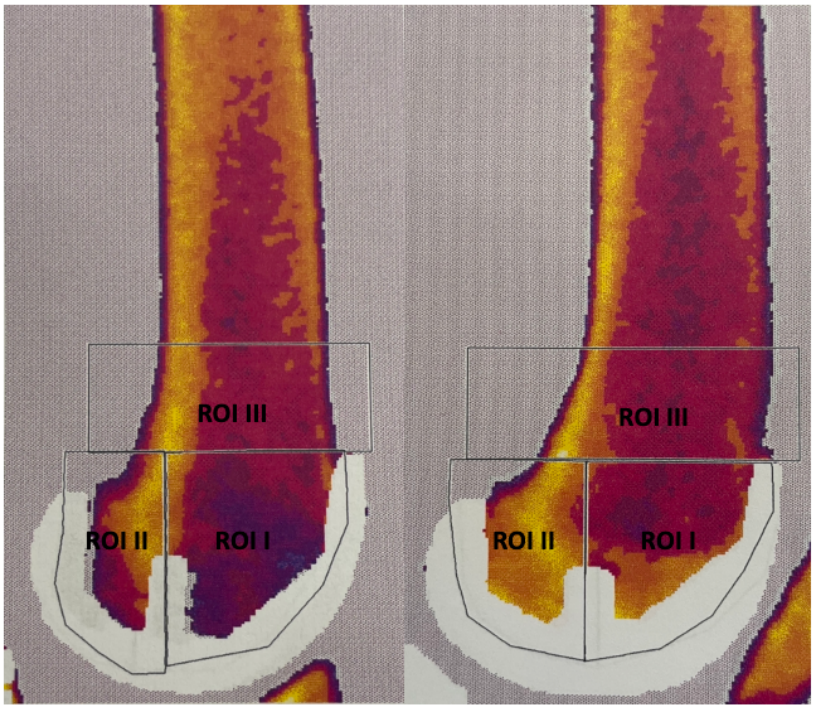

Figure 14: DEXA images distal femur with ROIs, left uncemented and right cemented, manuscript study IV [78].

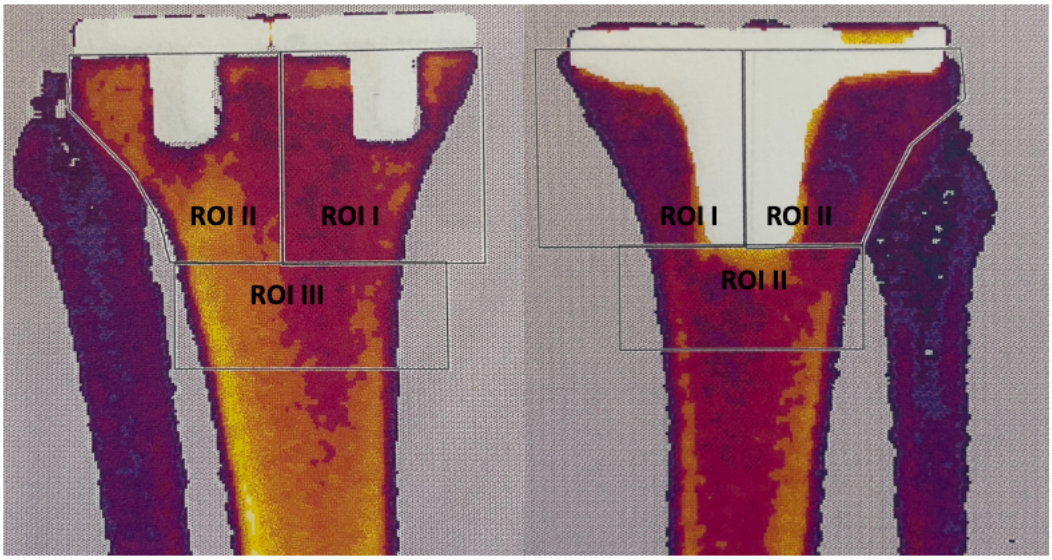

Figure 15: DEXA images proximal tibia with ROIs, left cemented and right uncemented, manuscript study III [78].

CT

Study IV

In study IV all patients had a CT scan was performed 3 months postoperatively. The Danish cohort had their CT examination performed at Rigshospitalet, department of diagnostic radiology. The Swedish cohort had their scans performed at Skane University Hospital, Lund Sweden, department of diagnostic radiology. The CT images included hips, knees, and ankles bilateral as well as a full scout of both extremities. SEMAR technique was used to reduce metal artifacts. Patients were placed in a supine position, to obtain the images patients were required to lay still throughout the examination. Subsequently to the examination all patients were anonymized and renamed as XXX1, XXX2, etc. All images were stored in PACS, and measurement sequences with correction in the axial and coronal plane were stored separately by the investigator for analyses, this way blinded analyses between the investigator and the radiologist could be obtained.

The examinations were used to assess the coverage and rotation of the asymmetrical Persona® tibial component. The component boundary was templated using the CT picture in which the component could be seen clearly. A line running from anterior to posterior in the component's center split it into a medial and a lateral half. The component was then split into an anterior and posterior part by a line that ran horizontally and perpendicular to the anterior-posterior line. The anterior-medial (AM), anterior-lateral (AL), posterior-medial (PM), and posterior-lateral (PL) sections were formed when these two lines were combined. Second, the cortex of the tibial bone was templated using the image in which the bone

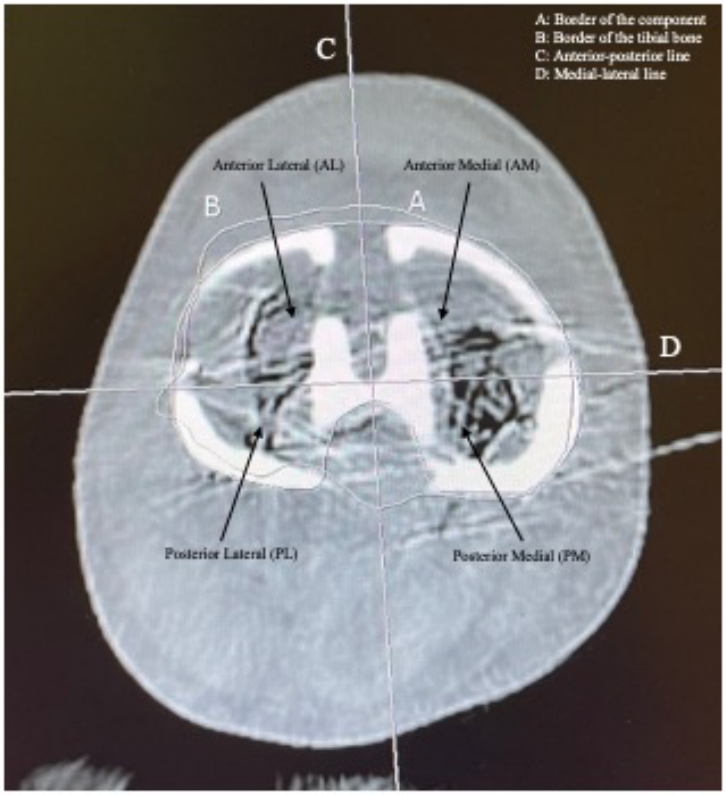

Figure 16: Measurement of the coverage, manuscript stydy IV [77].

could be seen clearly. If the component was cemented, the cortex of the tibial bone was defined using the first image that was free of cement (figure 16).

The medial 1/3 of the tibial tuberosity was identified and marked using the image of the tuberosity tibia (anterior). Then, a line was connected from the mark of the third of the tibial tuberosity to the PCL insertion location using the image that showed the PCL insertion. The rotation of the tibial component was expressed by calculating the angle between lines C and E (figure 17).

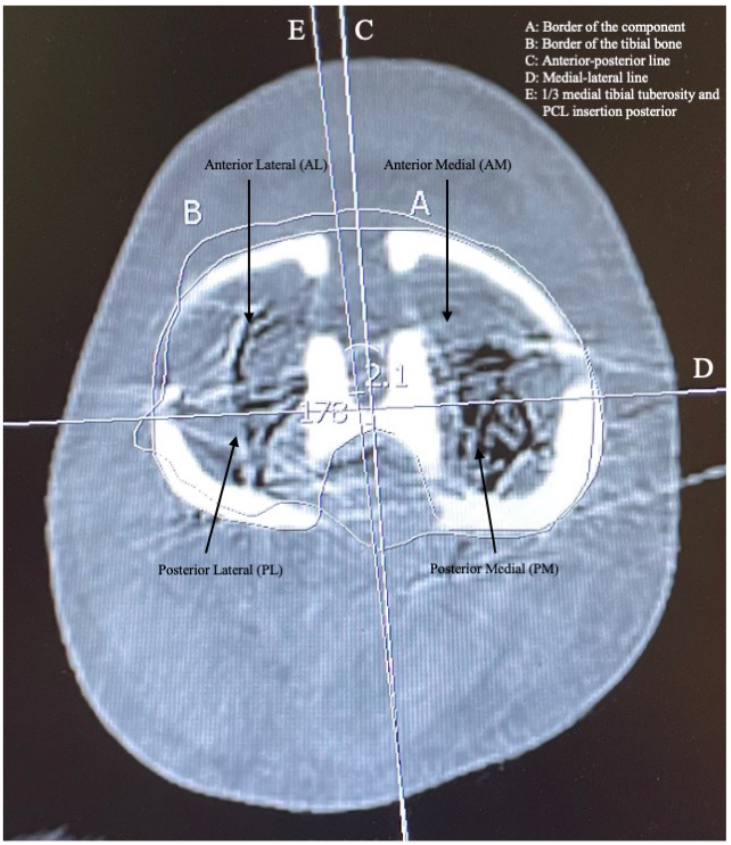

Figure 17: Measurement of the rotation, manuscript study IV [77].

Clinical outcomes

At follow-up intervals of 6, 12, and 24 months, OKS and KSS were collected both preoperatively and postoperatively. The OKS is a 12-item patient-reported questionnaire that assesses knee function and is rated from 0 (poor) to 48 (excellent) [80].

The KSS was completed by the lead investigator. It consists of a clinical and functional component. A total score below 60 is deemed bad, 60 to 69 fair, 70 to 79 acceptable, and 80 to 100 exceptional [81].

Statistics and ethics

Study I

MBRSA data were presented as MTPM and segmental motion (translation and rotation) with mean, range, and 95% confidence intervals (95CI), values are presented as signed values [33]. The right knee was used as a standard for the coordinate system.

The MBRSA data were not normally distributed, but the DEXA measurements were and a paired t-test was used to compare time-related changes (0-24 months) between baseline and 24 months postoperative. The changes in BMD were presented as percentages with corresponding 95%CI. The level of statistical significance was set at $p<0.05$ [35].

Study II

As MTPM calculated with MBRSA software is a vector it will always have a non-normal distribution hence the statistical analyses were performed accordingly. MTPM was the primary endpoint and a non-parametric test (Mann-Whitney U-test) was used to compare the fixation types (cemented and uncemented). Segmental motion (translation and rotation) was also reported and compared with Mann-Whitney U-test. Confidence intervals were reported as 95% and a *p*-value below 0.005 was defined as statistically significant.

Study III

The BMD data were found to be normally distributed and the statistical inference was calculated accordingly. After 24 months, differences in BMD between the cemented and uncemented group of femoral and tibial components were assessed using an unpaired t-test.

ANOVA was used to assess group changes over time. A paired t-test was used to assess BMD changes from postoperative to 24 months follow-up

P-values (<0.05) were used to determine statistical significance, and CI95 was a population parameter's likelihood of falling between two predetermined values.

Study IV

MBRSA results were reported as in study I and II, in this study linear regression was performed to investigate a possible relationship between MTPM and coverage/rotation of the tibial component.

R^2, 95CI, and 95% prediction interval were calculated.

Statistical analyses were performed in RStudio® (Version 1.2.1335© 2009–2019 RStudio, inc.). The standard deviation of the difference (SDdiff) was used to quantify the precision of MBRSA, and the precision error was calculated as 1.96 x SDdiff [33].
For the DEXA scans with measurements of BMD in the various ROIs of the proximal tibia and the distal femur, the precision error was expressed as the mean coefficient of variation (CV), which is defined as the product of the standard deviation (SD)/mean and 100%.

Registrations and approvals

Study I-IV (Danish cohort)
Approval was obtained from the regional ethical committee (case no. H-16035883) and the Danish data protection agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264). Registration on clinicaltrial.gov (NCT03563131) [82] was performed prior to inclusion.

Study IV (Swedish cohort)
Approval from the regional ethical board at Lunds University (Dnr 2017/73) and the local radiation committee was obtained. Prior inclusion registration on Clinicaltrials.gov (NCT03494348) [82] was performed.

For all studies apply that all patients were informed orally and written, and thereafter had 48 hours before the decision and written consent was obtained. The principles of the Helsinki declaration were followed. Data are available on reasonable request.

Sample size

Study I
Sample size calculation for this study was not performed. However, the included number of patients corresponds well with previous studies [49, 66, 83, 84] evaluating RSA and DEXA data.

Study II and IV (Danish cohort)

Mean MTPM after 2 years was defined as the primary effect parameter.

The protocol for this study was completed in 2016, at this time only three previously published studies evaluating femoral implants were existing [49-51]. These studies do not report the mean or SD of migration results presented with MBRSA. The study by Nilsson et al. [49] however reported mean MTPM after 2 years, 0.88 mm for cemented implants, which we used in our sample size calculation as the primary effect parameter. Ryd et al. [39] reports MTPM after 2 years as the best predictor for aseptic loosening for tibial implants after TKA and is the main reason we used this parameter in our sample size calculations. At the time this protocol for this thesis was designed a recent study by Ejaz et al. [85] estimated the SD of migration of cemented tibial implant measured with MBRSA. This study reports migration after 2 years as a mean ($\pm$SD) and the respective values in both groups were 0.47 ($\pm$0.16) and 0.45 ($\pm$0.21).

The SD was adjusted in the sample size calculation to constitute the same percentages of the mean values as in the tibial implant reported in the study by Ejaz et al. [85] because the level of MTPM of the tibial components was significantly lower than that seen for the aforementioned femoral implants [49]. Since no statistically significant difference between cemented and uncemented fixation was found in the earlier investigations measuring femoral component migration, we chose a minimal relevant difference that was quite low (MIREDIF) [49-51].

The sample size calculation was based on type I error = 5%, statistical power = 85%, MIREDIF = 0.3 mm, and SD = 0.35 mm. Based on this it was estimated that we needed to include 24 patients in each group. Due to potential dropouts, a total of 60 patients (30 pr. group) was included. In our study, early dropouts were observed and therefore a total of 66 patients were randomized with 63 patients for further follow-up.

Study III

The sample size calculation was based upon changes in BMD in the distal femur after TKA within the first postoperative year and we used data from a previous study

A difference of 8 % between groups was estimated to be clinically relevant and will give a sample size with high enough statistical power when comparing two fixation types. Alpha was set to 5%, beta to 90%, MIREDIF to 8%, and SD to 8.4%. Based on these numbers it was estimated that we should include 25 patients in each group. However, due to anticipated dropouts, the computation was done with 60 patients, 30 in each group.

Results

Study I

Femoral component – RSA measurements

Migration was measured in the entire cohort as well as on the individual level for the uncemented femoral implant.

Validation of the femoral RSA measurements

Precision error

From 22 femoral double measurements, the PE was calculated. Precision for MTPM was 0.19mm and for the translational segmental motion were PE 0.16mm, 0.07mm, and 0.18mm, and the rotational segmental motion was 0.20°, 0.25°, and 0.24° for X-, Y-, and Z-axis respectively.

Mean error and condition number

One ME value (0.43) was above the recommended by Valstar et al [33] at 0.35 mm. Otherwise, all values related to ME and CN were within the range of previous recommendations [35].

MTPM (entire cohort)

The evaluation of migration was performed at 1 week (baseline), 3 months, 6 months, 12 months, and 24 months postoperatively. The largest increase in MTPM was observed from the first week to three months (mean 0.65mm, 95CI 0.45 to 0.86). Subsequently, the migration showed a tendency of stabilization with the migration of 0.19mm from 3 to 6 months, 0.08mm from 6 to 12 months, and 0.04 from 12-24 months (figure 18).

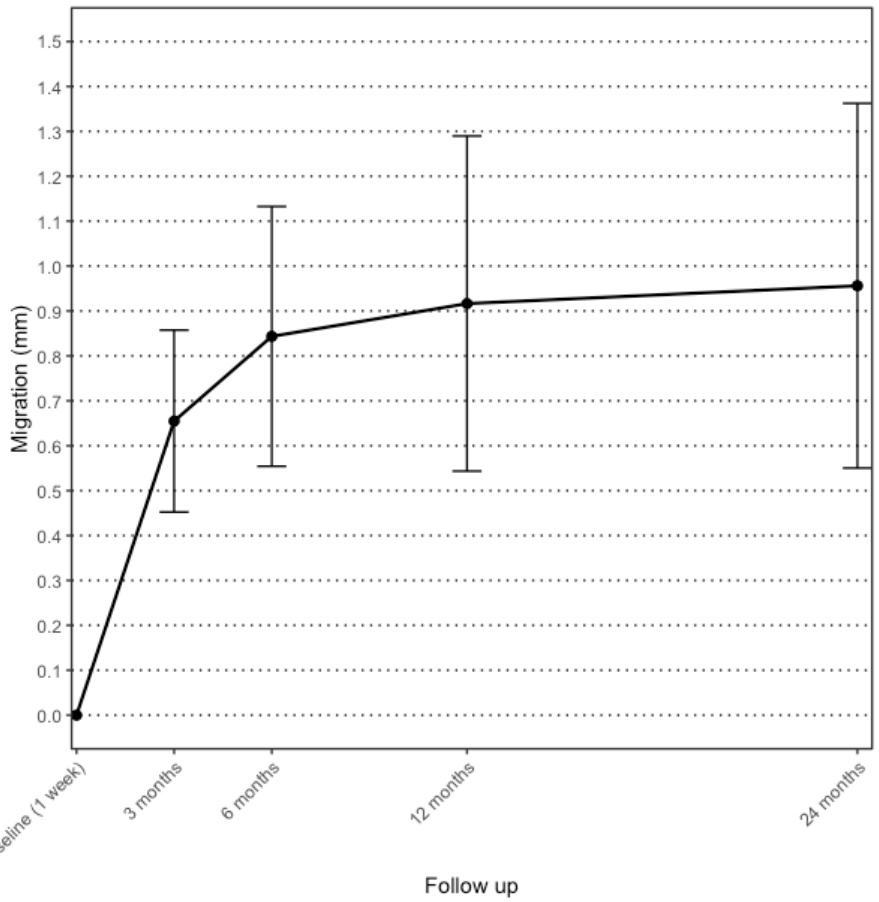

Figure 18: Mean MTPM for uncemented femoral implant at 1 week, and at 3, 6, 12, and 24 months of follow-up. Whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

MTPM (individual level)

A spaghetti plot was used to illustrate migration on the individual level. The plot enabled visualization of potential outliers in the cohort of which three outliers are of interest (patient no. 20, 17, and 15). Patient no. 20 demonstrated high migration in the initial 6 months (4.9mm) postoperative with a subsequent tendency to stabilize. Patient no. 17 demonstrated high initial migration 3 months (2.6mm) postoperative with following stabilization and patient no. 15 showed a continuous high migration without signs of stabilizing, ending with an MTPM of 2.2mm at 24 months (figure 19).

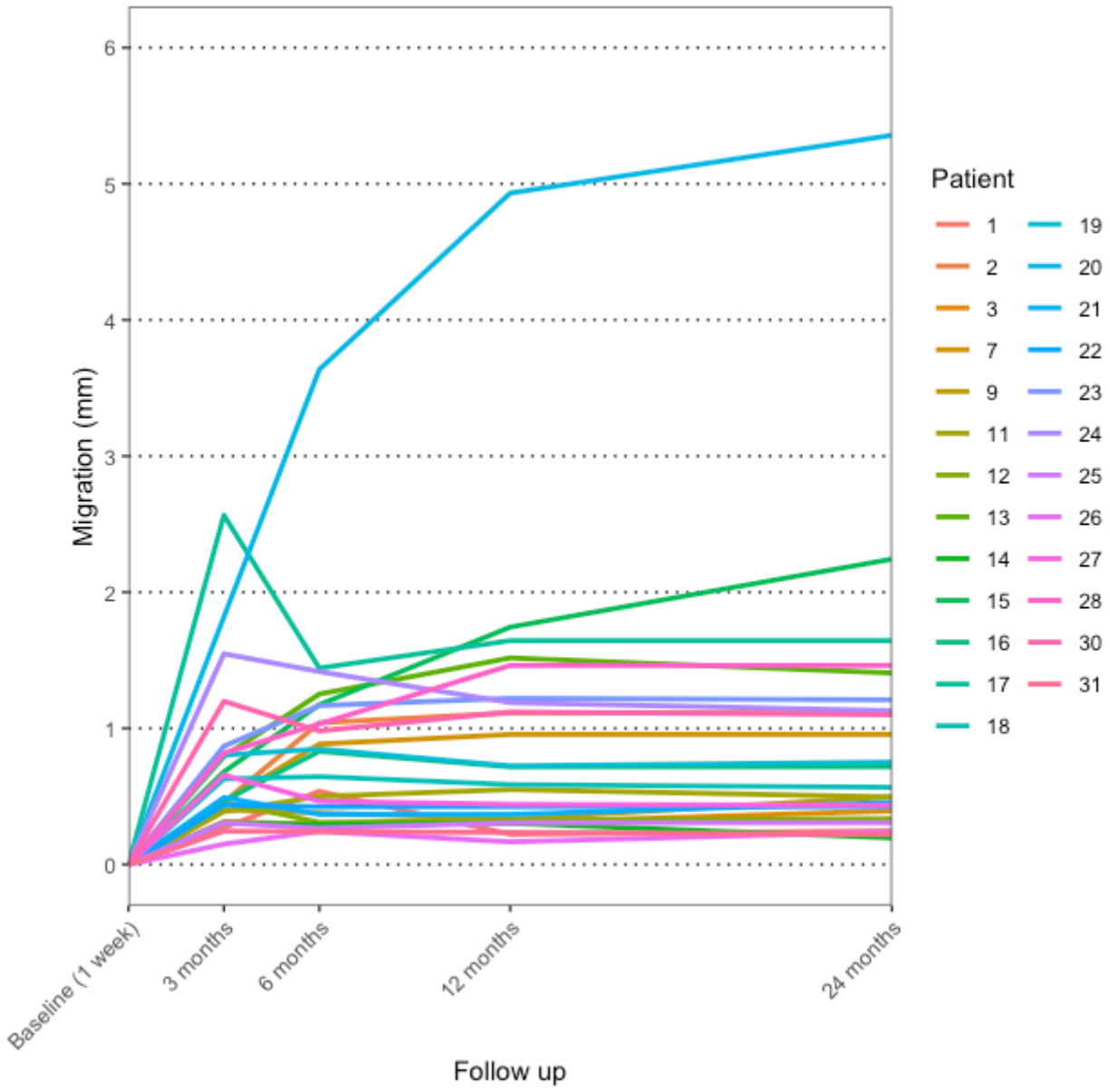

Figure 19: Spaghetti plot illustrating individual MTPM for the whole cohort of the femoral implant, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Segmental motion (translation)

X-translation

Translation along the X-axis demonstrated an initial increase followed by a decrease and thereafter stabilization, however, the translation was minimal (3 months: mean 0.09mm, 95CI -0.01 to 0.19, 6 months: mean 0.02mm, 95CI -0.08 to 0.12, 12 months: mean 0.05mm, 95CI -0.05 to 0.15 and 24 months: mean 0.09mm, 95CI -0.03 to 0.2) minimal (figure 20).

Y-translation

The highest increase in translation found in the femoral component was observed along the Y-axis in a superior/cranial direction (mean 0.16mm, 95CI 0.09 to 0.22) after 3 months with a tendency of stabilization (figure 20).

Z-translation

Translation on the Z-axis showed a similar pattern to translation on the X-axis, although after 6 months (mean 0.003mm, 95CI -0.11 to 0.12) from 3 months (mean 0.09mm, 95CI -0.07 to 0.27) a translation in the posterior direction was observed (figure 20).

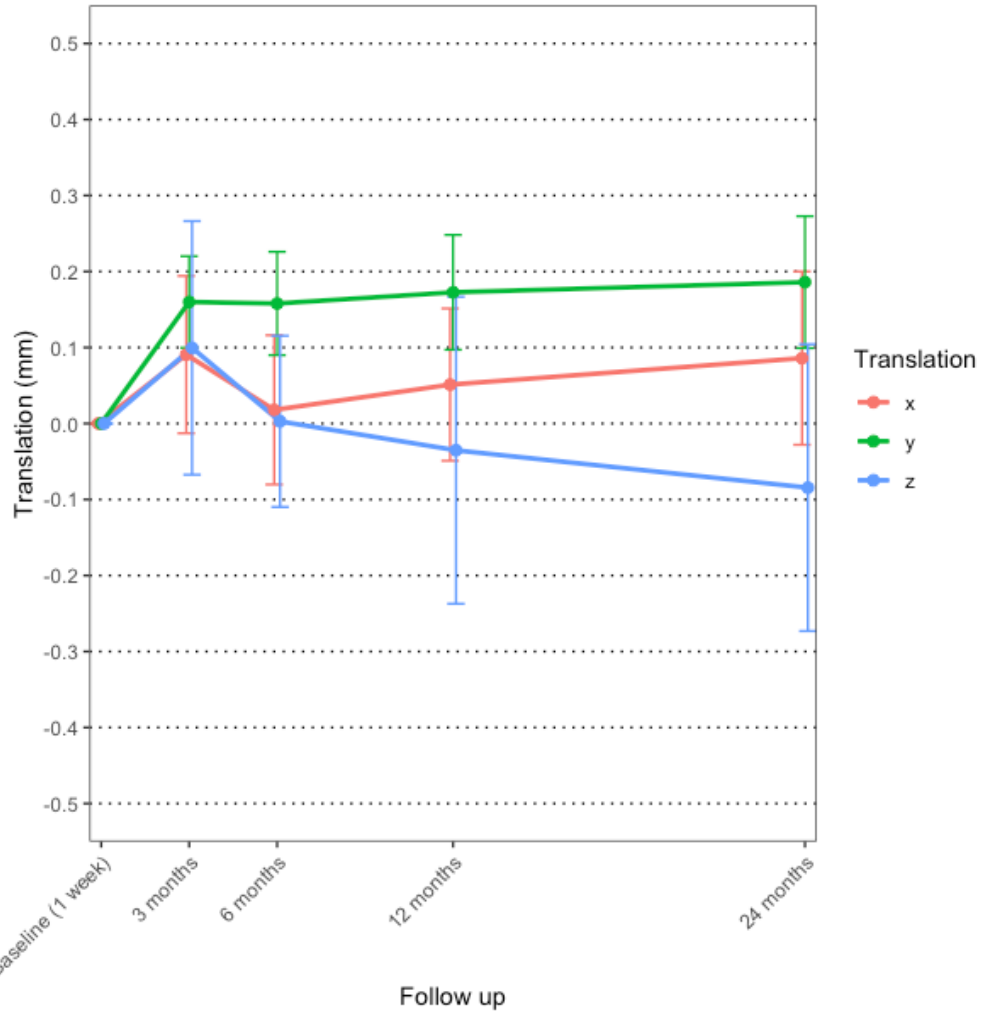

Figure 20: Mean translation of the femoral implant, whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Segmental motion (rotation)

X-rotation

Rotation on the X-axis showed an initial decrease (3 moths: mean -0.08°, 95CI -0.23 to 0.07) followed by an increase from 6-24 months although decreasing over time. The initial decrease represents a posterior tilt followed by an anterior tilt (increase) (figure 21).

Y-rotation

The highest rotation of the femoral component was observed along the Y-axis. A small initial increase (internal rotation) was followed by a substantially larger decrease (external rotation) of 0.18° although stabilizing from 12 to 24 months (figure 21).

Z-rotation

Rotation along the Z-axis was minimal indicating a small adduction/varus rotation (figure 21).

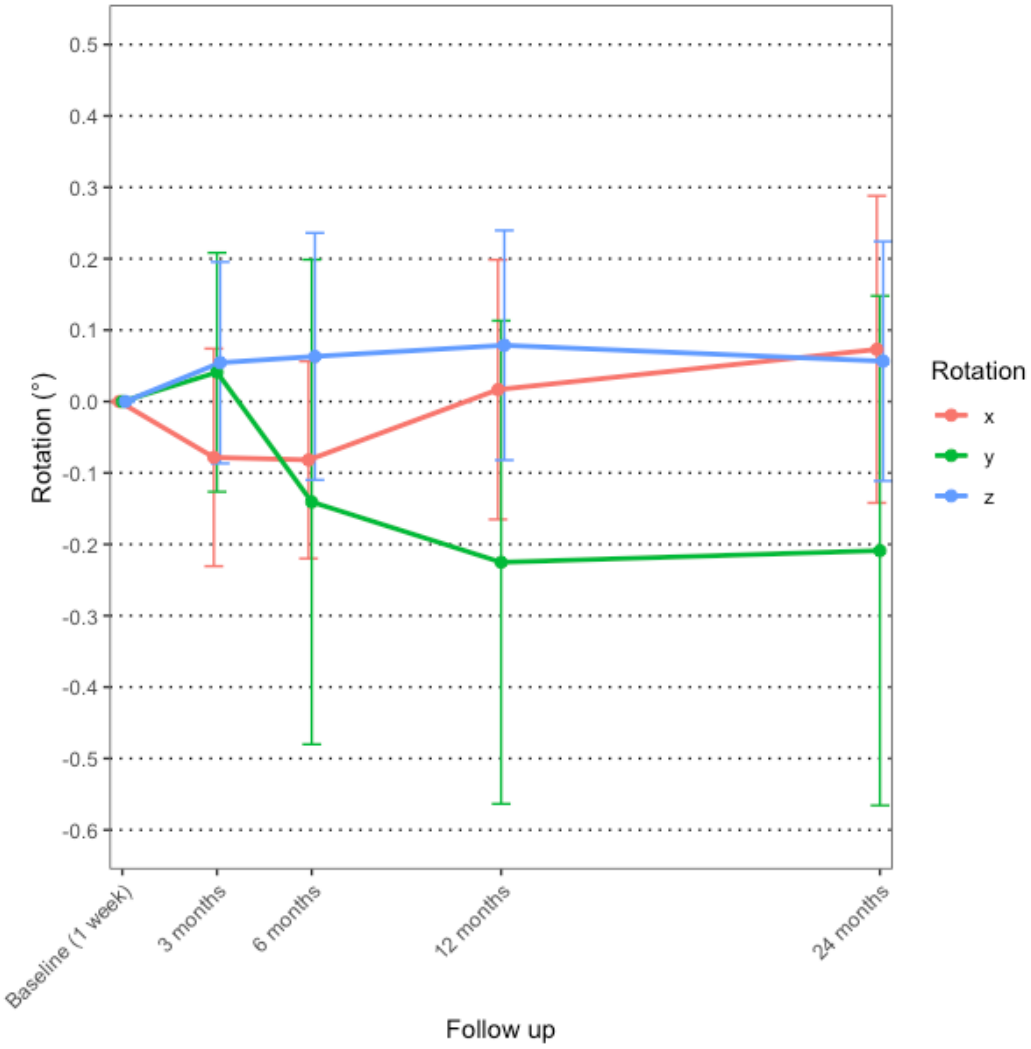

Figure 21: Mean rotation of the femoral implant, whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Tibial component – RSA measurements

Migration was measured in the entire cohort as well as on the individual level.

Validation of the tibial RSA measurements

Precision error

The PE for the MTPM was 0.33mm. PE for the translational segmental motion along the X, Y, and Z-axis was 0.14mm, 0.09mm, and 0.19mm respectively. The corresponding PE for the rotational segmental motion was 0.20°, 0.63°, and 0.21° respectively.

Mean error and condition number

One ME value (0.4) was above the recommended by Valstar et al [33] at 0.35 mm. Otherwise, all CN and ME were in the range of previous recommendations.

MTPM (entire cohort)

The migration pattern observed in the cemented tibial component was similar to that of the femoral component with the highest increase initially of 0.54mm (95CI 0.46 to 0.63) from baseline to 3 months postoperative and hereafter a tendency to stabilize (figure 22).

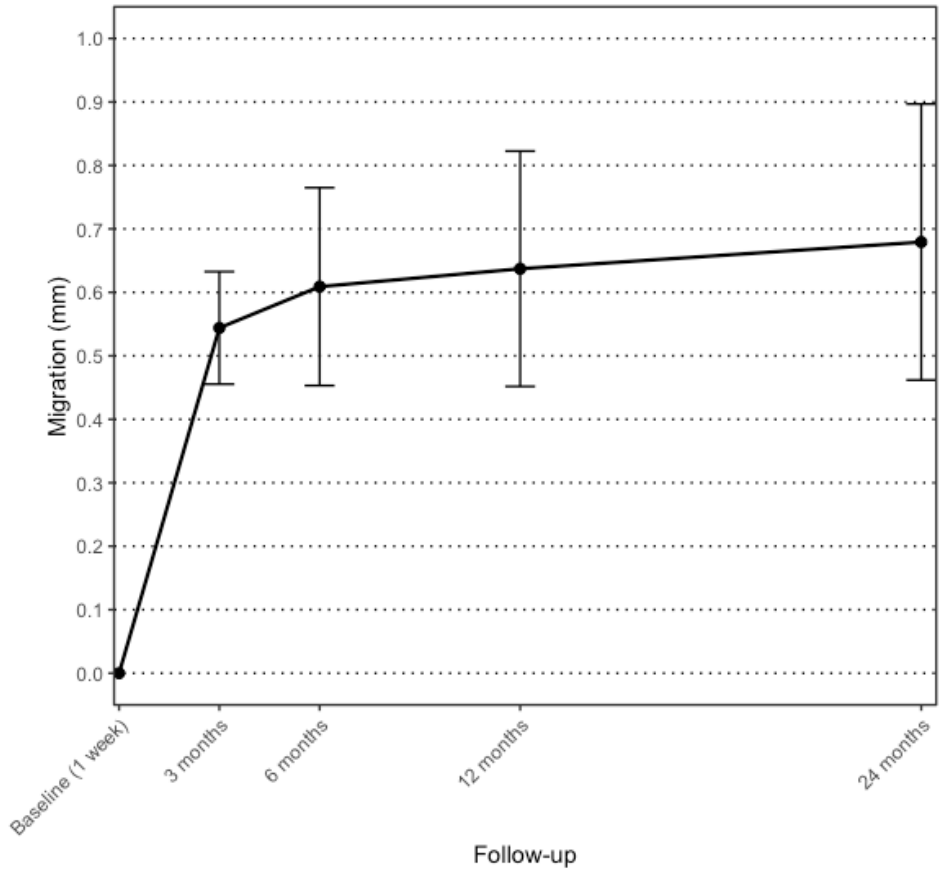

Figure 22: Mean MTPM for cemented tibial implant at 1 week, and at 3, 6, 12, and 24 months of follow-up. Whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

MTPM (individual level)

Two outliers were observed on the individual level namely patient no. 13 and no. 24. Patient no. 13 showed a continuous increase throughout the follow-up period with a total migration of 3.2mm after 24 months without signs of stabilization. Patient no. 24 showed an initial increase from baseline to 6 months (1.27mm) postoperative, followed by a small decrease from 6 to 12 months postoperative and hereafter an increase without noticeable stabilization (figure 21).

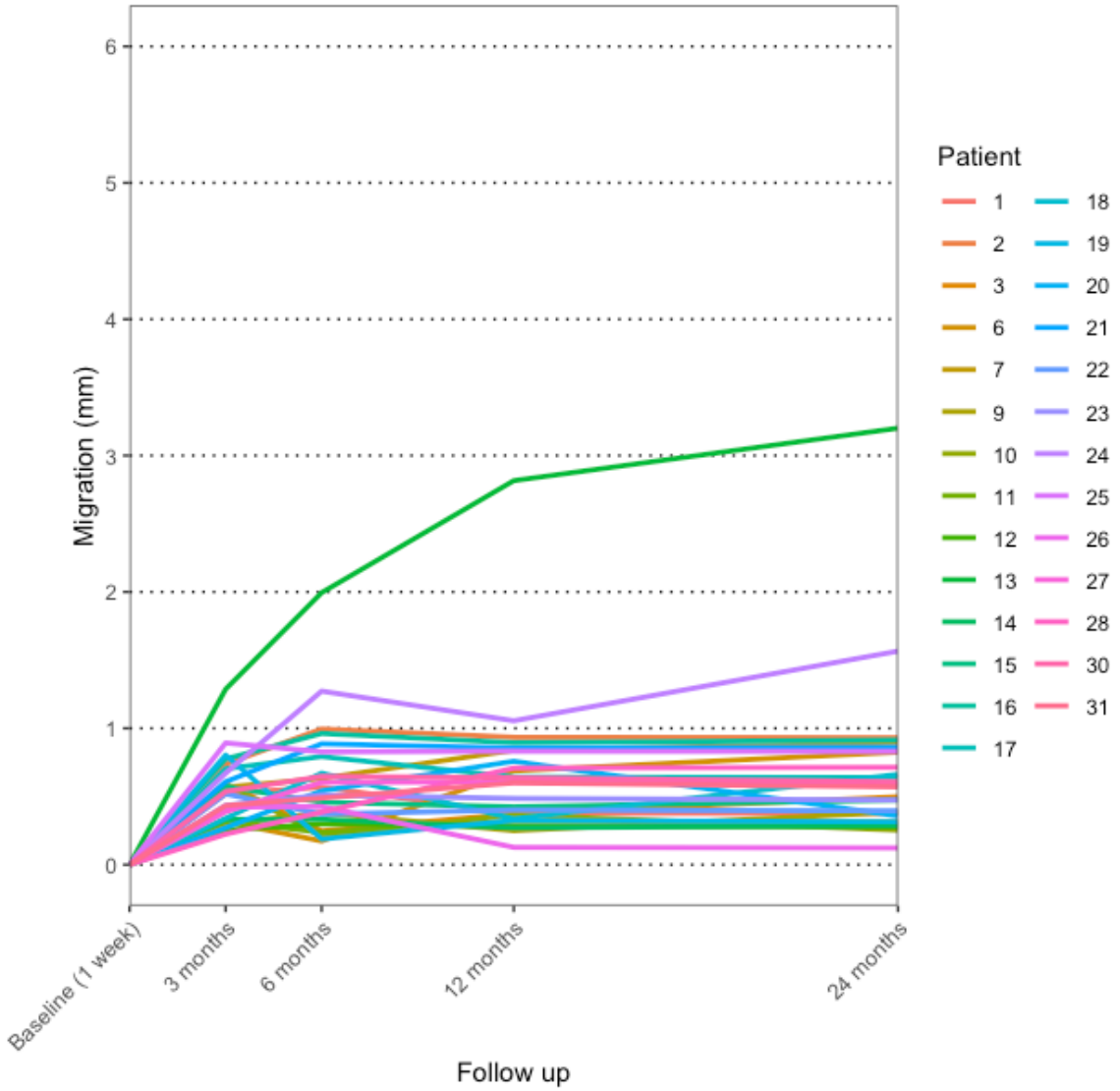

Figure 21: Spaghetti plot illustrating individual MTPM for the whole cohort of the tibial implants, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Segmental motion (translation)

X-translation

A minimal initial increase was observed followed by a continuous decrease indicating a lateral translation of the tibial implant after 24 months of mean -0.05mm (95CI -0.14 to 0.05) (figure 22).

Y-translation

A small increase indicating a superior translation followed by stabilization was observed after 24 months of 0.1mm (95CI 0.06 to 0.14) (figure 22).

Z-translation

The highest translation was observed along the Z-axis. An increase was observed from baseline until 12 months of follow up indicating an anterior translation of the tibial implant. From 12-24 months postoperative a minor decrease – almost stabilizing was observed. At 24 months a mean MTPM of 0.16mm (95CI -0.0003 to 0.313) (figure 22).

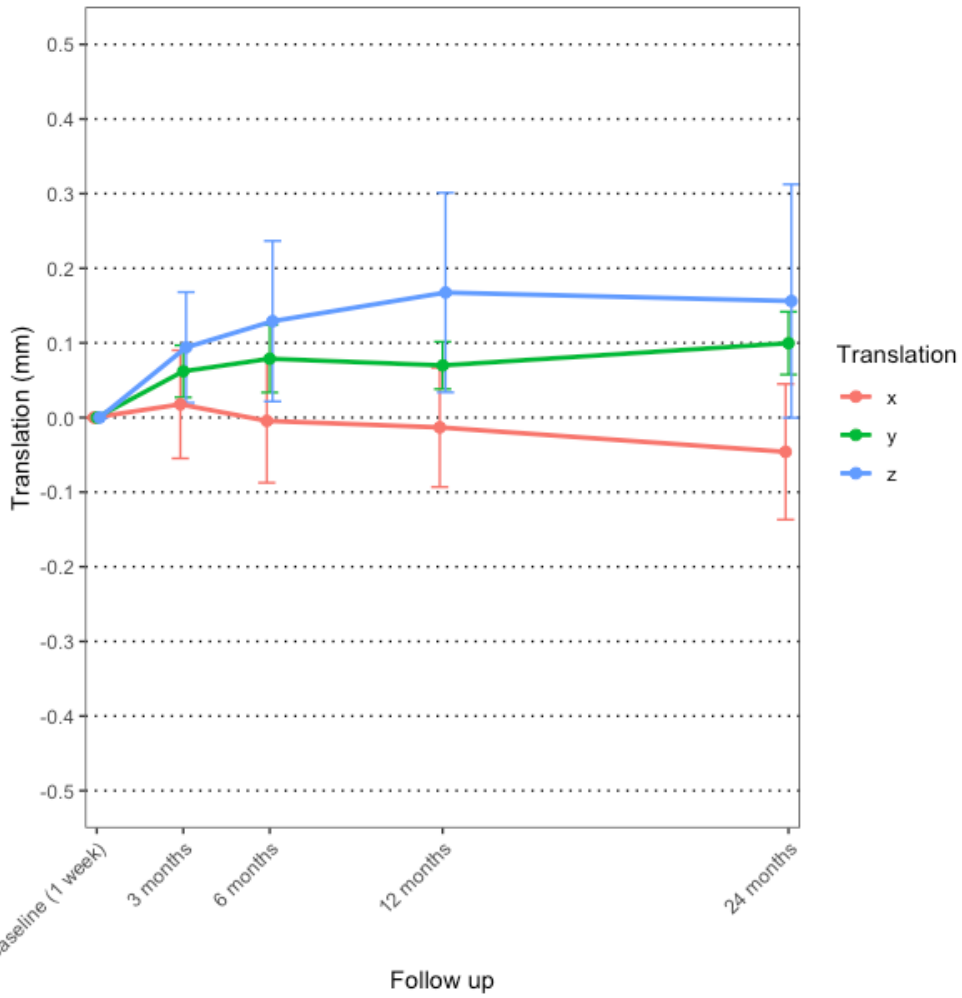

Figure 22: Mean translation of the tibial implant, whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Segmental motion (rotation)

X-rotation

An initial increase (anterior tilt/flexion) from baseline to 6 months (mean 0.16°, 95CI 0.03 to 0.29) was observed followed by a steady state period from 6 to 12 months and hereafter a decrease (posterior tilt/extension) from 12 to 24 months was observed (figure 24).

Y-rotation

The highest rotation on the Y-axis was observed with an initial negative value from baseline to 12 months (mean -0.1°, 95CI -0.26 to 0.06) postoperative indicating an external rotation of the tibial component. From 12 to 24 months, an increase was observed indicating an internal rotation of the component (figure 24).

Z-rotation

An almost steady state was observed from baseline to 6 months postoperative followed by an increase indicating valgisation of the component with a mean of 0.06° (95CI -0.07 to 0.19) after 24 months (figure 24).

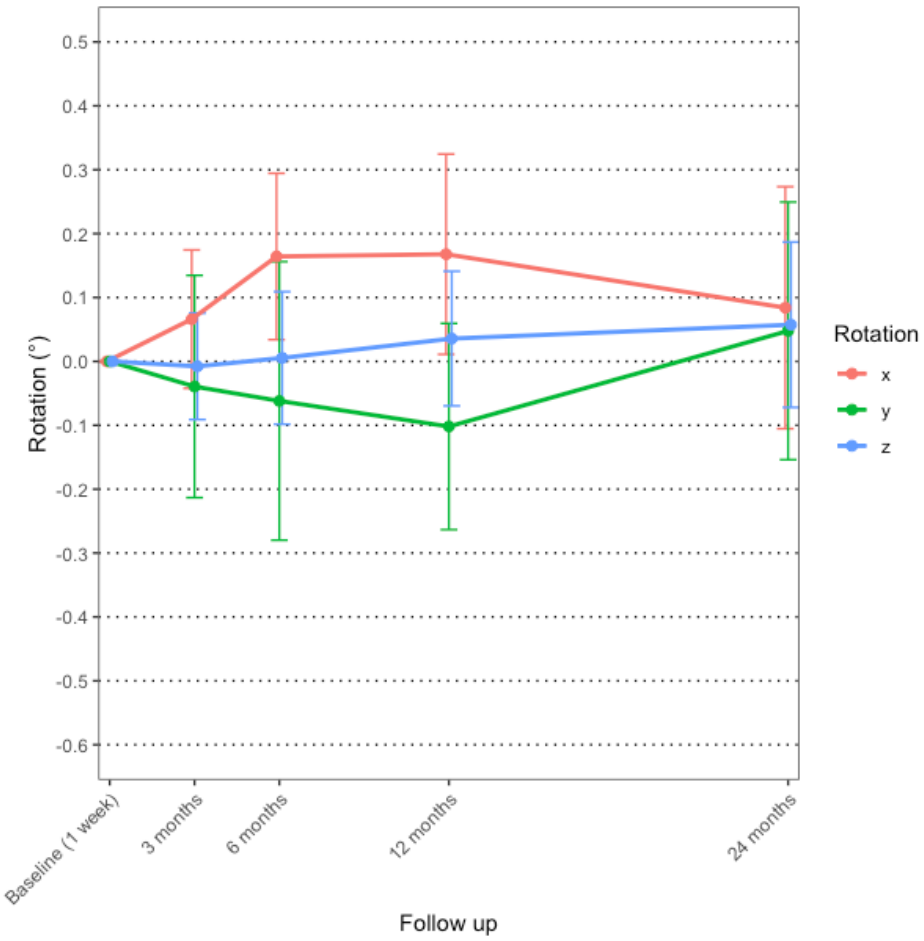

Figure 24: Mean rotation of the tibial implant, whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

DEXA measurements

Validation of the DEXA measurements

Coefficient variance

CV is calculated from 16 double measurements and is a representation of the PE. CV for ROI I, ROI II, and ROI III was 1.4%, 1.2%, and 0.9% for the femoral component and the corresponding values for the tibial component were 1.3%, 1.8%, and 2.1%.

Femoral bone mineral density

ROI I (anterior part)

The most substantial percentual change in BDM was observed in ROI I with a total decrease of 26.7% at 24 months after baseline postoperative.

The steepest decrease was seen from baseline to 3 months (16.3%, 95CI -20.7; -11.9) followed by a minor decrease of 3.1% (-19.4%, 95CI -24.4 to -14.4) from 3 to 6 months, 4.3% (-23.7%, 95CI -28.4 to -18.9) from 6 to 12 months and 3.1% (-26.7%, 95CI -31.3 to -22.2) from 12 to 24 months (figure 26). A statistically significant difference in the decrease from baseline to 24 months of follow-up was found ($p<0.001$).

ROI II (posterior part)

An initial decrease in BMD of 6.6% was observed in ROI II (-6.6%, 95CI -9.9 to -3.3). A tendency of stabilization was observed from 3 to 6 months (-7.3%, 95CI -11.9 to -2.6) and 6 to 12 months (-7.2%, 95CI -11.2 to -3.3). A minor decrease was observed from 12 to 24 months of 2% (-9.2%, 95CI -12.7 to -5.7) (figure 26). A statistically significant difference in the decrease from baseline to 24 months of follow-up was found ($p<0.001$).

ROI III (proximal part)

A tendency of stabilization from baseline to 12 months postoperative was observed with mean values at: 3 months of (0.15%, 95CI -2.7 to 3.1), 6 months (-0.8%, 95CI -4.5 to 2.9), 12 months (-0.4%, 95CI -3.7 to 2.9) in ROI III. A minor decrease was observed from 12 to 24 months of 2.9% (-3.3%, 95CI -6.3 to -0.2) (figure 26). A statistically significant difference in the decrease from baseline to 24 months of follow-up was found ($p<0.001$).

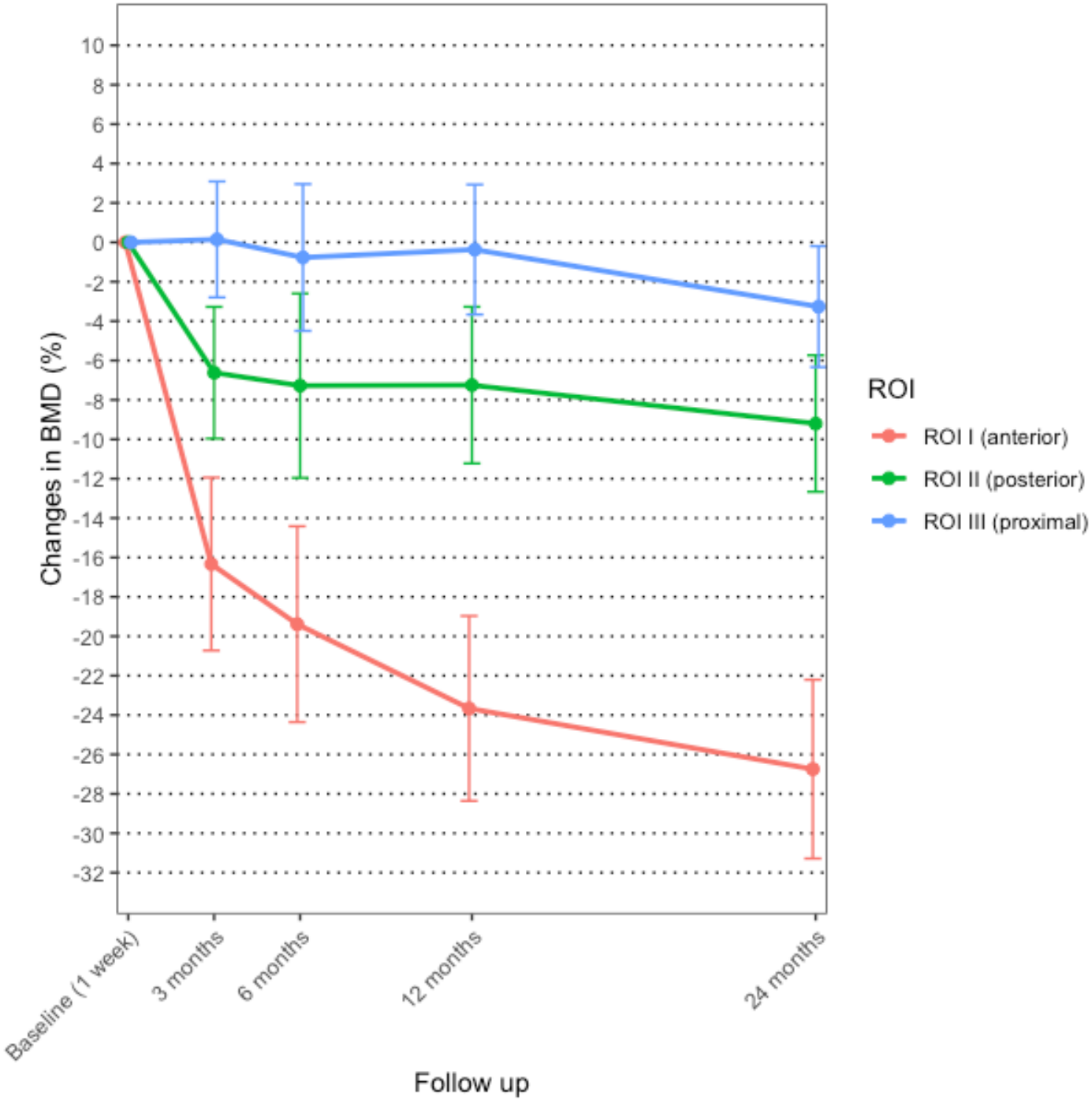

Figure 26: Percentage mean BMD changes in ROI for femoral implants, whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Tibial bone mineral density

ROI I (medial part)

An initial decrease in ROI I was observed from baseline to 3 months postoperative of -3% (-3, 95CI -5.9 to -0.1). A steady state was observed from 3 to 12 months (6 months: -3.6% (95CI -8.1 to -0.9), 12 months: -3.6%, (95CI -10.6 to 3.4). A substantial decrease was observed from 12 to 24 months of 4.6% (24 months: -8.2%, 95CI -4.4 to -12.1) figure 27. A statistically significant difference in the decrease from baseline to 24 months of follow-up was found ($p<0.001$).

ROI II (lateral part)

A continuous decrease from baseline to 24 months postoperative was observed for ROI II of 8.6% (95CI -12.2 to -5.1). The decrease from baseline to 3 months was 2.8% (95CI -6.8 to 1.2), from 3 to 6 months 2.5% (mean at 6 months was -5.3%, 95CI -9.7 to -0.8), 6 to 12 months 0.8% (mean at 12 months was -6.1%, 95CI -11.5 to -0.7) and 12 to 24 months was 2.5% (mean at 24 months was -8.6%, 95CI -12.2 to -5.1) (figure 27). A statistically significant difference in the decrease from baseline to 24 months of follow-up was found ($p<0.001$).

ROI III (distal part)

A decrease from baseline to 6 months of -6.6% (95CI -9.5 to -3.7) was observed (mean at 3 months was -1.9%, 95CI -4.9 to 1.2) in ROI III. A tendency of stabilization was observed from 6 to 12 months of -0.6% (mean at 12 months was -7.2%, 95CI -10.2 to -4.3) and similarly from 12 to 24 months of 0.3% (mean at 24 months was -6.9%, 95CI -9.5 to -4.4) (figure 27). A statistically significant difference in the decrease from baseline to 24 months of follow-up was found ($p<0.001$).

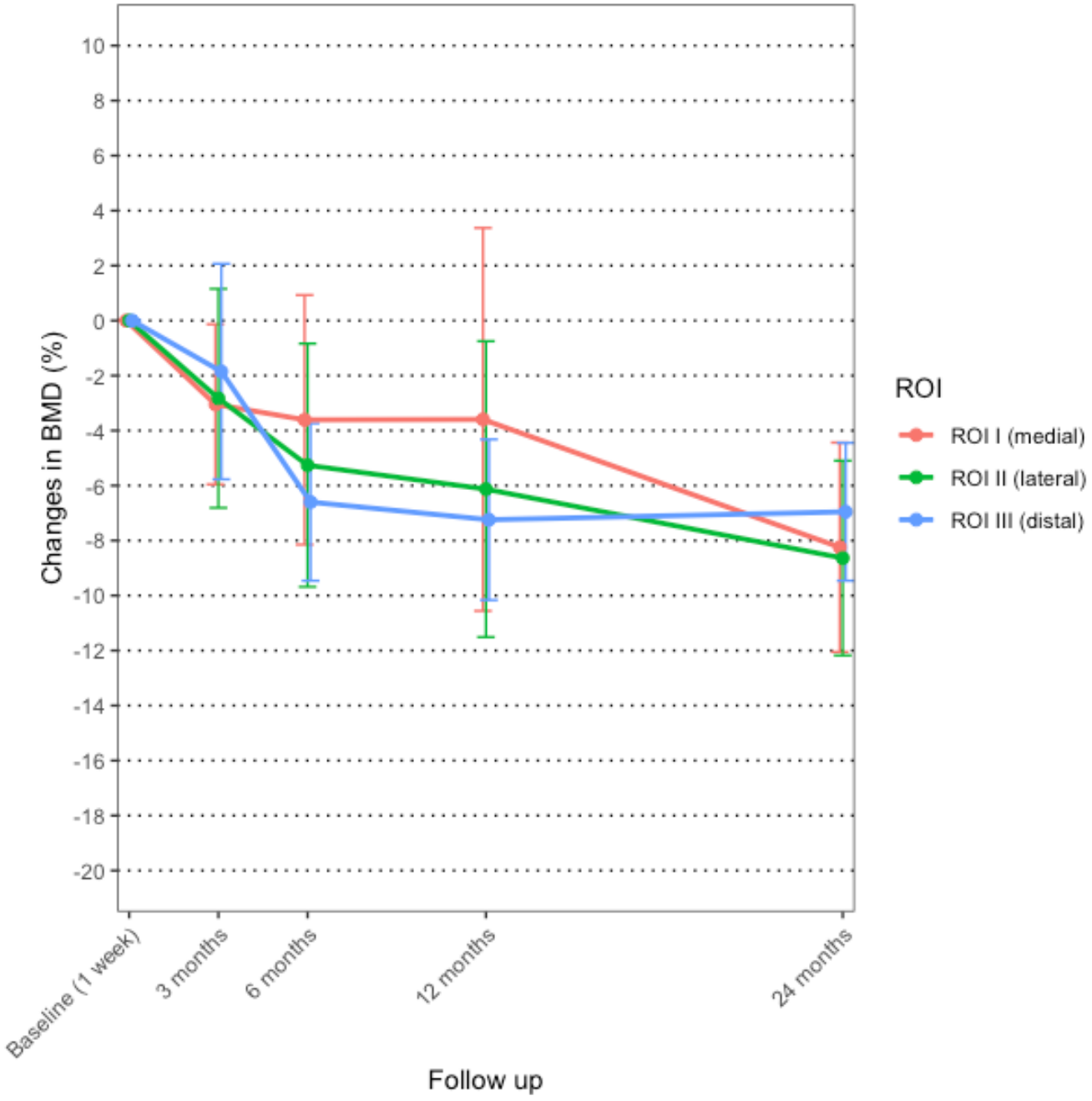

Figure 27: Percentage mean BMD changes in ROI for tibial implants, whiskers represent 95CI, created by Yilmaz et al. [35]. Reproduction is allowed in accordance with reproduction guidelines stated on the BMC website.

Functional outcomes

Clinical measurements were evaluated with OKS (n=29) and KKS (n=29).

OKS

The mean score preoperatively was 25/48 points (range 13-38). A statistically significant increase was seen 24 months postoperative with a mean score of 44/48 points (range 35-48) ($p<0.001$).

KKS

Patient-reported functional part:

The mean score preoperatively was 54/100 points (range 10-100). A statistically significant increase was seen 24 months postoperative with a mean score of 94/100 points (range 50-100) ($p<0.001$).

Clinical part:

The mean score preoperatively was 38/100 points (range 10-79). A statistically significant increase was seen 24 months postoperative with a mean score of 87/100 points (range 60-90) ($p<0.001$).

Study II

RSA measurements - femoral implants

Cemented and uncemented (trabecular metal) implants

Migration was measured in the entire cohort as well as on the individual level.

Validation of RSA measurements

Precision error femoral implants

The PE for MTPM was 0.5mm and based on calculations from 55 femoral double measurements. The PE for the X, Y and Z translation was 0.29, 0.07 and 0.16 mm respectively, with corresponding values of 0.25°, 0.33° and 0.31° for the rotational segmental motion on the X, Y and Z axis.

MTPM (entire cohort)

The majority of migration occurred from baseline to 3 months postoperative within both groups (cemented: 0.41mm, uncemented: 0.65mm). The migration pattern hereafter increased only slightly from 3 to 24 months with a tendency of stabilization within both groups from 6 months (figure 28). There was a statistically significant difference in MTPM from baseline to 24 months postoperative (p=0.02).

Migration data for each follow-up are reported in table 3.

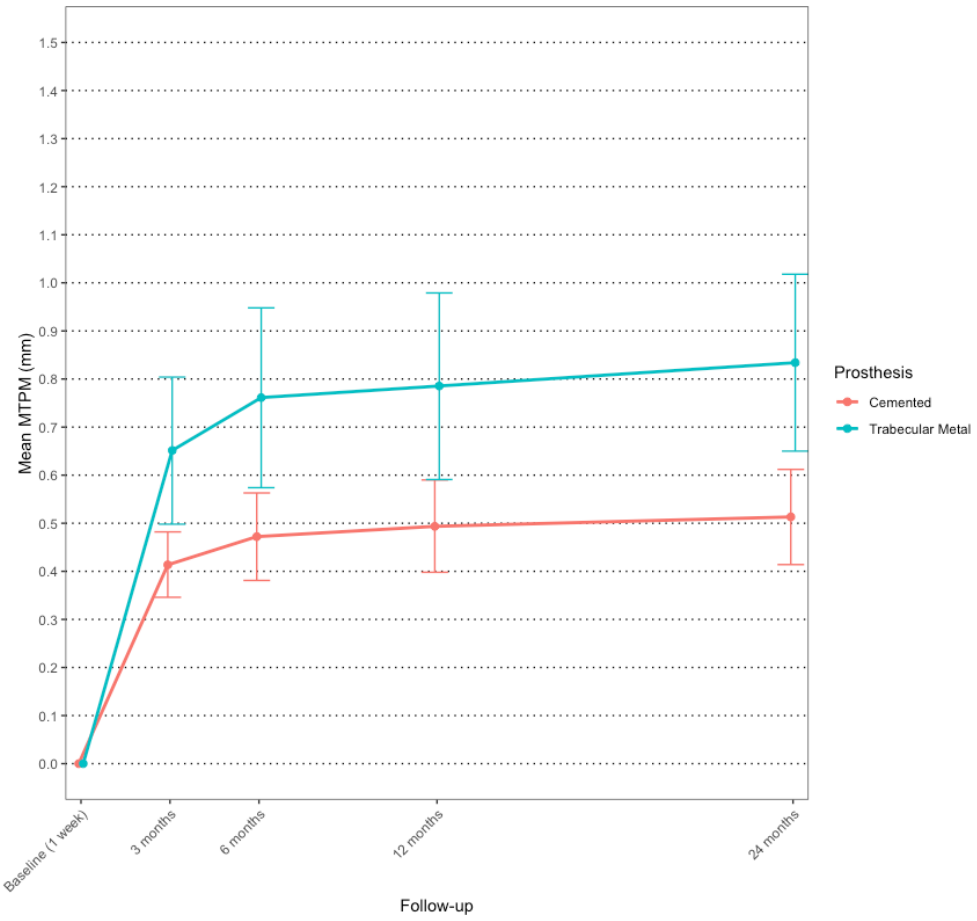

Figure 28: Mean MTPM for cemented and uncemented femoral implants, whiskers represents 95CI. From manuscript to study II [77].

MTPM (individual level)

As illustrated in figure 29 patients with a cemented femoral implant in general demonstrate less and more stable migration than patients with an uncemented implant. Two outliers (uncemented implants) demonstrate a substantially increased migration although reaching a level of stabilization. Moreover, two patients (no. 4 and no. 60) demonstrate a continuous migration at 24 months postoperative (figure 30). Migration >0.1mm from 12 to 24 months was observed in a total of 11 patients.

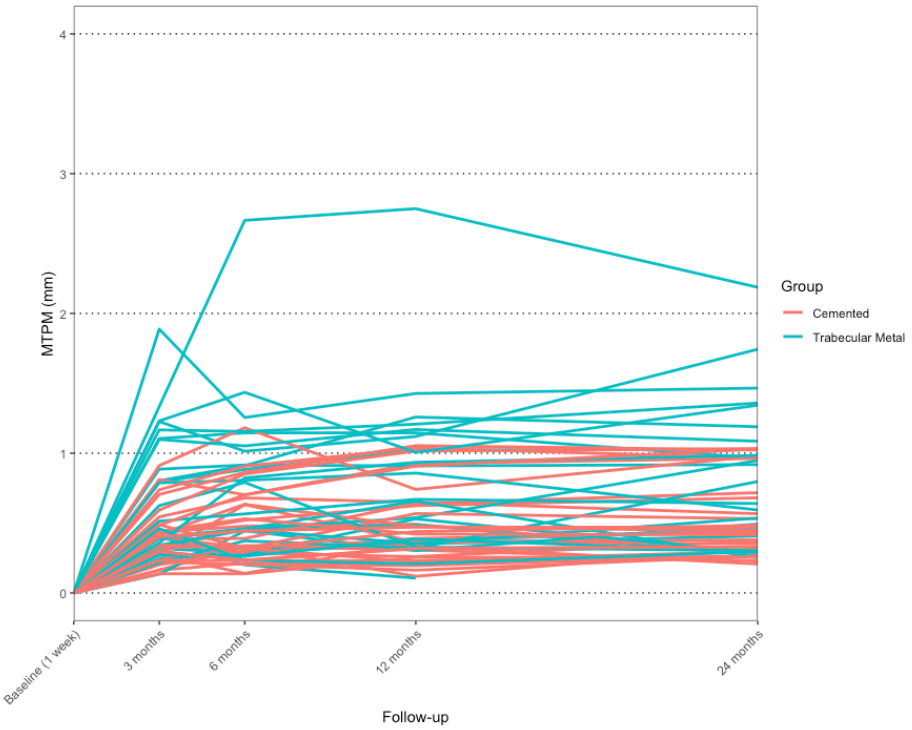

Figure 29: MTPM for cemented and uncemented femoral implants.

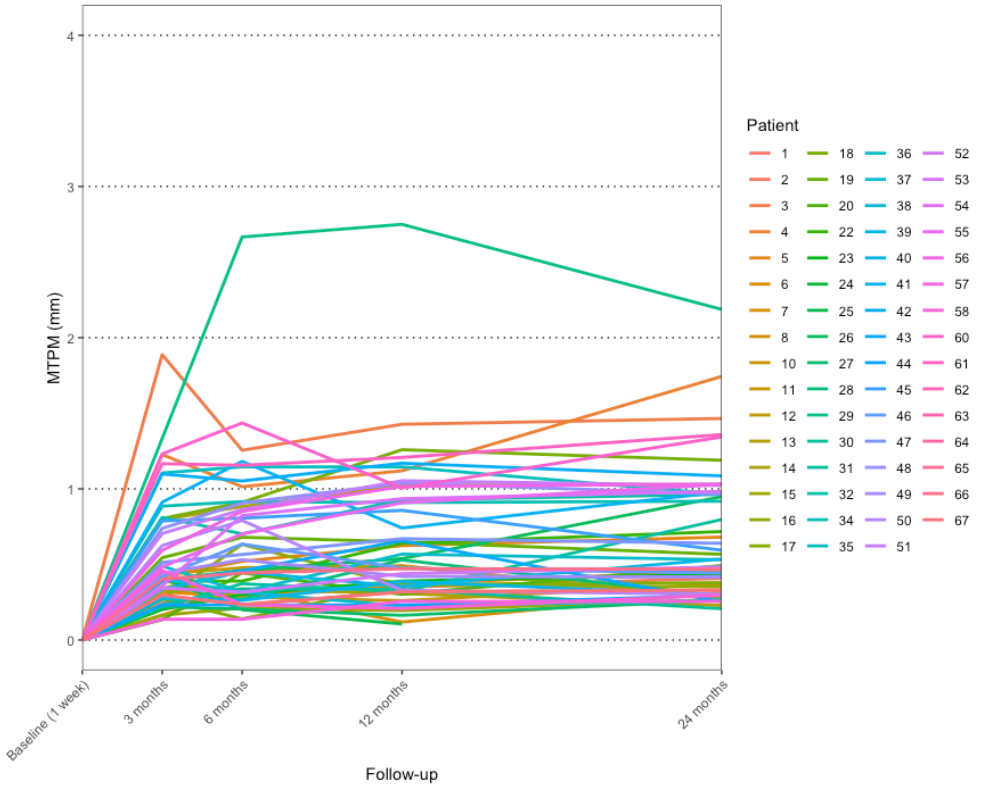

Figure 30: Individual MTPM for femoral implants.

RSA measurements - tibial implants

Cemented and uncemented (trabecular metal) implants

Migration was measured in the entire cohort as well as on the individual level.

Validation of RSA measurements

Precision error *tibial implants*

The PE of the MTMP for the tibial components was 0.33mm based on 60 double measurements. The PE for the X, Y, and Z translations was 0.12mm, 0.07mm, and 0.16mm respectively. For rotational segmental motion, the corresponding values were 0.18°, 0.51°, and 0.19°.

MTPM (entire cohort)

The highest migration was observed within the first three months within both the cemented (0.7mm) and uncemented groups (0.76mm). A stabilization was subsequently observed in both groups, and no statistically significant difference between the two groups from baseline to 24 months was reported (figure 31). Migration data for each follow-up are reported in table 3.

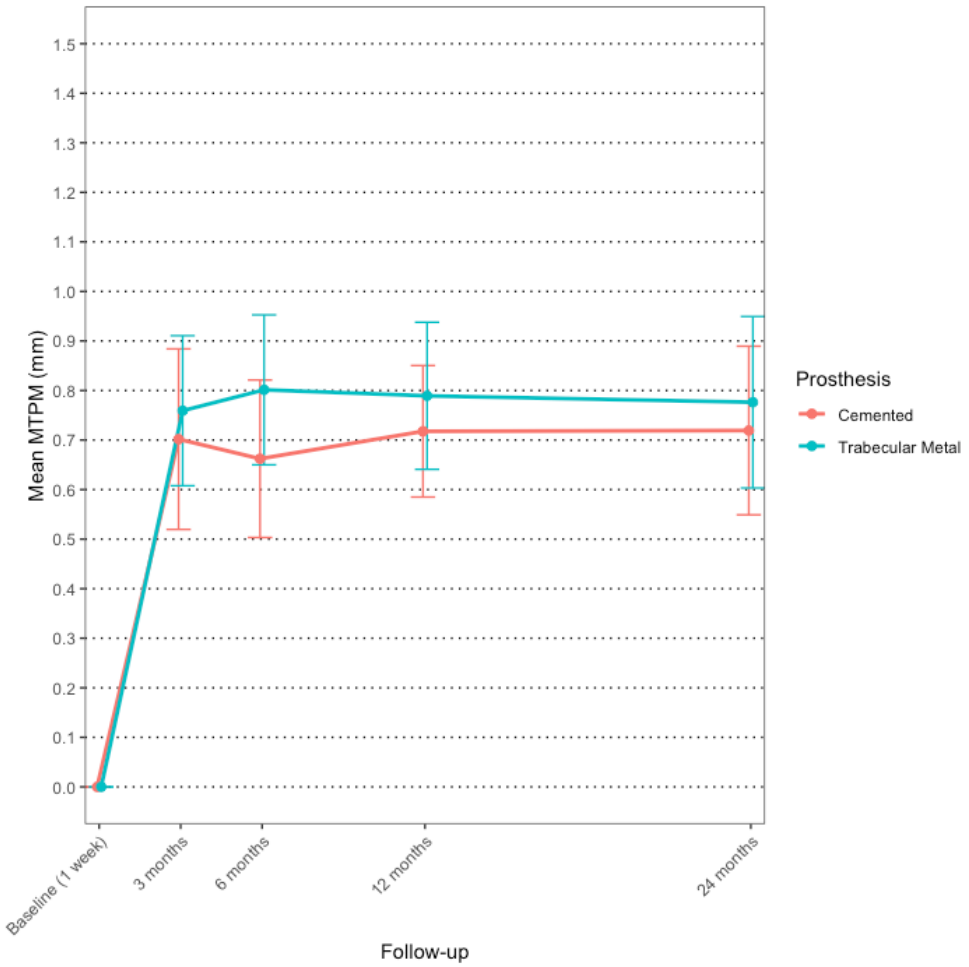

Figure 31: Mean MTPM for cemented and uncemented tibial implants, whiskers showing 95CI. From manuscript to study II [77].

MTPM (individual level)

Figure 32 illustrates that cemented and uncemented components migrate without a specific pattern. Figure 33 illustrates that continuous migration was observed in two patients (no. 1 and no. 67) at 24 months postoperative.

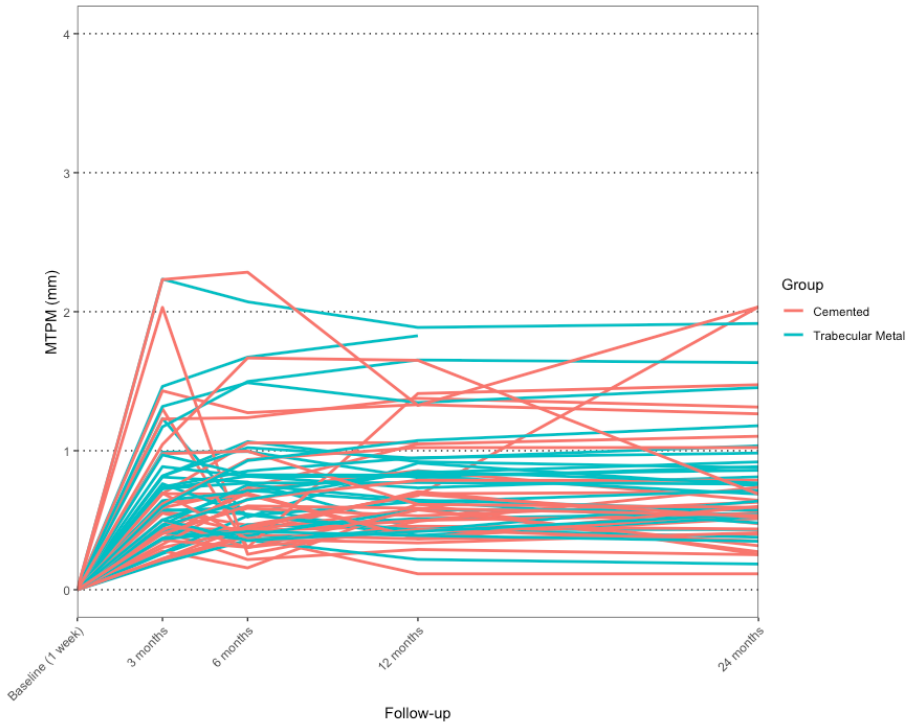

Figure 32: MTPM for cemented and uncemented tibial implants.

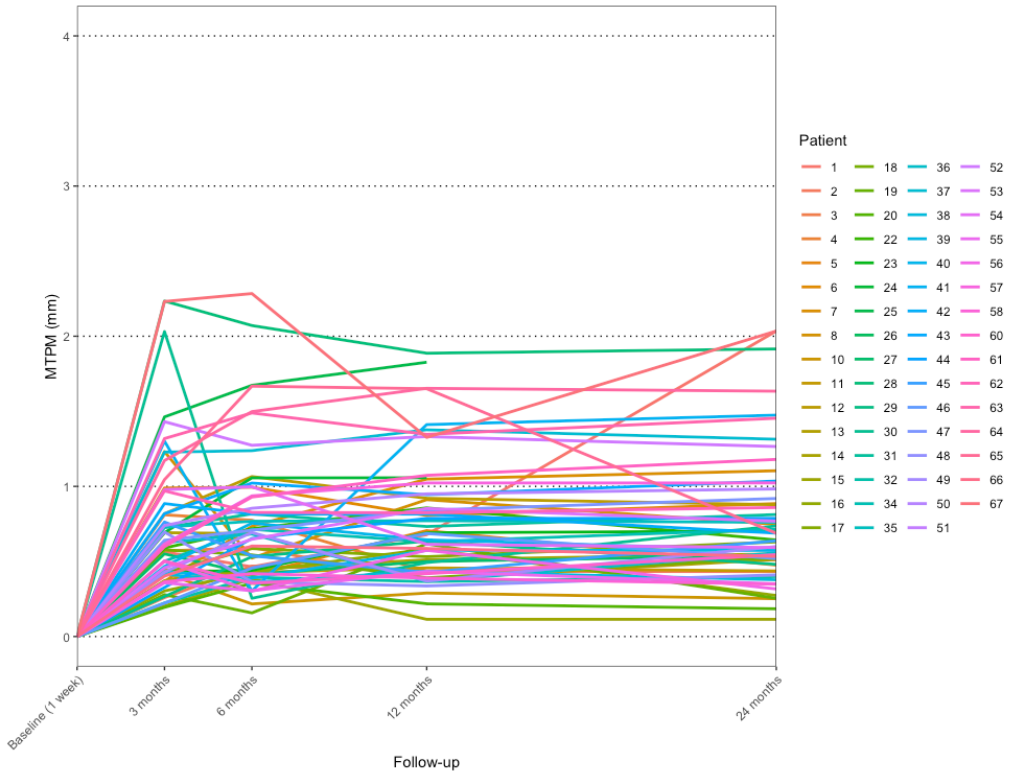

Figure 33: Individual MTPM for tibial implants.

Femoral segmental motion

The translation along the X, Y, and Z axis for the femoral component was generally low and stable, with the highest movement in Y-translation (superior/inferior axis) after 6 months for uncemented implants of 0.09mm in a superior direction. The highest movement for cemented implants was in X-translation (lateral/medial axis) after 3 months of -0.07mm in a lateral direction (table 3). The rotation around the same X, Y, and Z axis were low but not with the same stabilization tendency as with translation (table 3). The main rotation for uncemented implants was observed around the X (initial extension and afterward flexion) and Y axis (minor internal and afterward and external rotation) and for cemented implants around the X axis (flexion).

Tibial segmental motion

The translation along the X and Z axis was minor and with a tendency of stabilization. The main translation for cemented implants was observed along the Z axis with an initial translation of -0.099mm from baseline to 3 months followed by a tendency to stabilize. However, for the uncemented implants, the major translation was observed along the Y axis with an initial large translation in an inferior/caudal direction from baseline to 3 months of -0.26 subsequently stabilizing from 3 to 24 months. A statistically significant difference between cemented and uncemented implants was observed for the whole follow-up (table 3).

The main rotation was observed around the X-axis, both groups demonstrated a rotation around the X-axis indicating a posterior tilt with a statistically significant difference between the two groups at 3 and 6 months. The uncemented group demonstrated a large initial rotation of -0.55° from baseline to 6 months postoperative. The cemented implants demonstrated an initial external rotation of up to -0.23° after 6 months and afterward with stabilization close to neutral (table 3).

		3 months	p-value	6 months	p-value	12 months	p-value	24 months	p-value
Femur									
MTPM	Cemented	0.414 (0.137 to 0.911) [0.346 to 0.482]	0.04*	0.472 (0.137 to 1.18) [0.381 to 0.563]	0.03*	0.494 (0.119 to 1.05) [0.398 to 0.590]	0.02*	0.513 (0.207 to 1.03) [0.414 to 0.612]	0.02*
	Uncemented	0.651 (0.134 to 1.89) [0.498 to 0.804]		0.761 (0.201 to 2.66) [0.574 to 0.948]		0.785 (0.106 to 2.75) [0.591 to 0.979]		0.834 (0.252 to 2.19) [0.650 to 1.018]	
X-translation	Cemented	-0.066 (-0.541 to 0.171) [-0.122 to -0.010]	0.70	-0.035 (-0.558 to 0.321) [-0.093 to 0.023]	0.18	-0.041 (-0.803 to 0.242) [-0.109 to 0.027]	0.34	-0.026 (-0.405 to 0.415) [-0.087 to 0.035]	0.35
	Uncemented	-0.035 (-0.56 to 0.428) [-0.111 to 0.041]		0.351 (-0.543 to 0.516) [0.254 to 0.448]		0.034 (-0.419 to 0.433) [-0.044 to 0.112]		0.034 (-0.392 to 0.439) [-0.052 to 0.120]	
Y-translation	Cemented	0.002 (-0.387 to 0.215) [-0.042 to 0.046]	0.27	0.025 (-0.411 to 0.222) [-0.026 to 0.076]	0.37	0.033 (-0.321 to 0.29) [-0.015 to 0.081]	0.13	0.061 (-0.191 to 0.294) [0.017 to 0.105]	0.14
	Uncemented	0.053 (-0.174 to 0.436) [-0.004 to 0.110]		0.091 (-0.178 to 0.492) [0.022 to 0.160]		0.106 (-0.139 to 0.51) [0.041 to 0.171]		0.129 (-0.151 to 0.495) [0.063 to 0.195]	
Z-translation	Cemented	0.021 (-0.281 to 0.399) [-0.041 to 0.083]	0.71	0.033 (-0.365 to 0.944) [-0..063 to 0.129]	0.74	0.017 (-0369 to 0.539) [-0.064 to 0.098]	0.94	-0.016 (-0.391 to 0.483) [-0.089 to 0.057]	0.61
	Uncemented	-0.033 (-0.281 to 0.399) [-0.173 to 0.107]		-0.019 (-1.22 to 0.637) [-0.165 to 0.127]		-0.043 (-1.109 to 0.0539) [-0.163 to 0.077]		-0.013 (-0.967 to 0.683) [-0.153 to 0.127]	
X-rotation	Cemented	0.091 (-0.569 to 0.722) [-0.0149 to 0.197]	0.06	0.086 (-1.094 to 0.926) [-0.074 to 0.246]	0.11	0.098 (-0.719 to 0.872) [-0.053 to 0.249]	0.23	0.161 (-0.817 to 0.989) [0.015 to 0.307]	0.14
	Uncemented	-0.078 (-1.039 to 1.254) [-0.286 to 0.130]		-0.043 (-0.979 to 2.597) [-0.334 to 0.248]		0.063 (-0.942 to 2.647) [-0.202 to 0.328]		0.027 (-0.97 to 2.282) [-0.254 to 0.308]	
Y-rotation	Cemented	-0.031 (-0.529 to 0.441) [-0.122 to 0.060]	0.22	0.004 (-0.265 to 0.487) [-0.073 to 0.081]	0.23	-0.008 (-0.592 to 0.479) [-0.103 to 0.087]	0.76	-0.035 (-1.436 to 0.494) [-0.176 to 0.106]	0.26
	Uncemented	0.021 (-0.927 to 0.742) [-0.098 to 0.140]		-0.097 (-1.042 to 0.756) [-0.240 to 0.046]		-0.033 (-1.056 to 0.704) [-0.208 to 0.142]		-0.085 (-1.568 to 1.119) [-0.286 to 0.116]	
Z-rotation	Cemented	-0.08 (-0.841 to 0.508) [-0.173 to 0.013]	0.16	-0.028 (-0.851 to 0.716) [-0.103 to 0.047]	0.39	-0.049 (-0.935 to 0.188) [-0.137 to 0.039]	0.16	-0.026 (-0.516 to 0.667) [-0.110 to 0.070]	0.23
	Uncemented	0.007 (-0.476 to 0.529) [-0.089 to 0.103]		0.026 (-0.556 to 0.735) [-0.087 to 0.139]		0.068 (-0.765 to 0.927) [-0.060 to 0.196]		0.032 (-0.722 to 0.572) [-0.093 to 0.157]	
Tibia									
MTPM	Cemented	0.702 (0.203 to 2.23) [0.526 to 0.878]	0.18	0.662 (0.157 to 2.28) [0.503 to 0.821]	0.06	0.718 (0.114 to 1.65) [0.585 to 0.851]	0.39	0.719 (0.114 to 2.03) [0.549 to 0.889]	0.21
	Uncemented	0.759 (0.194 to 2.23) [0.607 to 0.911]		0.801 (0.355 to 2.07) [0.652 to 0.950]		0.789 (0.218 to 1.89) [0.640 to 0.938]		0.776 (0.185 to 1.92) [0.637 to 0.915]	
X-translation	Cemented	-0.051 (-0.865 to 0.269) [-0.139 to 0.037]	0.48	-0.069 (-0.613 to 0.289) [-0.141 to 0.004]	0.33	-0.065 (-0.586 to 0.297) [-0.131 to 0.001]	0.19	-0.413 (-0.453 to 0.304) [-0469 to -0.357]	0.18
	Uncemented	0.007 (-0.186 to 0.260) [-0.046 to 0.032]		-0.158 (-0.473 to 0.205) [-0.211 to -0.105]		-0.004 (-0.326 to 0.288) [-0.055 to 0.047]		0.0016 (-0.362 to 0.316) [-0.055 to 0.058]	
Y-translation	Cemented	0.024 (-0.192 to 0.389) [-0.018 to 0.066]	<0.001*	0.064 (-0.154 to 0.493) [0.020 to 0.108]	<0.001*	0.075 (-0.185 to 0.485) [0.028 to 0.122]	<0.001*	0.088 (-0.184 to 0.381) [0.041 to 0.135]	<0.001*
	Uncemented	-0.263 (-1.457 to 0.129) [-0.374 to -0.152]		-0.266 (-1.385 to 0.105) [-0.370 to -0.162]		-0.243 (-1.393 to 0.398) [-0.354 to -0.132]		-0.241 (-1.388 to 0.282) [-0.352 to -0.130]	
Z-translation	Cemented	-0.099 (-0.845 to 0.743) [-0.208 to 0.010]	0.61	-0.11 (-0.855 to 0.308) [-0.212 to -0.008]	0.42	-0.083 (-0.928 to 0.384) [-0.188 to 0.022]	0.81	-0.063 (-0.915 to 0.404) [-0.173 to 0.047]	0.95
	Uncemented	-0.084 (-0.699 to 0.354) [-0.164 to -0.004]		-0.129 (-0.517 to 0.201) [-0.195 to -0.063]		-0.088 (-0.749 to 0.193) [-0.188 to 0.022]		-0.044 (-0.685 to 0.338) [-0.133 to 0.045]	
X-rotation	Cemented	-0.097 (-1.125 to 0.968) [-0.248 to 0.054]	0.009*	-0.162 (-1.06 to 0.491) [-0.299 to -0.024]	0.002*	-0.163 (-1.14 to -1.28) [-0.306 to -0.0191]	0.07	-0.153 (-1.559 to 0.883) [-0.314 to 0.0074]	0.08
	Uncemented	-0.401 (-1.515 to 0.293) [-0.559 to -0.243]		-0.519 (-1.76 to 0.491) [-0.694 to -0.345]		-0.459 (-1.69 to 0.139) [-0.064 to 0.282]		-0.421 (-1.97 to 0.924) [-0.644 to -0.199]	
Y-rotation	Cemented	-0.156 (-1.769 to 1.85) [-0.406 to 0.094]	0.02*	-0.231 (-1.663 to 0.874) [-0.423 to -0.039]	0.007*	-0.015 (-1.277 to 2.122) [-0.234 to 0.204]	0.39	0.068 (-1.559 to 2.169) [-0.176 to 0.312]	0.40
	Uncemented	0.151 (-0.561 to 1.425) [-0.027 to 0.329]		0.149 (-0.681 to 1.839) [-0.037 to 0.335]		0.109 (-0.88 to 1.536) [-0.068 to 0.286]		0.172 (-0.722 to 1.242) [0.023 to 0.321]	
Z-rotation	Cemented	0.066 (-0.552 to 0.769) [-0.033 to 0.165]	0.86	0.119 (-0.334 to 0.749) [0.031 to 0.207]	0.64	0.126 (-0.312 to 0.512) [0.048 to 0.204]	0.52	0.126 (-0.489 to 0.744) [0.029 to 0.223]	0.50
	Uncemented	0.048 (-0.929 to 1.011) [-0.099 to 0.195]		0.144 (-0.959 to 0.994) [-0.020 to 0.308]		0.067 (-1.014 to 0.769) [-0.071 to 0.205]		0.017 (-1.033 to 0.671) [-0.130 to 0.164]	

Table 3: MTPM and segmental motion of cemented and uncemented femoral and tibial implants. Manuscript study II [77].

Study III

DEXA measurements

Femoral bone mineral density

Validation of femoral DEXA measurements

The PE was based on 63 double examinations with values of 1.86%, 1.6%, and 1.39% for ROI I, II, and III respectively.

ROI I (anterior part)

The highest decrease in BMD was observed in ROI I within both the cemented and uncemented groups. A continuous decrease from baseline to the end of follow-up was observed in both groups reaching -20.67% in the cemented group and -32.89% in the uncemented group at 24 months postoperative. A statistically significant difference between the two groups was observed throughout the entire follow-up period (table 4, figure 34).

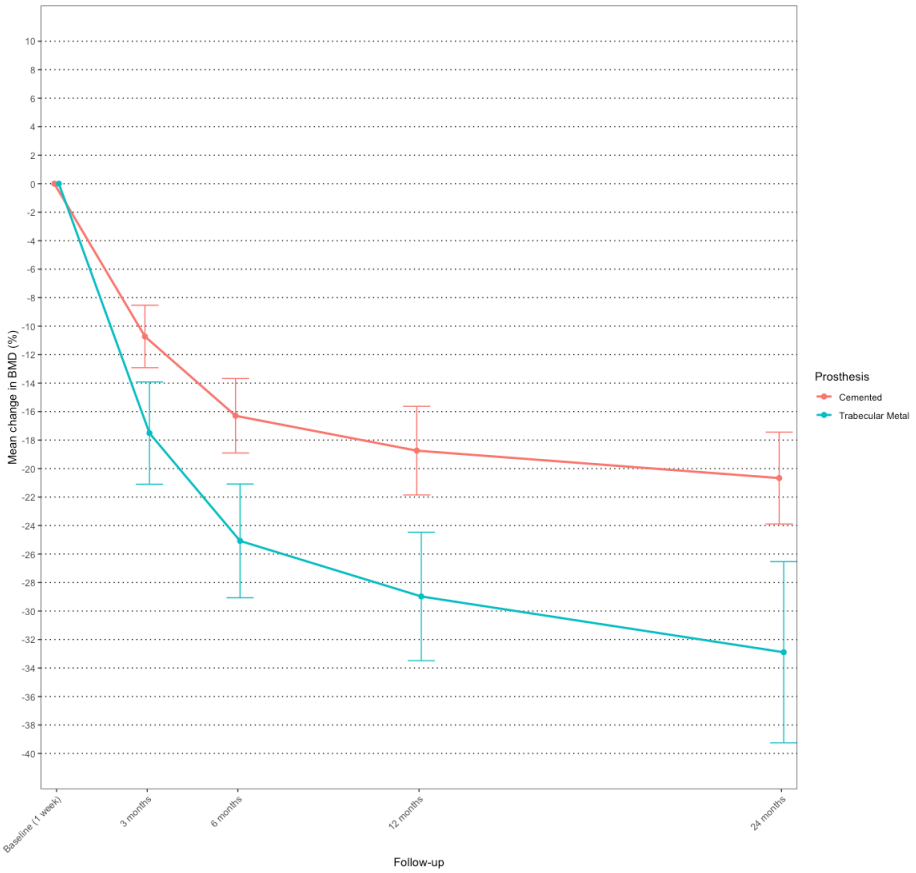

Figure 34: Percentage mean BMD changes in ROI I for femoral implants, whiskers represent 95CI. Manuscript study III [78].

ROI II (posterior part) and ROI III (proximal part)

A continuous decrease from baseline to 24 months postoperative was observed within both groups in both ROI II and ROI III with no statistically significant difference between the two groups (table 4, figure 35).

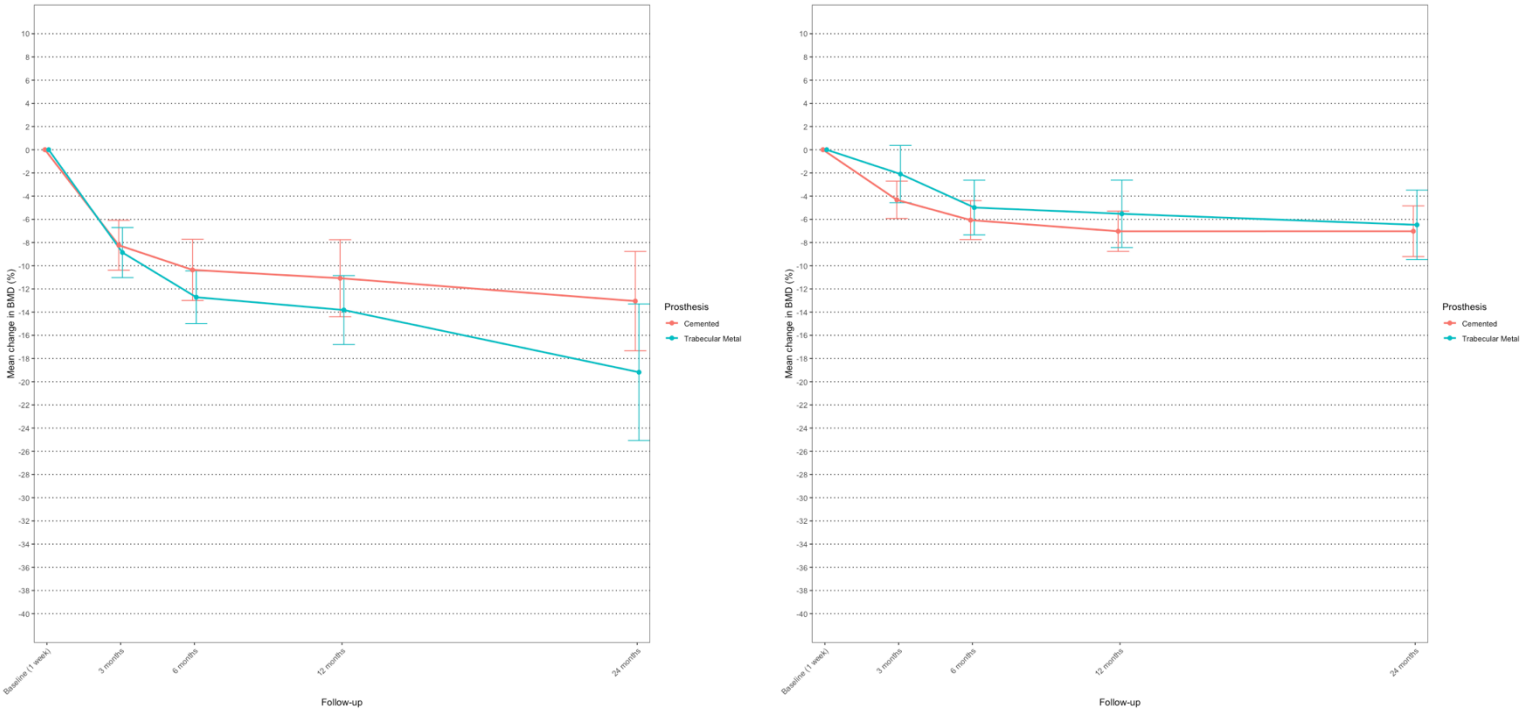

Figure 35: Percentage mean BMD changes in ROI II (left) and III (right) for femoral implants, whiskers represent 95CI. Manuscript study III [78].

Tibial bone mineral density

Validation of tibial DEXA measurements

The same double examinations were used to calculate the PE for the tibial ROIs; ROI I 2.12%, ROI II 2.5% and, ROI III 2.13%.

ROI I (medial part)

The largest decrease was seen from baseline to 3 months postoperative in both groups of which the cemented group demonstrated a decrease of 8.2% and the uncemented group 3.3%. Subsequently, both groups stabilized after a minor increase in BMD. No statistically significant differences were observed between the two groups (table 4, figure 36).

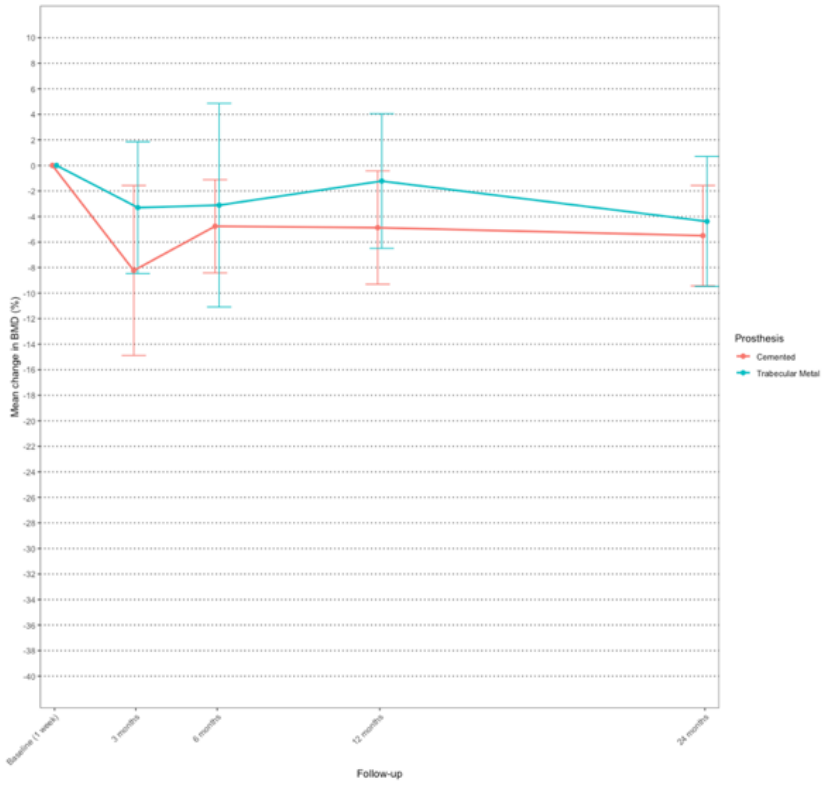

Figure 36: Percentage mean BMD changes in ROI I for tibial implants, whiskers represent 95CI. Manuscript study III [78].

ROI II (lateral part)

The cemented group demonstrated only a minor decrease initially at 3 months (-1.13%) hereafter stabilizing. The uncemented group showed an initially larger decrease of 4.43% at 3 months however increasing to -0.75% at 6 months followed by stabilization. No statistically significant differences were observed between the two groups (table 4, figure 37).

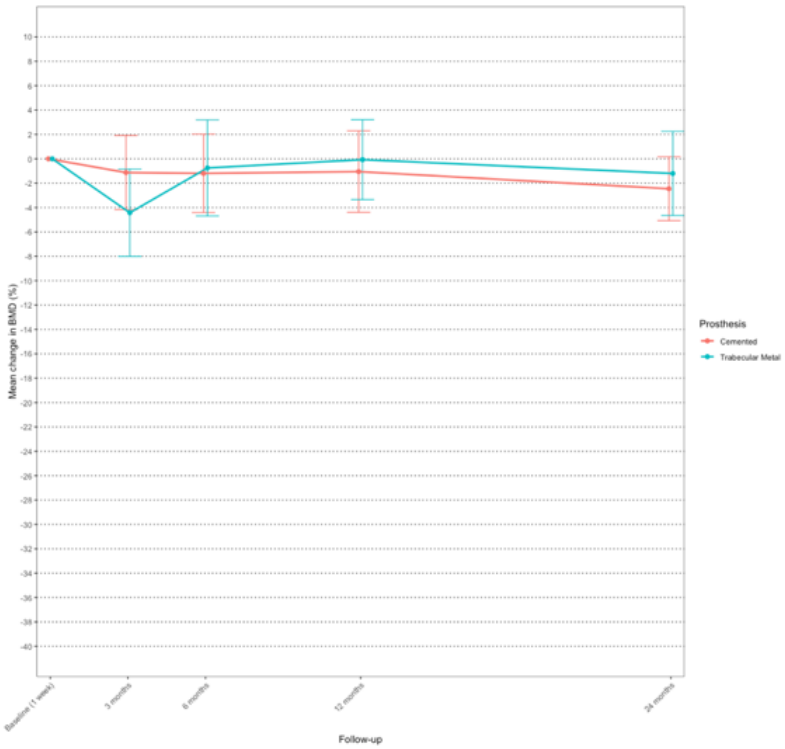

Figure 37: Percentage mean BMD changes in ROI II for tibial implants, whiskers represent 95CI. Manuscript study III [78].

ROI III (distal part)

The cemented group showed a stabile period from baseline to 3 months followed by a decrease of 1.75% from 3 to 6 months and hereafter stabilizing. The uncemented group showed an initial decrease of 1.77% from baseline to 3 months followed by a return to baseline values close to 0 until the end of follow-up. No statistically significant differences were observed between the two groups (table 4, figure 38).

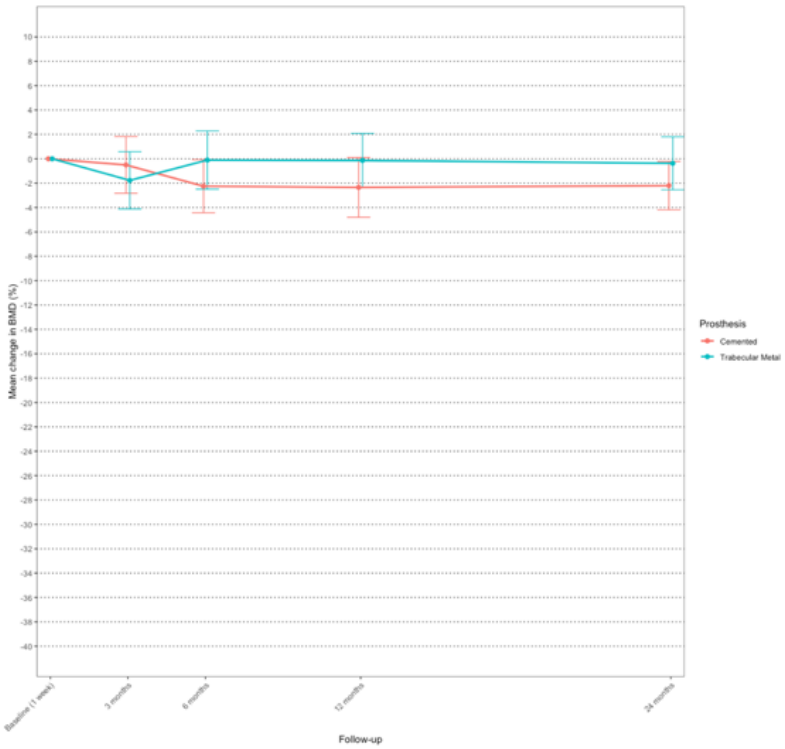

Figure 38: Percentage mean BMD changes in ROI III for tibial implants, whiskers represent 95CI. Manuscript study III [78].

		3 months	P-values	6 months	P-values	12 months	P-values	24 months	P-values	ANOVA	0-24 months
Femur											
ROI I	Cemented	-10.73 (-12.923 to -8.53)	0.029*	-16.29 (-18.91 to -13.68)	0.005*	-18.74 (-21.85 to -15.63)	0.001*	-20.67 (-23.89 to -17.44)	0.004*	0.0016*	<0.001*
	Uncemented	-17.51 (-21.10 to -13.92)		-25.08 (-29.07 to -21.08)		-28.98 (-33.48 to -24.47)		-32.89 (-39.26 to -26.53)		<0.001*	<0.001*
ROI II	Cemented	-8.23 (-10.38 to -6.08)	0.691	-10.36 (-13.00 to -7.72)	0.197	-11.08 (-14.40 to -7.72)	0.104	-13.05 (-17.33 to -8.77)	0.203	0.018*	<0.001*
	Uncemented	-8.86 (-11.02 to -6.70)		-12.72 (-14.99 to -10.44)		-13.82 (-16.79 to -10.85)		-19.18 (-25.07 to -13.30)		0.0115*	<0.001*
ROI III	Cemented	-4.32 (-5.93 to -2.71)	0.153	-6.07 (-7.74 to -4.39)	0.473	-7.03 (-8.76 to -5.30)	0.406	-7.03 (-9.22 to -4.84)	0.776	0.277	<0.001*
	Uncemented	-2.10 (-4.57 to 0.37)		-4.98 (-7.34 to -2.62)		-5.52 (-8.43 to -2.62)		-6.48 (-9.47 to -3.48)		0.466	<0.001*
Tibia											
ROI I	Cemented	-8.23 (-14.89 to -1.58)	0.190	-4.76 (-8.41 to -1.11)	0.205	-4.87 (-9.31 to -0.43)	0.111	-5.50 (-9.42 to -1.57)	0.247	0.518	0.005*
	Uncemented	-3.30 (-8.46 to 1.86)		-3.11 (-6.49 to 4.05)		-1.22 (-6.49 to 4.05)		-4.38 (-9.47 to 0.71)		0.535	0.0958
ROI II	Cemented	-1.13 (-4.17 to 1.92)	0.182	-1.19 (-4.41 to 2.03)	0.867	-1.05 (-4.39 to 2.30)	0.489	-2.45 (-5.08 to 0.17)	0.106	0.984	0.101
	Uncemented	-4.43 (-8.01 to -0.84)		-0.75 (-4.69 to 3.19)		-0.07 (-3.34 to 3.21)		-1.20 (-4.65 to 2.25)		0.768	0.291
ROI III	Cemented	-0.50 (-2.84 to 1.83)	0.203	-2.25 (-4.43 to -0.07)	0.163	-2.35 (-4.79 to 0.09)	0.298	-2.20 (-4.19 to -0.21)	0.883	0.679	0.0234
	Uncemented	-1.77 (-4.12 to 0.58)		-0.10 (-2.49 to 2.28)		-0.14 (-2.35 to 2.08)		-0.37 (-2.54 to 1.80)		0.955	0.5989

Table 4: Percentage mean BMD changes for femoral and tibial implant, manuscript study III [78].

Study IV

CT measurements

Coverage

In the included cohort, a mean coverage of 86% (SD 5.7) of the tibial plateau was observed.

The cemented components demonstrated a coverage of 87.2% (SD 5.2), while the corresponding number was 85% (SD 6.9) in the uncemented components.

The coefficient of determination (R^2) between MTPM and coverage in the entire cohort was 2%, in the cemented group 0.01% and, in the uncemented group 16%, indicating a weak relationship between the two variables (figure 39 – A, B, C).

Rotation

The majority of the components (87%) were positioned in external rotation (mean: 4.6°; SD: 3.2°). Only a few components (n=9/8%) were positioned in internal rotation (mean: 3.6°; SD: 1.9°) and the remaining 5 components were in neutral (figure 39 – D, E, F). For the cemented group (n=82) a mean external rotation of 4.1° (SD 3.0°) was observed with a corresponding value of 5.4° (SD 3.5°) in the uncemented group (n=29).

As with coverage, the coefficient of determination between MTPM and rotation was performed demonstrating an R^2=5% in the entire cohort, R^2=5% in the cemented group, and, R^2=6% in the uncemented group.

Overhang/under coverage

The largest overhang was observed in the posterior medial portion of the component (mean 60.6 mm^2, 95CI: 49.1 to 71.8). Secondly was the overhang in the posterior lateral part (mean 34.3 mm^2, 95CI 25.6 to 42.9), followed by the anterior lateral part (mean 31.4 mm^2, 95CI 24.3 to 38.6) and lastly, the least overhang was observed in the anterior medial section (mean 15.2 mm^2, 95CI 10.8 to 19.6).

The posterior medial part had the largest mean under-coverage area (207.6 mm^2, 95CI 189.7 to 225.4) although very similar to that of the posterior-lateral part with a mean under-coverage of 200.7 mm^2 (95CI 181.8 to 219.7) (table 5).

The intra- and inter-tester reliability of total coverage were ICC=0.98 and ICC=0.99 respectively, and for rotation ICC=0.95 and ICC=0.97 respectively.

In order to see any systematic discrepancies in the investigator's measures of coverage and rotation and between the investigator and the radiologist, Bland Altman plots were created (figure 40 A, B, C, D).

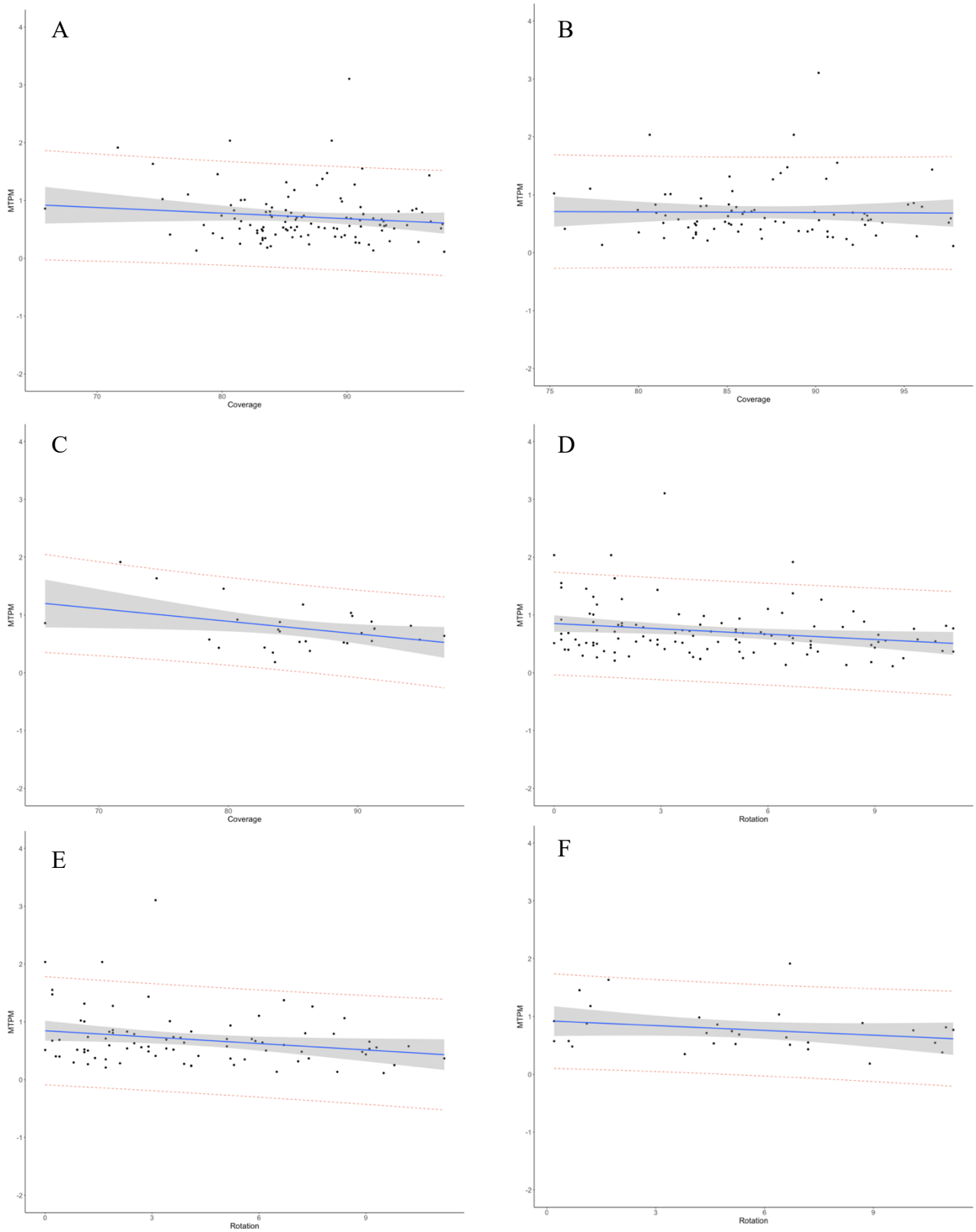

Figure 39: Linear regression models. A) Coverage and MTPM for total cohort. B) Coverage and MTPM for cemented implants. C) Coverage and MTPM for uncemented implants. D) Rotation and MTPM for total cohort. E) Rotation and MTPM for cemented components and F) Rotation and MTPM for uncemented implants. Manuscript study IV [80].

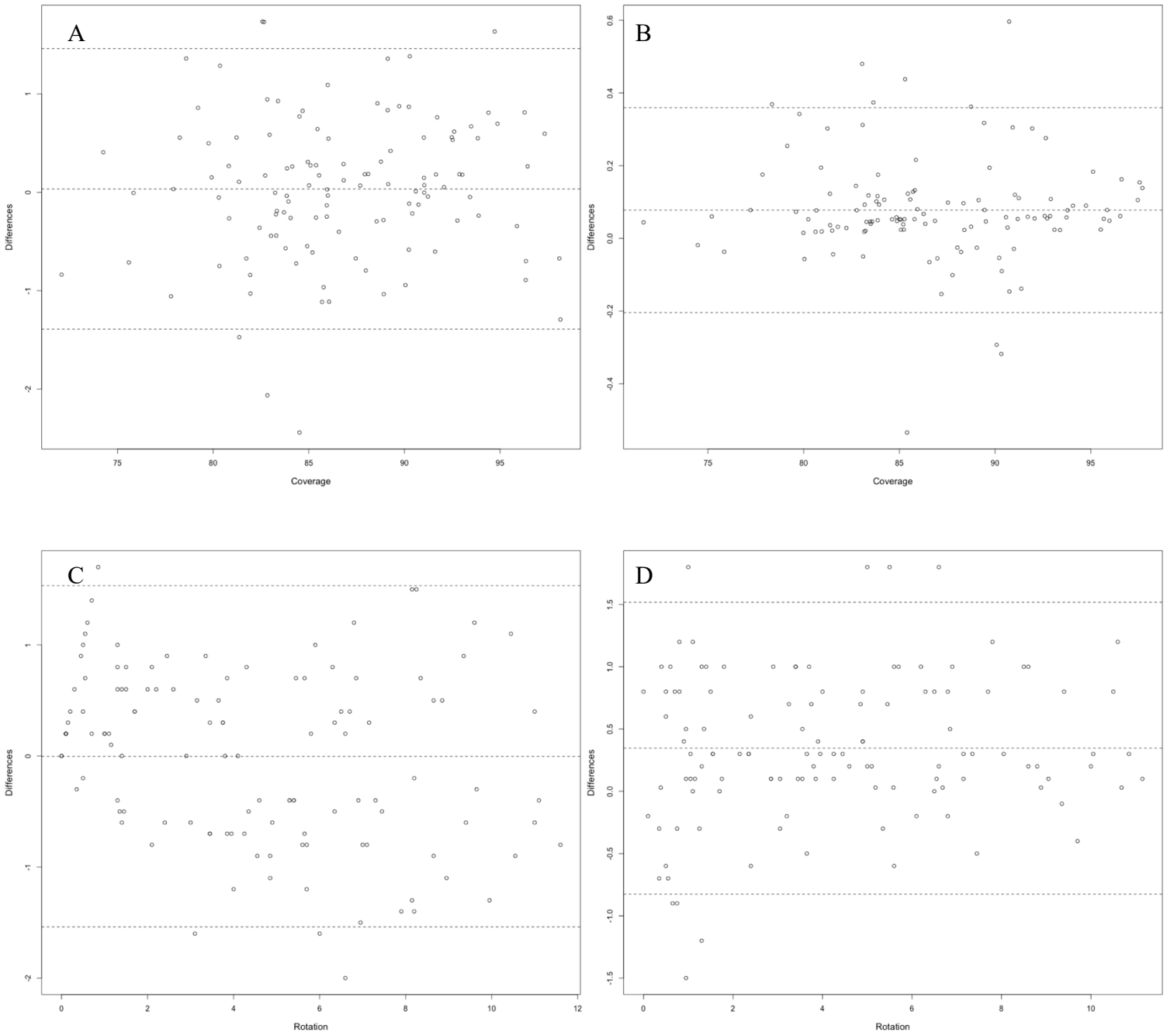

Figure 40: Bland Altman plots visualizing A) Intertester coverage. B) Intratester coverage. C) Intertester rotation, and D) Intratester rotation. Manuscript study IV [80].

	Investigator Mean (Range)	Radiologist Mean (Range)
Overhang (mm^2)		
AM (n=47)	15.2 (1.10 to 63.3)	15.4 (0.9 to 65.6)
AL (n=55)	31.4 (1.8 to 151.4)	31.5 (1.8 to 151.4)
PM (n= 84)	60.6 (1.7 to 249.5)	60.7 (1.2 to 249.2)
PL (n=54)	34.25 (2.6 to 134.7)	34.4 (2.7 to 132.1)
Under coverage (mm^2)		
AM (n=106)	82.1 (1.7 to 294.6)	82.5 (1 to 296.6)
AL (n=105)	80.9 (2.1 to 211.2)	81.8 (2.1 to 209.6)
PM (n=119)	207.6 (18.9 to 504.9)	210.2 (18.4 to 503.8)
PL (n=118)	200.7 (42.7 to 511.2)	200.8 (39.1 to 506.3)
Rotation (°)		
Inward	4.2 (1 to 7.5) (n=9)	4.6 (1.2 to 8.9) (n=14)
Outward	4.6 (0.2 to 11.2) (n=97)	5.1 (0.2 to 12) (n=91)
Neutral	0 (n=5)	0 (n=6)

Table 5: Overview of overhang, under coverage, and rotation measurements from the investigator and the radiologist.

Discussion

The studies included in this thesis aimed to evaluate the relatively new Persona® TKA implants. We measured migration of the hybrid, fully cemented and uncemented trabecular metal fixated femoral and an asymmetrical tibial implant. To our knowledge, we are the first ones to publish results on the uncemented femoral implant as well as uncemented tibial implants measured with RSA. Additionally, this thesis is also the first to present data on the adaptive remodeling of the bone related to the Persona® TKA implants measured with DEXA. Lastly, the positioning of the tibial implant on the tibial plateau was evaluated with CT scans, and also to our knowledge the first results contributing evidence regarding the positioning of the tibial implant. Existing knowledge on the mechanical function of the Persona® TKA implants is sparse hence contributing is of great importance.

Migration of the femoral and tibial components (study I and II)

Migration is micro-movements of the components expressed as MTPM and segmental motion. Migration measured with RSA can be used to assess the risk of aseptic loosening and identify which implants with high or continuous migration that have increased risk of revision surgery [32, 33, 39]. The Boneloc failure in 1991 led to a large scaled disaster and revision surgery in thousands of patients [86]. This massive disaster occurred due to the lack of data testing the migration of the product before implementing Boneloc in large scale clinical settings.

If the phased introduction presented by Malchau et al. [38] had been followed the Boneloc disaster might have been avoided or reduced. Therefore, the migration of the relatively new Persona® prosthesis has been evaluated with MBRSA [87, 88].

Migration of the femoral and tibial implants was evaluated with MBRSA in study I, II and IV.

The most pronounced amount of migration was observed within the first 3 – 6 months postoperative followed by a stabilization in all 3 studies.

Kärrholm et al. [89] demonstrated that the prosthetic design, surface finish, and method of fixation had an impact on early migration. Only a few studies have evaluated the implant survival of the femoral component depending on the type of fixation (cemented vs. uncemented) of which none have demonstrated a difference between the fixation types [49-51, 90, 91].

Evidence comparing and/or evaluating femoral components with MBRSA or RSA remains sparse, mostly due to the low risk of aseptic loosening of the femoral component and the technical differences with applying the conventional RSA technique on measurements of the femoral implant migration. Previous studies have reported migration between 0.72mm to 0.88 mm after 2 years for cemented femoral components [49, 51]. Henricsson et al. [90] evaluated long-term migration with 10 years of follow-up and found a median of 0.85 mm and 1.14 mm at the end of follow-up for cemented and uncemented femoral components respectively. Additionally, Henricsson et al. [90] reported a yearly continuous migration from 2 to 10 years of 0.09 to 0.1mm. In study I, a mean MTPM of the uncemented femoral component of 0.96 mm was reported after 2 years. In study II we found a mean MTPM of 0.834mm in the uncemented group and 0.513mm in the cemented group at 2 years and this was a statistically significant difference. Our results are in concordance with migration reported in previous studies and therefore, the observed difference in migration is not considered to have a clinical impact on the risk of aseptic loosening. Furthermore, the migration of the uncemented implants stabilized after the first 6 months, but on a higher level than the cemented implants.

Park et al. [92] suggest that MTMP less than 0.09 to 0.1 yearly regardless of fixation mode is associated with a good outcome. In study I we found a migration of 0.04 mm between 12 to 24 months of follow-up in the uncemented femoral components. Correspondingly migration of 0.019mm and 0.049 mm was found in study II among cemented and uncemented components indicating a good outcome for the patients in both studies could be expected.

Several studies have compared the fixation type of the tibial component, the first studies evaluating uncemented tibial implants found a high and continues migration in uncemented tibial implants [40-42, 84, 93]. More recent studies indicate however a high initial migration but with a stabilization and without significant differences between groups [43-47]. Similar patterns of migration in the fixation types to that of the femoral component have also been demonstrated in the tibial component. Previous studies have demonstrated a larger migration of uncemented femoral implants ranging from 0.84mm to 1.84mm after 2 years than in cemented implants ranging from 0.43mm to up to 1.0mm after 2 years [93, 94]. Laende et al. [94] pooled RSA data and presented mean migration at 2 years for three different types of cemented tibial prostheses (mean 0.44mm, 0.45mm, and 0.62mm), and five different types of uncemented tibial implants (mean 0.84mm, 0.86mm, 0.94mm, 1.13mm and 1.84mm).

In study I the mean MTPM for the cemented tibial implant after 2 years was 0.69mm, and in study II the corresponding values for cemented and uncemented components were 0.72mm and 0.78mm. respectively. We found no statistically significant differences between the groups in study II. The RSA measurements for the cemented component in study I and II and the uncemented component in study II are in concordance with previous studies evaluating tibial components with RSA [94-98]. A newly published RCT study by Christensson et al. [87] evaluated the migration of the cemented femoral and tibial Persona® implants when comparing two different polyethylene inserts. The migration data found by Christensson et al. [87] demonstrate similar values for the cemented tibial and femoral implants as to those presented in study I and II. Additionally, a recent study by Koster et al. [88] similarly found no difference in migration when comparing an asymmetrical Persona PS with a symmetrical NexGen LPS implant.

Ryd et al. [39] concluded that migration of the tibial component of ≥0.2mm from 1 to 2 years postoperatively was a predictor of aseptic loosening of the implant. In neither study I or II the implants demonstrated a mean migration ≥0.2mm indicating a low risk of aseptic loosening.
In study I, a mean migration from 1 to 2 years postoperatively of 0.049mm was observed in the cemented implants, and correspondingly 0.001mm and 0.013mm in the cemented and uncemented implants in study II respectively.

Additionally, a large systematic review and meta-analysis of 21,000 TKA surgeries by Pijls et al. [95] found an association between high migration within the first year postoperative and risk of revision after 5 years. Migration <0.54mm was suggested as acceptable whereas migration >1.6 mm. was considered unacceptable. Components with migration in between the threshold values were considered at risk of aseptic loosening after five years [95]. Both study I and II demonstrated values "at risk" with a mean migration at 1 year postoperatively of 0.63 mm in study I and 0.718mm and 0.789mm in the cemented vs. uncemented implants in study II.

BMD of distal femur and proximal tibia (study I and III)

Low BMD is correlated with the breaking strength of the bone. Therefore, patients, with low BMD are at higher risk of experiencing a fracture. A decrease in BMD is commonly observed postoperatively in TKA patients. For that reason, studies investigating BMD around orthopedic implants are needed to assess the risk of periprosthetic fractures.

Changes in BMD can be influenced by a variety of factors such as the prosthetic design and attachment. Different surfaces and coatings are utilized to promote in-growth in both cemented and uncemented components. The uncemented prosthesis is dependent on external factors to enhance the in-growth as the component is press-fitted into the bone [55, 99, 100].

Previous studies demonstrated a decrease in BMD between 15 to 29% 2 years postoperative related to the tibial components, with the majority of the decrease observed in the medial proximal tibial plateau [35, 60-62]. Generally, the decrease in BMD related to the tibial component is caused by stress-shielding [101, 102]. In study I, the largest decrease (8.2%) was seen in the medial part of the bone adjacent to the cemented tibial component. Similarly, the main decrease in BMD was also observed in the medial part in study III. The BMD decrease was 4.38% and 5.5% in the cemented and uncemented components respectively. We did not find a statistically significant difference between the uncemented and cemented components.

The decrease in BMD found in study I and III are remarkably lower when compared with most other studies [35, 60-62, 101, 102]. The pronounced differences between our results and those found in previous studies could possibly be explained by differences in the age of the included populations as people receiving a TKA today are younger and hence assumed to have a higher functional level prior to surgery. Furthermore, the postoperative TKA regime has undergone huge changes from hospitalization of at least 1 week priorly to being discharged to the latest second day postoperative nowadays. Additionally, rehabilitation has changed from passive exercises to focusing on active mobilization as the main aspect.

In the bone adjacent to the femoral component the majority of the BMD decline has been demonstrated to be in the anterior part of the distal femur [52-57]. At 1 year postoperative a decline of 41% and 44% was seen in two studies [53, 55] whereas a decline between 36-41% was demonstrated 2 years postoperative in other studies [52, 54, 56, 62]. Clinically, a decrease in BMD

in the distal femur of this amount is considered important, because there is a well-known relation between BMD and the breaking strength of bone, and furthermore most of the periprosthetic fractures after TKA supracondylar [48, 54, 56, 67, 69, 72, 103, 104].

In accordance with previous studies, the largest decrease in BMD was observed in the anterior part of the distal femur in both study I and III. In study I a decrease of 27% was observed in the uncemented femoral components and in study III a decrease of 21% and 33% in the cemented and uncemented components was observed respectively. A statistically significant difference in BMD decrease was observed between cemented and uncemented femoral components in study III.
A possible explanation for the difference in BMD decrease observed between cemented and uncemented femoral components could be that the surface of the uncemented component facilitates the dismantling of the adjacent bone.
As the largest decline in BMD was observed in the uncemented group we speculate that the uncemented group could be at a greater risk of experiencing periprosthetic supracondylar fractures.
We did not observe any supracondylar fractures in either study I or III. However, longer follow-up is recommended as the event of fractures might occur later than 2 years postoperative as one previous study demonstrated incidence of supracondular femoral fractures of 7 years after primary TKA surgery [105]

Our results demonstrated a lower decline in the decrease of BMD than those found in previous studies. A potential factor could similarly as previously described be related to a decreasing age in the population receiving a TKA as well as changes in the surgical regimes.
There is no consensus describing a potentially harmful threshold of how much a BMD can decrease before the bone reaches its breaking point.

We did not observe any significant differences in BMD of the ankle when comparing the surgical limb with the non-surgical limb after 2 years in either study I or III. Therefore, the changes in BMD observed in the distal femur and proximal tibia are not considered to be related to age related bone loss or a general immobilization, but rather the result of the surgical trauma and subsequently foreign body reaction and stress-shielding.

Positioning of the tibial component (study IV)

Positioning of the tibial component is considered of great importance for the functional outcomes of TKA surgeries. Persistent postoperative pain is a complaint in approximately 20% of TKA patients [20]. Internal rotation of the tibial component as well as coverage of the tibial plateau are considered factors in the mechanisms causing persistent postoperative pain [21, 23, 106-108].

There is common consent in the literature about the negative impact of positioning the component in an internal rotation. However, recommended values determining a "safe zone" for positioning the component do not exist to our knowledge. Panni et al. [109] found that an internal rotation >10° increased the risk of poor outcomes, Bell et al. [110] found that internal rotation >5.8° was related to pain and Klasan et al. [111] suggested a "safe zone" between 7° internal and 3° external rotation. A study by Kim et al. [112] recommended an external rotation of 2° to 5° as preferable as an external rotation of 2° increases the probability of failure of the tibial component. Lastly, Maderbacher et al. [113] found that 6° external rotation is most optimal to restore tibial rotation.
Company guidelines for the Persona® recommend a rotation within 5° from the line passing through 1/3 medial tuberosity to PCL insertion [114].

Study IV evaluated the positioning of the asymmetrical tibial component in cemented and uncemented patients. The majority of the patients (87%) in study IV were positioned in an external rotation with a mean rotation of 4.6°. A total of 9 patients (8%) were placed in an internal rotation with a mean of 3.6° and the remaining 5 patients were neutral. Our findings are within the recommendations of the company as well as the suggested margin by Kim et al. [112]. However, our results are marginally exceeding the external rotation recommended by Klasan et al. [111] but only by 1.6°.

The mean coverage in our study is 86% (uncemented: 85% and cemented: 87%), which suits the range from previous studies [111, 115, 116]. An improvement in implant survival and a reduction in the incidence of subsidence are both shown to occur when coverage is greater than 75% in prior studies [106, 117-119]. We found no relationship between MTPM and coverage or rotation, and our study was not powered to evaluate a possible effect on postoperative pain of the placement of the tibial implant.

Limitation

A major limitation of our study was that the baseline RSA measurements were performed with a mean of 7 days postoperative. As it is known that migration is highest initially, we must assume that we have missed some migration data between surgery and our baseline measurement. However, the average migration of our cemented implants was quite similar to what has been reported in previous studies measuring migration of the cemented Persona® TKA [87, 88].

Baseline DEXA measurements were performed at the same time as the RSA measurements and therefore exposed to the same delay of the baseline data, hence we must acknowledge the lack of data on possible bone remodeling from surgery to baseline. Therefore, the loss reported in study I and III might have been slightly underestimated. It is crucial to keep in mind that local disease-related alterations may have increased the preoperative BMD measurements when interpreting results relating to a decline in BMD after TKA surgery [73]. As a result, the decline observed postoperatively may not actually reflect a low BMD brought on by the procedure, but could to some extend represent a return to normal density of the periprosthetic bone.

As the purpose of the studies included in this thesis was not to evaluate functional outcomes, we did not conduct a power analysis prior to enrolment. Study I and II include additional results on KSS and OKS besides mechanical measurements of the implants, however, the results might be biased due to being underpowered.

Conclusion

The Persona® TKA with hybrid, cemented and uncemented fixation have been evaluated throughout this thesis and shown to be secure implants with respect to implant migration and adaptive remodeling pattern of the bone closely related to the implants. The patterns for migration showed, for all fixation types, and both for the femoral and tibial implants, that the highest increase occurred within the first 3-6 months followed by stabilization with acceptable values indicating that it is an implant with a low risk of aseptic loosening. The uncemented femoral components showed a statistically significant higher migration than the cemented implants, however, the migration was still on an acceptable level and showed a migratory pattern with stabilization, and thus we do not believe that the difference between the cemented and uncemented components is of any clinical significance. We did not find any statistical differences in migration between fixation types of the tibial implant and all values were acceptable.

The asymmetrical design of the tibial implants demonstrated good coverage as well as an optimal rotational alignment of the implants. We found no influence of the rotational alignment or coverage on the tibial component migration.

Based on our results related to implant migration the risk of aseptic loosening was found to be low and therefore these implants can be used in clinical settings. Furthermore, the rotational alignment and coverage of the implants demonstrated an optimal positioning which additionally supports the argument for using these implants in clinical settings.

We found a difference in the adaptive bone remodeling related to the femoral components with a higher degree of bone loss (33% vs. 21% in ROI I) in the uncemented implants which might indicate a higher risk of later implant-related supracondylar fractures. Similarly, the adaptive bone remodeling around the tibial implants was observed in the cemented implants (8.2% vs. 3.3% in ROI I) although not reaching statistical significance. Further research with longer follow-up is needed to evaluate the possible increased risk of supracondylar fractures.

Perspectivation

Our results strongly indicate that the Persona® TKA implants demonstrate acceptable mechanical results suitable for use in clinical settings. Acceptable mechanical results are essential prior to clinical use, however, mechanical results do not implicit good functional results and high patient satisfaction. The asymmetrical Persona® tibial implant was developed with the aim of minimizing persistent postoperative pain thought to be caused by malrotation of the implant. Although this thesis confirms a good positioning of the tibial implants, the aim was not to evaluate functional outcomes and pain-related patient dissatisfaction. Worldwide the populational demography is changing which leads to an increase in the number of TKA surgeries. Additionally, a tendency of a different lifestyle as well as demands to quality of life have led to a growing number of TKA surgeries in the younger generation. Therefore, both the mechanical results but also excellent functional outcomes are required when implementing TKA prosthesis.

Further research should aim to evaluate patient-reported outcomes in a larger study population as the functionality of TKA surgery is of great importance to regaining and maintaining an active life. It is of great importance to investigate if the Persona® TKA will perform better with regards to a reduction in the group of patients who are not satisfied with their TKA surgery because of remaining pain postoperatively.

Lastly, follow-up of the patient cohorts in this present thesis is mandatory to evaluate the long-term implant migration and adaptive bone remodeling to secure that the implants are also a secure TKA option long-term.

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Appendix

Study I

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Bone remodeling and implant migration of uncemented femoral and cemented asymmetrical tibial components in total knee arthroplasty - DXA and RSA evaluation with 2-year follow up

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Abstract

Background: Aseptic loosening is one of the major reasons for late revision in total knee arthroplasty (TKA). The risk of aseptic loosening can be detected using radiostereometric analysis (RSA), whereby micromovements (migration) can be measured, and thus RSA is recommended in the phased introduction of orthopedic implants. Decrease in bone mineral density (BMD), as measured by dual-energy x ray absorptiometry (DXA), is related to the breaking strength of the bone, which is measured concurrently by RSA. The aim of the study was to evaluate bone remodeling and implant migration with cemented asymmetrical tibial and uncemented femoral components after TKA with a follow up period of 2 years.

Methods: This was a prospective longitudinal cohort study of 29 patients (number of female/male patients 17/12, mean age 65.2 years), received a hybrid Persona® TKA (Zimmer Biomet, Warsaw, IN, USA) consisting of a cemented tibial, an all-polyethylene patella, and uncemented trabecular metal femoral components. Follow up: preoperative, 1 week, and 3, 6, 12 and 24 months after surgery, and double examinations for RSA and DXA were performed at 12 months. RSA results were presented as maximal total point of motion (MTPM) and segmental motion (translation and rotation), and DXA results were presented as changes in BMD in different regions of interest (ROI).

Results: MTPM at 3, 6, 12, and 24 months was 0.65 mm, 0.84 mm, 0.92 mm, and 0.96 mm for the femoral component and 0.54 mm, 0.60 mm, 0.64 mm, and 0.68 mm, respectively, for the tibial component. The highest MTPM occurred within the first 3 months. Afterwards most of the curves flattened and stabilized. Between 12 and 24 months after surgery, 16% of femoral components had migrated by more than 0.10 mm and 15% of tibial components had migrated by more than 0.2 mm. Percentage change in BMD in each ROI for distal femur was as follows: ROI I 26.7%, ROI II 9.2% and ROI III 3.3%. BMD and at the proximal tibia: ROI I 8.2%, ROI II 8.6% and ROI III

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7.0% after 2 years compared with 1 week postoperative results. There was no significant correlation between maximal percentwise change in BMD and MTPM after 2 years.

Conclusion: Migration patterns and changes in BMD related to femoral components after TKA in our study correspond well with previous studies; we observed marginally greater migration with the tibial component.

Keywords: Total knee replacement, Total knee arthroplasty, Persona®, MBRSA, DXA

Introduction

Total knee arthroplasty (TKA) is, in general, a very successful treatment for patients with symptomatic osteoarthritis (OA), and register studies indicate implant survival of more than 90% after 10 years [1, 2]. One of the major causes of long-term revision is aseptic loosening [1, 3].

The risk of aseptic loosening can be detected by radiostereometric analysis (RSA), whereby micromovements, described as migration, can be measured, and thus RSA is recommended as a standard in the phased introduction of new orthopedic implants [4] with 2-year follow up [5]. Migration is seen with both cemented and uncemented implants but most implants stabilize during the first postoperative year; however, some implants migrate continuously, and this incurs high risk of subsequent aseptic loosening and implant revision [6, 7]. With tantalum markers attached to the polyethylene insert and bone, small micromovements of the implant can be detected using marker-based RSA [8]. Model-based RSA (MBRSA), used in this study, has been developed from marker-based RSA; the precision error of this technique has been found to be acceptable and does not require tantalum markers attached to the polyethylene insert [9, 10]. RSA is highly accurate and can be performed in small study populations [6].

Dual-energy x ray absorptiometry (DXA) can be used to measure changes in bone mineral density (BMD) after TKA [11, 12]; a significant decrease in BMD is often seen after TKA in both the proximal tibia [13–17] and the distal femur [18]. Since BMD "is strongly related to the breaking strength of bone" [19–21], at least for theoretical reasons, we believe that change in BMD where an implant is anchored is another important and relevant parameter in the early phase when introducing a new implant for clinical use, and maybe correlation between migration and BMD can be detected.

The aim of this study was to evaluate implant migration using MBRSA and bone remodeling using DXA, and to assess correlation between implant migration and bone remodeling in patients with cemented asymmet-rical tibial and uncemented femoral TKA components over a follow up period of 2 years.

Material and methods

Patients

We performed a prospective longitudinal cohort study of patients (Fig. 1) (demographics are shown in Table 1) who underwent primary hybrid TKA for treatment of OA at Gentofte Hospital between 21 March and 12 October 2017. Patients between the ages of 40 and 70 years, diagnosed with OA and scheduled for primary TKA were included in the study after providing informed con-sent. Patients with diseases that could influence bone metabolism, patients who did not comprehend the given information, and patients who declined to participate were excluded. The hybrid Persona® (Zimmer Biomet, Warsaw, IN, USA) TKA implant consists of a cemented asymmetrical tibial, uncemented trabecular metal (TM) femoral, cruciate-retaining (CR) polyethylene insert and cemented all-polyethylene patella components. All surgery was performed by three experienced knee surgeons following guidelines provided by the manufacturer.

We included 31 patients in the study; 29 patients were available for follow up as 1 patient declined to participate in the study after surgery, 1 patient had a change of tibial insert to an ultra-congruent (UC) during initial surgery, and 1 patient did not attend to the preoperative appointment (but are still included due to 1 week RSA are used as a baseline for further analysis) (Fig. 1). No revision surgery was performed.

RSA

During surgery, at least six tantalum beads (0.8 mm, Tilly Medical Products, Lund, Sweden) were placed in both the proximal tibia, the polyethylene insert and the distal femur, using an inserter that positions and inserts markers in bone one at a time (Wennbergs Finmark AB, Gunnilse, Sweden). The same assistant positioned the beads in each procedure to minimize variation and we aimed for the widest possible non-linear spread between the beads. The tantalum markers placed in the polyethylene insert were not used for the analyses in this study because MBRSA was used to evaluate migration and segmental motion.

RSA performed 1 week after surgery (mean 7.8, range 6–13 days) was used as the baseline for RSA measurements and follow up examinations were performed at 3, 6, 12, and 24 months after surgery. RSA was performed with the patient in a standardized supine position, with the knee placed in a biplane plexiglass calibration cage (Calibration cage 21; Tilly Medical Products, Lund, Sweden). Two moveable ceiling-fixed x ray tubes (Arcoma Precision T3, Siemens, 0.7mm AI/75 kV, filtration 1.5 mm) were positioned at a 90° angle to each

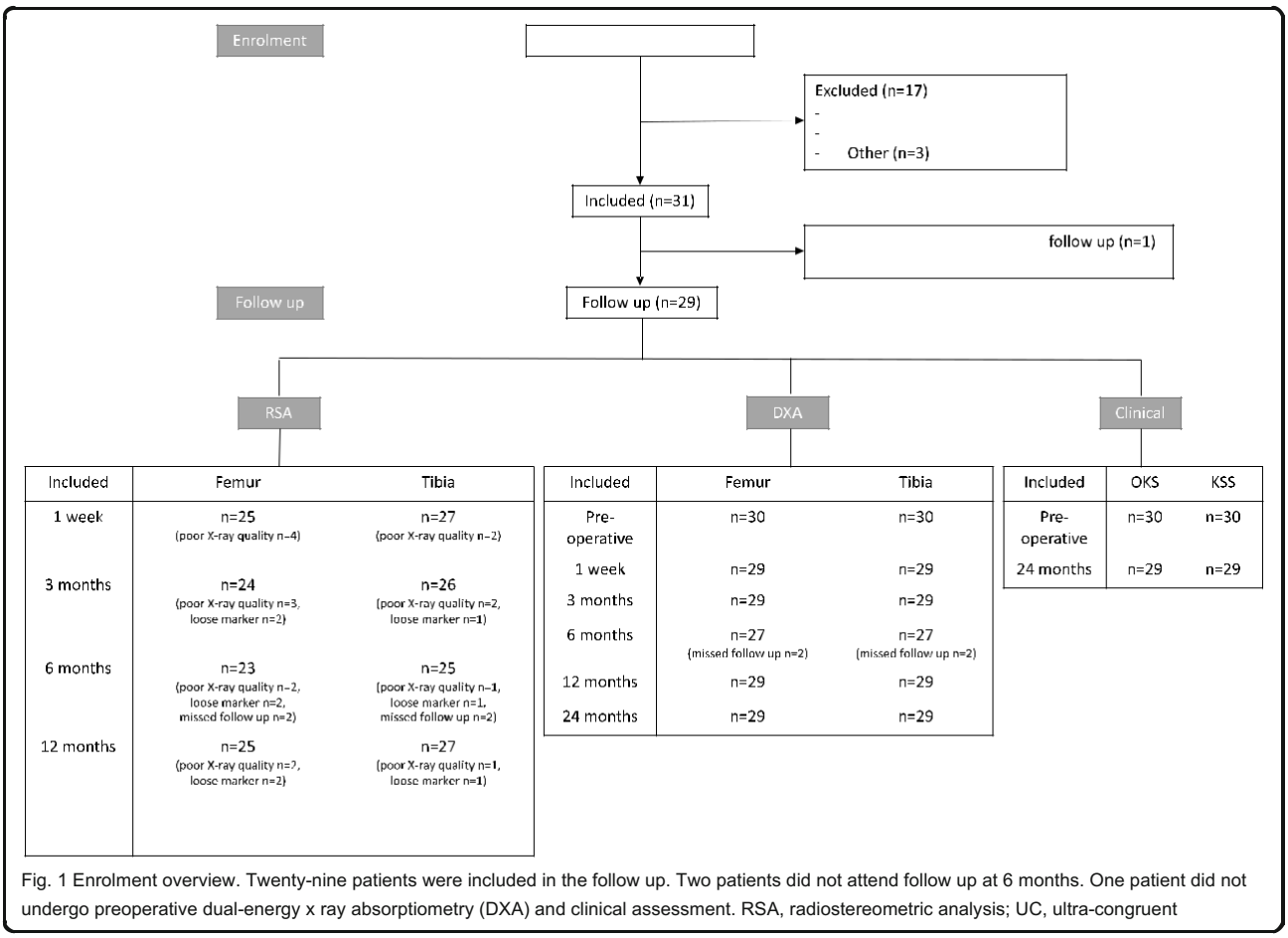

Fig. 1 Enrolment overview. Twenty-nine patients were included in the follow up. Two patients did not attend follow up at 6 months. One patient did not undergo preoperative dual-energy x ray absorptiometry (DXA) and clinical assessment. RSA, radiostereometric analysis; UC, ultra-congruent

other, one positioned for the anterior-posterior projec-tion and the other for the medial-lateral projection. Both tubes were placed 100 cm from the x ray detectors in moveable cassettes, and intensity was set at 50 kV and 25 mA seconds (mAs). The radiographic images were stored in digital imaging and communication in medi-cine (DICOM) format with a resolution of 10 pixels per millimeter, in the picture archiving and communication system (PACS). All examinations were performed by the same two researchers.

RSA analysis (Fig. 2) was performed using model-based software [22, 23] (Model-based RSA 4.1, 2003–2014 RSAcore Department of orthopedics Leiden University Medical Center) in cooperation with the department of orthopedics, Skane University Hospital in Lund, Sweden. Computer-aided design (CAD) [23] models were delivered from Leiden (RSAcore Department of orthopedics Leiden University Medical Center) based on prosthesis design information from the company.

The distribution of tantalum markers is expressed by the condition number (CN), whereas mean error (ME) is an expression of the stability of the tantalum markers; both CN and ME are calculated by the analysis software. We were aiming for a low CN, which indicates a non-linear distribution with wide dissemination of the markers. The upper limits for CN and ME were set at 150 and 0.35 mm, respectively, according to guidelines [24]. Migration is presented as maximal total point of motion (MTPM), which represents the point of max-imum motion and is highly sensitive for loose markers (tantalum beads attached to the bone). Segmental mo-tion is expressed as translation along the X (medial-lat-eral), Y (proximal-distal) and Z (anterior-posterior) axes and rotation X (flexion-extension), Y (internal-external) and Z (valgus-varus).

Double RSA radiographic images (n = 22) were obtained at the 12-month follow up. Patients were requested to stand up between each examination and were positioned again after 5 min in the aforementioned supine position and additional RSA radiographic images were obtained. We evaluated the measurement precision for RSA. Precision was defined as the standard deviation of the difference (SD_{diff}) and precision error was expressed as 1.96 x SD_{diff} [24].

Table 1 Demographic overview

	All (n = 29)	Female (n = 17)	Male (n = 12)
Mean age at surgery in years (range)	65.1 (52.8–70)	63.8 (52.8–70)	67.1 (53.3–69.7)
Weight in kg (range)	85.4 (58–120)	81.6 (58–114)	92 (75–120)
BMI (range)	29.2 (18.5–41.5)	29.1 (18.5–38)	30 (23.2–41.5)
Smoking			
Never:	15	9	6
Current:	4	2	2
Former:	10	6	4
Anesthesia			
General:	10	6	4
Spinal:	19	11	8
Polyethylene inserts in mean mm (range)	12 (10–16)	12 (10–14)	12 (10–16)
Patella size			
32:	7	6	1
35:	17	11	6
38:	5	–	5
Femur component size			
5:	2	1	1
6:	3	3	–
7:	5	4	1
8:	6	4	2
9:	6	5	1
10:	2	–	2
11:	5	–	5
*25 Standard and 4 narrow components			
Tibia component size			
D:	5	5	–
E:	8	7	1
F:	7	5	2
G:	7	–	7
H:	2	–	2

DXA

DXA was performed 1 week postoperatively (mean 7.8, range 6–13 days), and after 3, 6, 12, and 24 months. The distal femur in the affected limb was scanned in the sagittal plane, with the patient positioned in the lateral decubitus position, with the affected knee placed nearest to the examination table and in slight flexion, to obtain a true lateral projection. The proximal tibia on the affected limb was scanned in the anterior-posterior plane, with the patient placed in the supine position with the knee fully extended and the lower limb slightly rotated in-ward, to avoid superimposition of the fibula and tibia.

DXA was performed by two experienced technicians using a Norland XR-46 bone densitometer (Norland Corp., Fort Atkinson, WI, USA). The proximal tibia and distal femur were scanned using customized software for research with a pixel size of 0.5 × 0.5 mm and a speed of 45 mm/sec.

Both femoral and tibial DXA scans were analyzed by creating three regions of interest (ROI) on the computerized scan plots (Fig. 3A and B) for measurement of BMD.

Double DXA scans (n = 16) were obtained at the 12-month follow up. Patients were requested to stand up between each examination and were positioned again after 5 min using the aforementioned positioning and then rescanned. The precision error of the BMD measurements in the various ROI of the proximal tibia and the distal femur was calculated from the double measurements and expressed as the mean coefficient of variation (CV) (CV = (standard deviation (SD)/mean) × 100%).

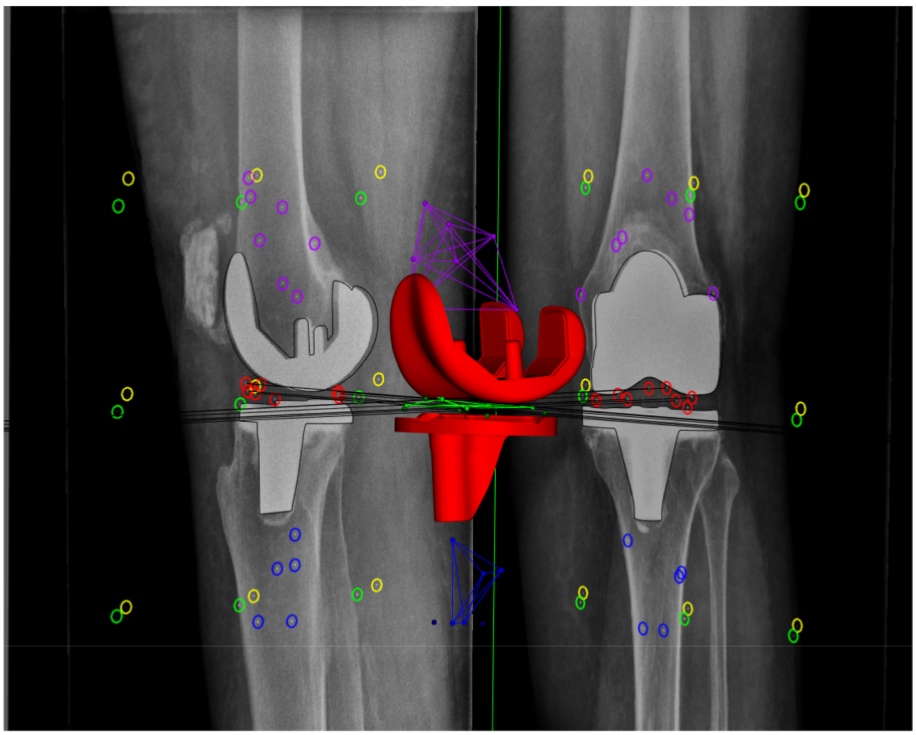

Fig. 2 Radiostereometric analysis (RSA) images with computer-aided design (CAD) model during analyses

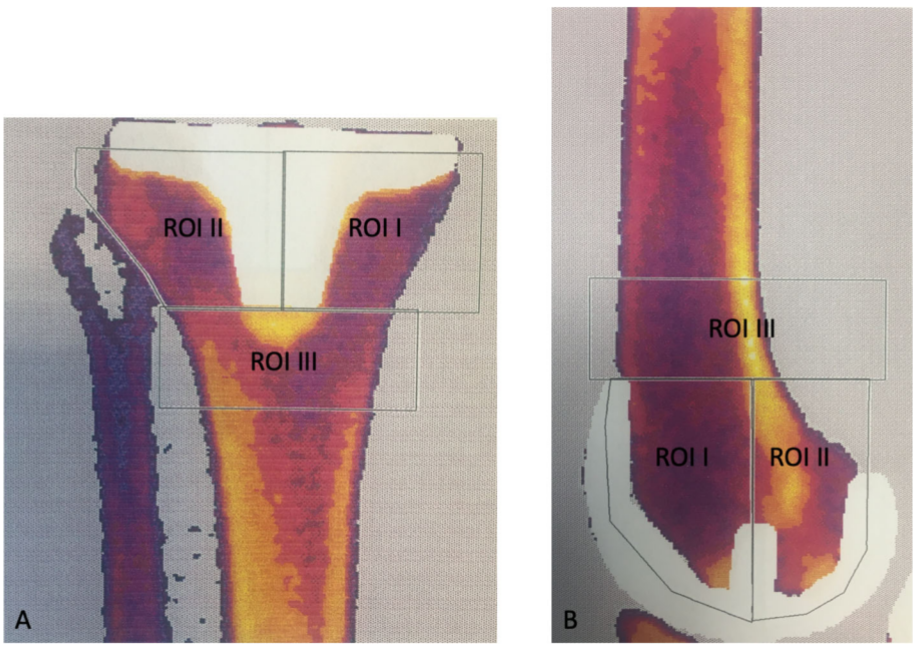

Fig. 3 Dual-energy x ray absorptiometry (DXA) scan of proximal tibia illustrating region of interest (ROI) I (medial), ROI II (lateral), and ROI III (distal) (A) and of distal femur illustrating ROI I (anterior), ROI II (posterior) and ROI III (proximal) (B)

Clinical follow up

The Knee Society score (KSS) and the Oxford knee score (OKS) were calculated preoperatively and postoperatively after 1 and 2 years. The KSS is a physician-completed score and consists of a clinical and a functional score. Clinical scores include pain, extension lag, total range of flexion, alignment, stability (anterior-posterior and mediolateral), and if present, flexion contracture. Functional scores include quality of walking, whether walking aids are used, and the ability to use stairs. A KSS score below 60 is considered poor, 60–69 fair, 70–79 good, and 80–100 excellent [25].

The OKS is a patient-reported score and consists of 12 items to assess function during the past 4 weeks, where a score of 0 (minimum) may indicate severe OA and 48 (maximum) may indicate satisfactory function [26].

Statistical analysis and ethical statements

Data on MBRSA translation (millimeters) and rotation (degrees) were expressed as mean values with 95% confidence intervals (95CI). As recommended by Valstar et al. [24], all translation and rotation values were pre-sented as signed values. The t test for paired data was used to compare time-related change (0–24 months) in BMD, and percentage time-related mean change in BMD was presented with 95CI. The OKS and KSS were expressed as the mean with 95CI and preoperative and 2-year followup values were compared using the paired t test.

The size of our study population size corresponds well with the number of required participants as determined from previous sample size calculations for RSA and DXA studies when comparing two different implants. RSA has high accuracy and therefore a small number of participants can be studied [24].

Mean annual migration of 0.09–0.10 mm for femoral components is comparable with a good long-term outcome [7, 27]. According to Pijls et al. [28], after 1 year, tibial components with a MTPM ≤ 0.54 mm are classified as acceptable, those with MTPM of 0.55–1.6 mm are classified as at risk, and those with MTPM > 1.6 are classified as unacceptable. Revision in 2018 [29] indicates MTPM < 0.5 mm at 6 months is an indicator of good clinical outcome. Annual migration ≤ 0.2 mm indicates stabilization and a good predictable factor [6]. Statistical analyses were executed in RStudio® (Version 1.2.1335© 2009–2019 RStudio, inc.).The level of statistical significance was set at p <0.05 and confidence intervals were reported at 95%.

Approval from the local Ethical Committee (case no. H-16035883) and Danish Data Protection Agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264)

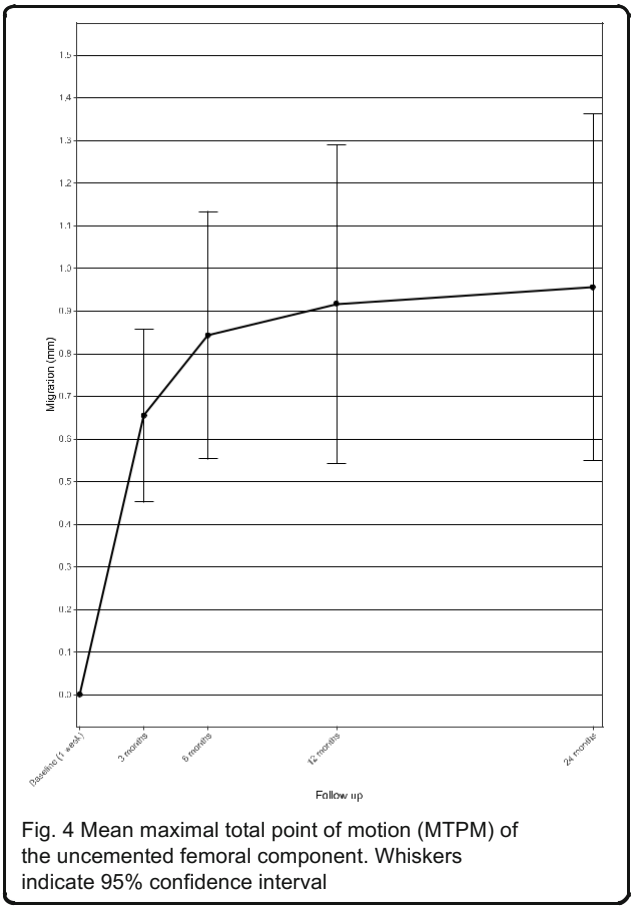

Fig. 4 Mean maximal total point of motion (MTPM) of the uncemented femoral component. Whiskers indicate 95% confidence interval

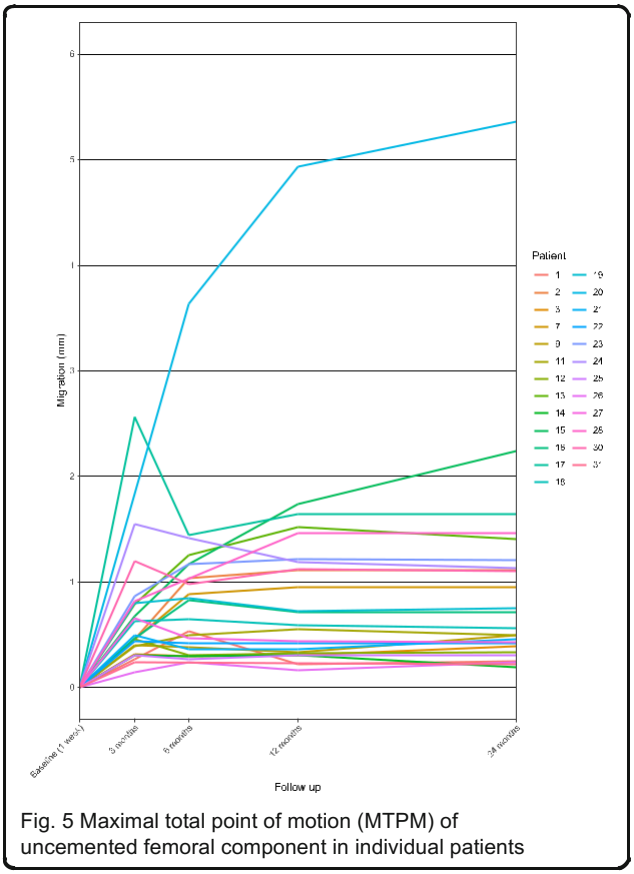

Fig. 5 Maximal total point of motion (MTPM) of uncemented femoral component in individual patients

was obtained. All patients were informed about the study orally and in writing by the principal investigator and informed consent was obtained prior to inclusion, in accordance with the Helsinki Declaration.

Results

RSA

Femur

The precision error for measurement of MTPM from 22 femoral double examinations was 0.19 mm. Precision error for the segmental motion was 0.20°, 0.25°, and 0.24° for X, Y, and Z rotations, respectively, and precision error for the corresponding translational segmental motion was 0.16 mm, 0.07 mm, and 0.18 mm, respectively.

The greatest increase in mean MTPM (0.65 mm) occurred within the first 3 months. Afterwards, the curve flattened and stabilized, and the mean MTPM after 24 months was 0.96 mm (Fig. 4).

Mean MTPM was 0.84 mm (range 0.24–3.64 mm) after 6 months, 0.92 mm (range 0.17–4.93 mm) after 12 months and 0.96 mm (range 0.2–5.36 mm) after 24 months. Implant migration > 0.10 mm was observed between 12 and 24 months in 16% of patients (4 out of 25 patients).

A spaghetti plot demonstrates the individual MTPM (Fig. 5). Patient number 20 initially had extremely high implant migration, which tended to stabilize after 12 months at 4.9 mm, and patient number 17 had high implant migration within the first 3 months, which stabilized after 6 months. Importantly, patient number 15 had implant migration that appeared to continue with-out stabilizing, as seen in the other patients. There have been no clinical complications observed so far.

The highest mean rotational and translational segmental motion was found around the Y axes (Fig. 6); mean rotation during the first 24 months was − 0.21°, where negative values indicate external rotation.

The mean CN was 58.4 (range 20.5–97.0) and mean ME was 0.16 (range 0.03–0.43). All CN values were acceptable, whereas one ME value (0.43) was above the maximum value of 0.35 as recommended by guidelines [24].

Tibia

The precision error for measurement of MTPM from evaluation of the 22 double tibial examinations was 0.33

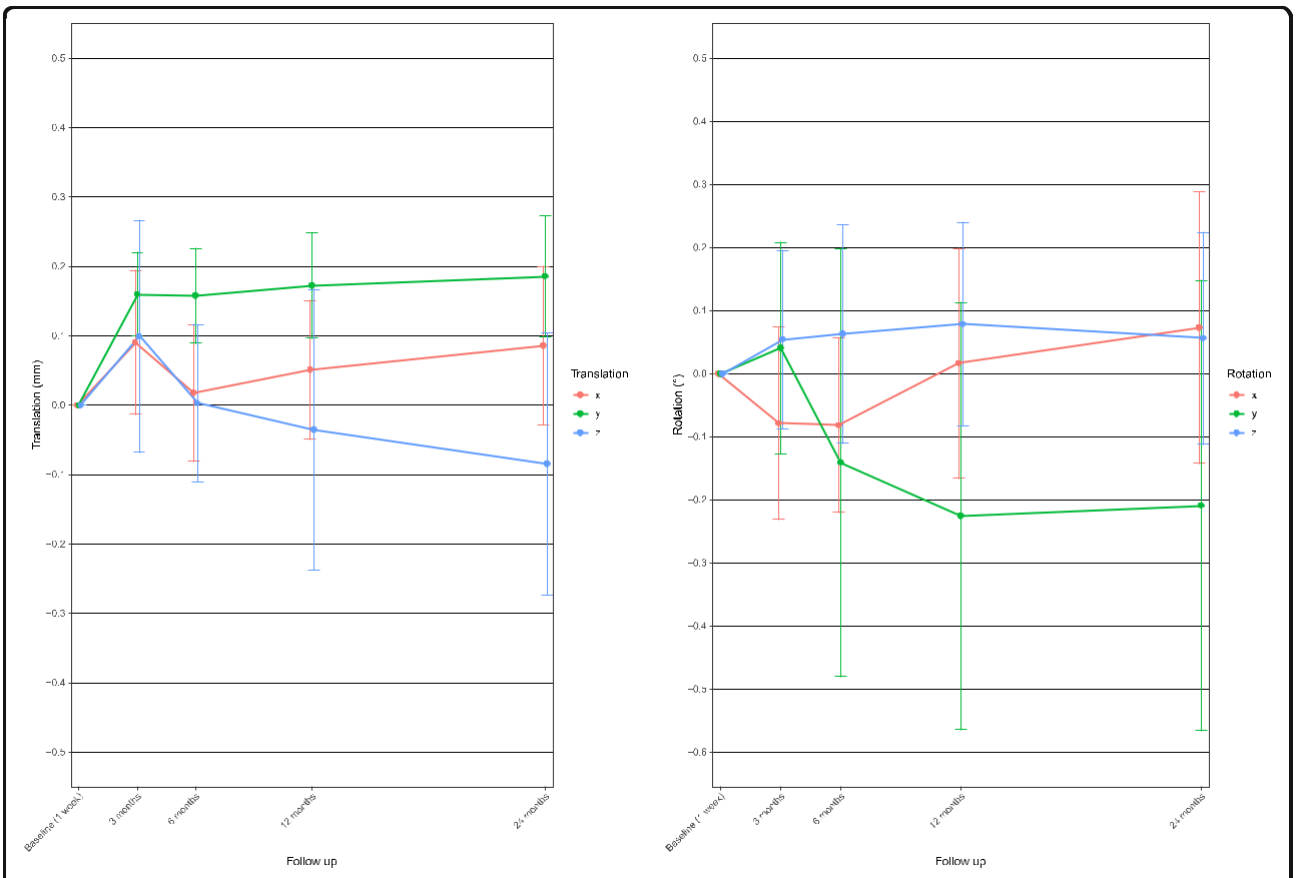

Fig. 6 Mean X, Y, and Z rotation (right) and X, Y, and Z translation (left) of the uncemented femoral component. Whiskers indicate 95% confidence interval

mm, 0.20°, 0.63°, and 0.21° for rotational segment motion, X, Y, and Z rotations, respectively, and 0.14 mm, 0.09 mm, and 0.19 mm, respectively, for the corresponding translational segment motion. The greatest increase in mean MTPM (0.54 mm) was seen after 3 months of follow up and then the curve considerably flattened as an expression of stabilization of the tibial component, with mean MTPM of 0.61 mm (range 0.17–1.99 mm) after 6 months, 0.65 mm (range 0.13–2.82 mm) after 12 months, and 0.69 mm (range 0.12–3.2 mm) after 24 months (Fig. 7). Implant migration greater than 0.2 mm was observed in 15% of patients (4 out of 27 patients) between 12 and 24 months. At 12 and 24 months of fol-low up there were 12 patients with MTPM ≤ 0.54 mm, 14 patients with MTPM between 0.54 and 1.6 mm, and 1 patient with MTPM > 1.6 mm (ME 0.29 and 0.32 at 12 and 24 months, respectively), which was therefore cate-gorized as unacceptable.

The spaghetti plot for the tibial component showing the individual MTPM (Fig. 8) indicates high migration of 3.2 mm after 24 months in patient 13 and a late in-crease in migration (1.06 mm to 1.6 mm) between 12 and 24 months in patient 24. Migration appears not to have stabilized after 24 months in these two patients.

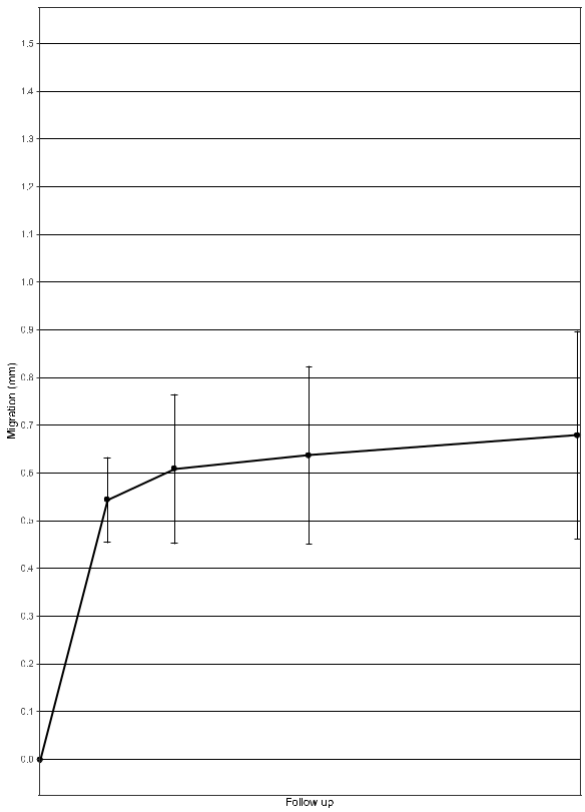

Fig. 7 Mean maximal total point of motion (MTPM) of the cemented tibial component. Whiskers indicate 95% confidence interval

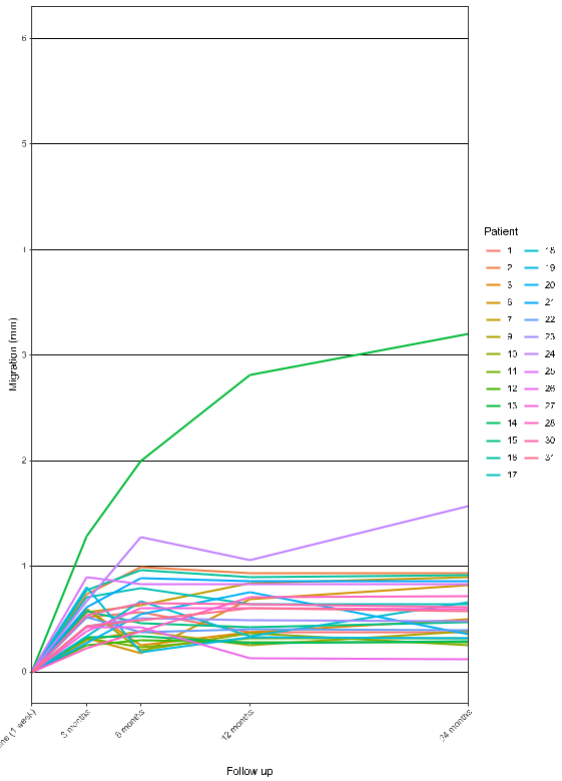

Fig. 8 Maximal total point of motion (MTPM) of cemented tibial component in individual patients

Rotational and translational movement is reported in Fig. 9. The main movement responsible for MTPM at 3 months is rotation along the Y axes and at 6, 12, and 24 months it is translation along the Z axes.

Mean CN was 51.1 (range 32.9–133.1) and mean ME was 0.17 (range 0.06–0.4). All CN values were acceptable and one ME value (0.4) was above the maximum value of 0.35 as recommended by guidelines [24].

DXA

The precision error expressed as the CV for measure-ment of BMD at each ROI was calculated from 16 double examinations. The CV for the distal femur was 1.4% (95CI 0.89–1.9), 1.3% (95CI 0.43-2.11), and 0.9% (95CI 0.5–1.4) for ROI I, ROI II, and ROI III, respect-ively. The corresponding results for the proximal tibia were 1.3% (95CI 0.69–1.95), 1.8% (95CI 0.86–2.68), and 2.1% (95CI 0.9–3.25), respectively.

At both the distal femur and the proximal tibia and at all ROI, there was a statistically significant decrease in BMD at 2 years compared with the immediate postoper-ative measurement (Fig. 10).

The greatest mean BMD decrease at the distal femur was at ROI I (anterior) with 26.7% decrease (95CI 17.3–

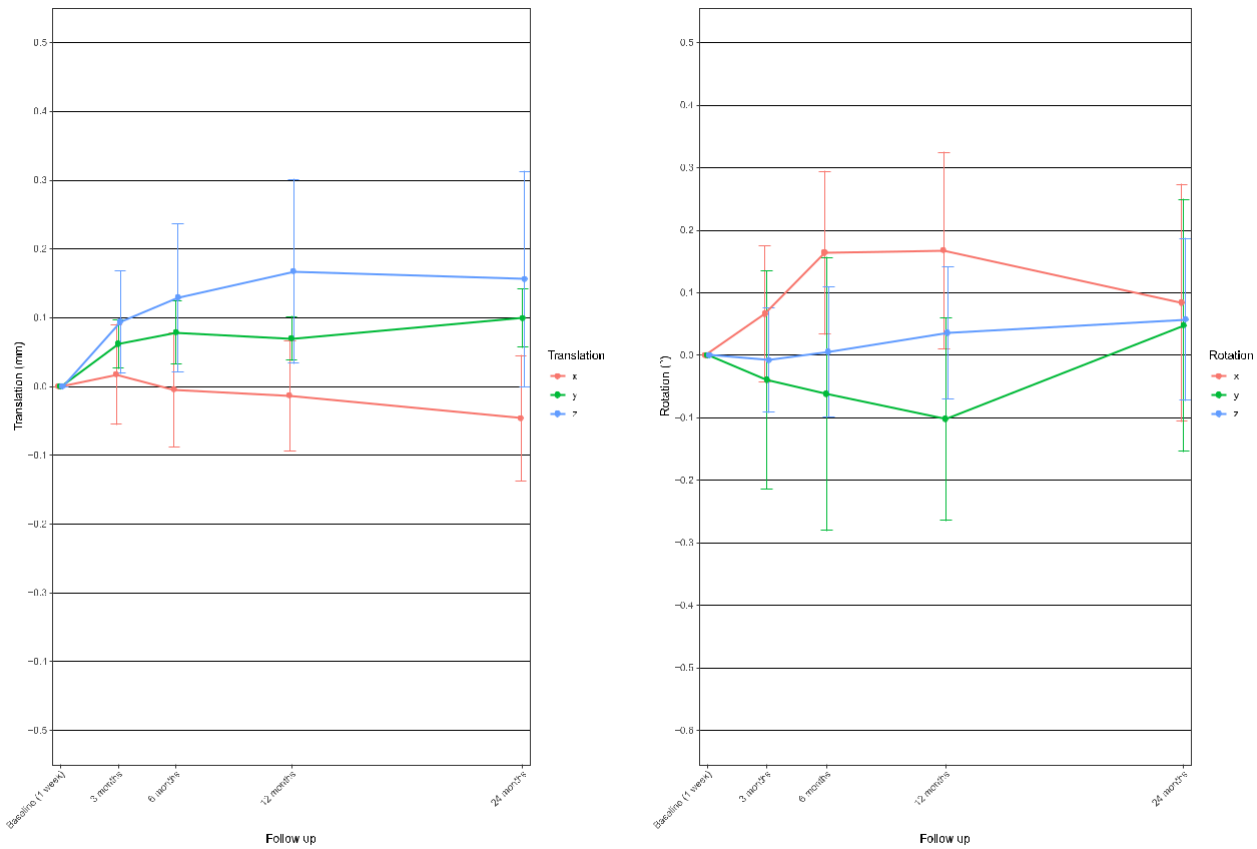

Fig. 9 Mean X, Y, and Z rotation (right) and X, Y, and Z translation (left) of cemented tibial component. Whiskers indicate 95% confidence interval

36.1%) after 2 years, while the decrease at ROI II (posterior) and at ROI III (proximal) was 9.2% (95CI -3–21.5%) and 3.3% (95CI -5.55–12.1%) respectively. A decrease in BMD after 24 months was also observed in the proximal tibia and it was almost the same at all three ROI with 9.5% (95CI 4.7–14.3%) at ROI I (medial), 9.6% (95CI 2.5–16.7%) at ROI II (lateral), and 7.2% (95CI 0.6–13.8%) at ROI III (distal), respectively. There was no significant correlation between MTPM and BMD after 2 years (Fig. 11).

Clinical results

The 2-year clinical outcome determined by the OKS (n = 29) showed a significant increase (p <0.001) from a score of 25 (range 13–38) preoperatively to 44 (range 35–48) at the 2-year follow up. The KSS for function in-creased from 54 (range 10–100) preoperatively to 94 (50–100) at 2 years (p <0.001), and the corresponding KSS clinical score increased from 38 (range 10–79) to 87 (range 60–90) (p <0.001).

Discussion

A prospective follow up of 29 patients with uncemented femoral component and cemented asymmetrical tibial component was evaluated using MBRSA, DXA, and clinical outcome. We found that the uncemented femoral component had the highest MTPM within the first 3 months with mean migration of 0.65 mm and 16% of patients (4 out of 25 patients) with migration > 0.10 mm at 12–24 months.

Revisions related to femoral components, regardless of fixation, are rare [7, 27]. This may be one of the main reasons why the femoral component is less commonly evaluated with RSA compared to tibial components. A recent study suggests that annual migration < 0.09–0.10 jj is comparable with a good long-term outcome [27], but to our knowledge there have been no studies to estimate the proportion of implant migration and the risk of aseptic loosening with the femoral component.

Gao et al. [30] identified a median MTPM of 0.87 mm at 24 months postoperatively in younger patients (age < 60 years) and Nilsson et al. [31] reported a mean MTPM of 0.89 ± 0.08 mm.

The findings on femoral components in our study correspond well with previous studies [7, 30–32]. With a mean increase in MTPM < 0.10 mm per year we can expect a good long-term outcome. Four patients in our

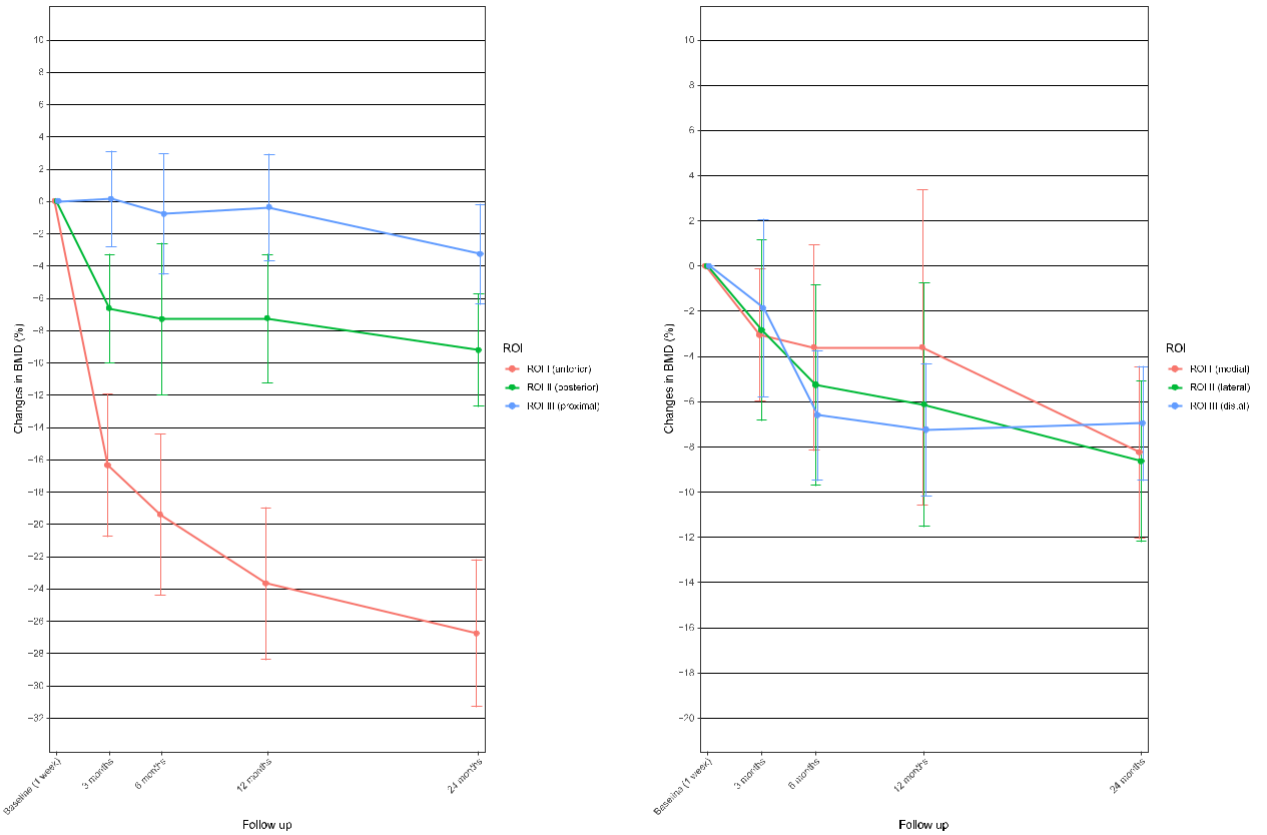

Fig. 10 Mean bone mineral density (BMD) percentage change for region of interest (ROI) I, ROI II, and ROI III for the distal femur (left) and proximal tibia (right). Whiskers indicate 95% confidence interval

study had migration > 0.10 mm from 12 to 24 months; two of these had values fairly close to the proportion with 0.17 and 0.11 mm, but two outliers had very high migration (MTPM after 24 months 2.24 and 5.36 mm, respectively). With a rise in the proportion of 0.5 and 0.43 mm, correspondingly the ME was 0.3 and 0.12, respectively; these patients need to be followed further to evaluate their clinical outcome. No complications were observed at the 24-month follow up.

One possibility for further studies could be to examine the migration pattern of femoral components in patients who underwent revision due to aseptic loosening, to identify any pattern.

For the tibial components as with the femoral component, the greatest increase in mean MTPM (0.54 mm) was seen after 3 months of follow up. Mean MTPM was 0.61 mm after 6 months, 0.65 mm after 12 months, and 0.69 mm after 24 months. Between 12 and 24 months after surgery, 14.8% of patients (4 out of 27 patients) had migration > 0.2 mm.

Pijls et al. [28] identified association between early migration (MTPM at 12 months) and late implant revision (prosthesis survival after 5 years). A threshold of 0.54 jj MTPM after 1 year was categorized as an acceptable rate of aseptic loosing after 5 years, whereas the unacceptable threshold for MTPM was 1.6 mm, and values in between were considered components at risk [28]. In our study, 12 patients had MTPM ≤ 0.54 mm at 12 and 24 months of follow up, 14 patients had MTPM between 0.54 and 1.6 mm and were therefore (according to Pijls' [28] classification) at risk of aseptic loosening after 5 years, and 1 patient had MTPM > 1.6 mm at 12 and 24 months (ME 0.29 and 0.32) follow up, which was therefore categorized as unacceptable. Importantly, note that no revision surgery was performed up to the 2-year follow up.

From Leande et al. [33] interpretation of the plot for cemented tibial components indicates 16 patients out of 58 patients at risk, with MTPM values > 0.54 at 1-year follow up, and 14 patients at risk at 2-year follow up, with 2 patients having MTPM values > 1.6, which is therefore considered unacceptable [33].

Many RSA studies have been effectuated using a different type of fixation and prosthesis design for the tibial component. If we compare our results with previous studies using cemented fixations [28, 29, 32–34], our

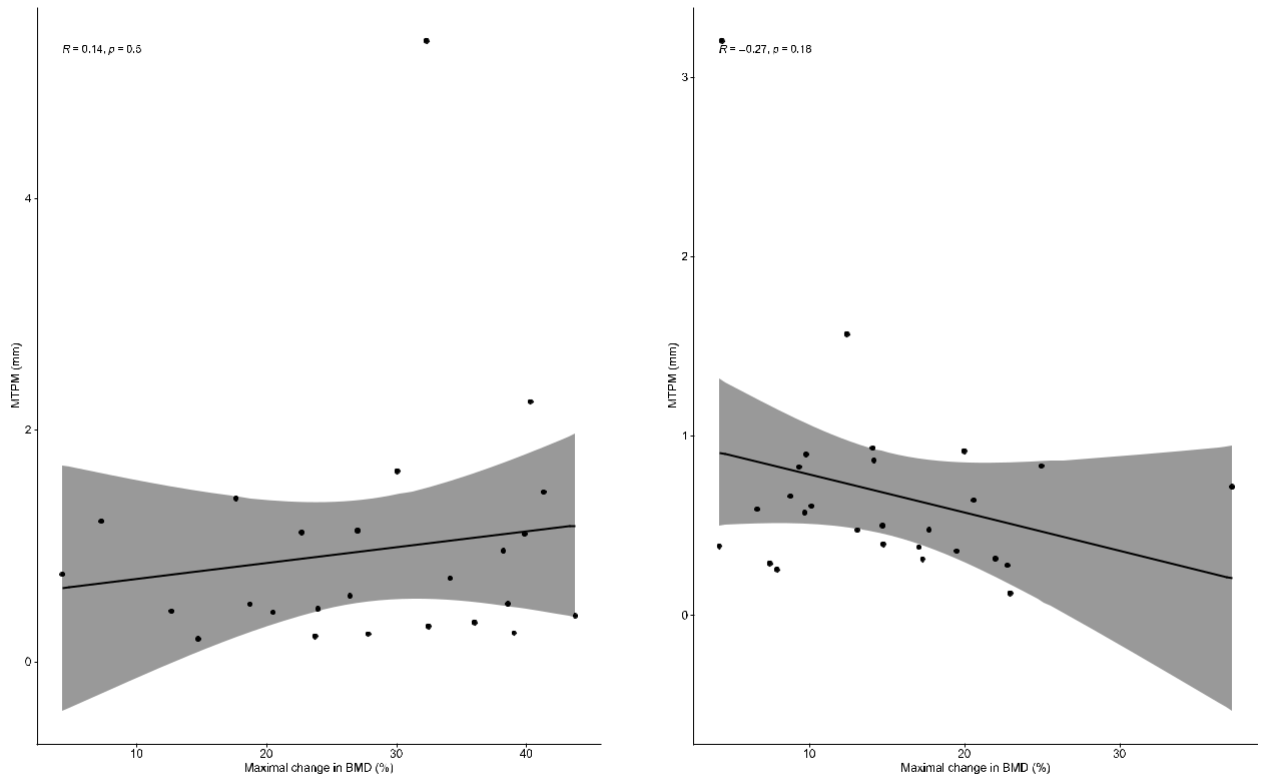

Fig. 11 Analysis of correlation between maximal total point of motion (MTPM) and bone mineral density (BMD) 2 years after surgery. Femoral component (left) and tibial component (right). The gray area indicates 95% confidence interval

results are similar or marginally higher. A 5-year follow up is already planned in this study and it is important to observe the components at risk.

Furthermore, Ryd et al. [6] state that MTPM migration > 0.2 mm from 1 to 2 years after surgery is a predictable factor for subsequent loosening of the components. In our study, 14.8% of patients (4 out of 27) had MTPM > 0.2 mm between 1 and 2 years, and therefore this should be considered when evaluating the prosthesis migration pattern in this study design.

A decrease in BMD of 26.7% was observed in ROI I at the distal femur after 24 months, and the respective decrease in ROI II and ROI III was 9.2% and 3.3%, respectively. The corresponding decrease in BMD at the proximal tibia in ROI I, II, and III was around 9%. The decrease in BMD at the distal femur and proximal tibia after TKA is a known consequence of postoperative adaptive bone remodeling [35–39]. BMD in the anterior part of the distal femur is clinically especially important in TKA because it is a common location for periprosthetic fractures [40–42]. Because BMD is closely related to trabecular bone strength [43], a significant decrease in BMD in this region will indicate an increased risk of periprosthetic fracture complications.

Quantitative studies have been performed on periprosthetic bone remodeling at the distal femur after primary TKA, but in general, the greatest bone loss is seen in the anterior part of the bone where the decrease in BMD typically reaches 23.6–36.0% after 2 years with uncemented femoral components [16, 35, 36]. Petersen et al. [18] identified a decrease in BMD of 44% in ROI I 1 year postoperatively.

The greatest decrease in BMD at the proximal tibia is often in ROI I (medial) and previous studies have identified a decrease with cemented tibial components be-tween 4.4% after 1 year [35] and up to 38.6% after 2 years [44]. In our study, we identified a decrease in BMD of 9.5% in ROI I (medial) after 2 years, which is at the lower end of that found in previous studies [14, 16, 44–46]. The decrease in BMD in ROI II varies from 3% [35] to 20% [16] and in ROI III from 6.5% [35] to 36.8% [44]. In our study decreases in BMD of 9.6% in ROI II and 7.2% in ROI III were observed and this corresponds well with the findings of previous studies [14, 15, 45, 46].

To our knowledge, there are no studies to indicate the range of decrease in BMD associated with periprosthetic fracture; one of the reasons for this could be that periprosthetic fracture is not only associated with a decrease in BMD but also has a multifactorial genesis. Decrease in BMD in the present study was caused by local adap-tive bone remodeling.

Limitations

This study has no randomization between a current standard prosthesis and the new implant, which would be the preferred way to test a new implant; with the pa-tients blinded to the type of prosthesis, the clinical out-come could be determined more accurately. Results from 29 patients for one type of prosthesis are accept-able for studying implant migration and adaptive bone remodeling after TKA, but to interpret functional results more patients are needed.

Conclusion

Migration patterns for femoral component and changes in BMD in our study correspond well with findings in previous studies, and we observed marginally higher migration with the tibial component. There was no significant correlation between MTPM and BMD. Those components at risk need further evaluation with 5-year postoperative follow up.

Abbreviations

95CI: 95% Confidence interval; BMD: Bone mineral density; CAD: Computer-aided design; CN: Condition number; DXA: Dual-energy x ray absorptiometry; KSS: Knee Society score; MBRSA: Model-based radiostereometric analysis; ME: Mean error; MTPM: Maximal total point of motion; OA: Osteoarthritis; OKS: Oxford knee score; PACS: Picture archiving and communication system; ROI: Region(s) of interest; RSA: Radiostereometric analysis; TKA: Total knee arthroplasty

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43019-021-00111-5.

Additional file 1.

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Disclosures

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Authors' contributions

MY performed data collection, analyzed data, drafted the manuscript and designed the figures. CH applied for approval at data protection agency and ethical committee and performed data collection. GF contributed to the interpretation of the results and supervised the manuscript. TL performed and supervised data collection and was the leading surgeon on TKA performed in this study. AO contributed to the interpretation of the results and supervised the manuscript. MM planned the study, contributed to the interpretation of the results and supervised the manuscript. All authors provided critical feedback and helped to develop the research and manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials

The dataset used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval from the local Ethical Committee (case no. H-16035883) and Danish Data Protection Agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264) was obtained.
All patients were informed orally and in writing by the principal investigator and prior to inclusion informed consent was obtained, in accordance with the Helsinki Declaration.

Consent for publication

All authors give consent for publication.

Competing interests

The authors have no competing interests.

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1. Declaration by	
Name of PhD student	Müjgan Yilmaz
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Title of the PhD thesis	Cemented and uncemented trabecular metal total knee arthroplasty with asymmetrical tibial design. Comparison using model-based radiostereometric analysis, dual-energy x-ray absorptiometry, and computed tomography.

2. The declaration applies to the following article	
Title of article	Bone remodeling and implant migration of uncemented femoral and cemented asymmetrical tibial components in total knee arthroplasty - DXA and RSA evaluation with 2-year follow up
Article status	
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3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
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4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	C
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] The PhD student (Müjgan Yilmaz) provided to all stages of the research.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
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7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 27/12-22 PhD student: Müjgan Yilmaz

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[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

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Study II

Implant migration in cemented and uncemented knee arthroplasty with an asymmetrical tibial component. A randomized controlled trial with a 2-year model-based RSA follow-up

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Declarations

Disclosures:

Dr. Yilmaz has nothing to disclose.

Dr. Holm has nothing to disclose.

Dr. Lind has nothing to disclose.

Dr. Flivik reports institutional grants from Zimmer-Biomet, outside the submitted work. Furthermore, reports institutional grants outside the submitted work from Stryker, Depuy Synthes, JRI Ltd, Materialize, and Ortoma.

Dr. Odgaard reports grants from Zimmer-Biomet, outside the submitted work.

Dr. Petersen reports grants from Zimmer Biomet, during the conduct of the study; grants from Ethicon UK, grants from Zimmer Biomet, outside the submitted work.

Ethics approval and consent to participate:

Approval from the local Ethical Committee (case no. H-16035883) and Danish Data Protection Agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264) were obtained.

All patients were informed orally and in writing by the principal investigator and prior to inclusion informed consent was obtained in accordance with the Helsinki Declaration.

Prior to inclusion, the randomized controlled study was registered at clinicaltrial.gov (protocol ID: PERSONA-RH-18, clinicaltrial.gov ID: NCT03563131)

Consent for publication:

All authors give consent for publication.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interest:

The authors have no competing interests.

Funding:

Grants from Zimmer Biomet were given to Rigshospitalet during the conduct of the study.

Authors' contributions:

Müjgan Yilmaz: Performed data collection, analysed data, drafted the manuscript and designed the figures.

Christina Holm: Applied for approval at data protection agency and ethical committee.

Gunnar Flivik: Contributed to the interpretation of the results and supervised the manuscript.

Thomas Lind: Performed and supervised data collection and was the leading surgeon on the total knee arthroplasty performed in this study.

Anders Odgaard: Contributed to the interpretation of the results and supervised the manuscript.

Michael Mørk Petersen: Planned the study, contributed to the interpretation of the results and supervised the manuscript.

All authors provided critical feedback and helped to develop the research and manuscript.

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Abbreviations

OA:	Osteoarthritis
TKA:	Total Knee Arthroplasty
RSA:	Radiostereometric Analysis
MBRSA:	Model-based Radiostereometric Analysis
CAD:	Computer-Aided Design
PE:	Precision error
RCT:	Randomized Controlled Trial
KSS:	Knee Society Score
OKS:	Oxford Knee Score
CN:	Condition number
ME:	Mean error
MTPM:	Maximal Total Point Motion
PACS:	Picture Archiving and Communication System
95CI:	95% Confidence Interval
DICOM:	Digital Imaging and Communications in Medicine

Introduction

Total knee arthroplasty (TKA) has very high implant survival rates above 90% after 10 years and is therefore considered a highly successful treatment for advanced symptomatic osteoarthritis OA [1, 2]. Despite high survival rates, complications needing surgical revision due occur with aseptic loosening as the main cause of late revision [3-5]. With the introduction of new implant design, there is a need to monitor and predict the risk of complications including aseptic loosening [6].
Patient satisfaction is usefully high after orthopaedic procedures, however, satisfaction after TKA surgery remains low around 80% for various reasons but mainly due to persistent pain [7-10].
The asymmetrical tibial component is designed with the intention du minimize the group of patients with persistent postoperative pain by allowing a better fit of the component on the bone and minimizing the risk of positioning it in an inward rotation perioperative.

Radiostereometric Analyses (RSA) measurements are highly accurate and can detect the risk of aseptic loosening within a 2-year follow-up and with relatively small sizes [11-13].
This is one of the main reasons why RSA is recommended in the phased introduction of new orthopaedic implants [6].
Model-based RSA (MBRSA) is a further improvement from marker-based RSA and does not require tantalum markers positioned in the implant (or the polyethene insert), but implant migration can instead be analysed using Computer-Aided Design (CAD) models of the implant, and the precision error (PE) when using MBRSA is found to be acceptable and useable in clinical settings [14, 15].
The risk of late aseptic loosening can be evaluated with Radiostereometric Analyses (RSA), which require small tantalum beads attached to the implant and the surrounding bone during TKA surgery, and thus very small movements between implant and bone, defined as migration, can be detected [16, 17]. The main migration is commonly observed within the first three postoperative months then and most implants stabilize within the first postoperative year. However, some implants will have a high and/or continuous migration, and these implants are at risk of later aseptic loosening and revision [11, 16].
Previous studies have not demonstrated any significant difference in implant survival when comparing cemented and uncemented prostheses [3, 18-25].

The aim of this study is to evaluate the migration and segmental motion of cemented and uncemented femoral and asymmetrical tibial components with MBRSA in a randomized controlled trial (RCT) design with a 2-year follow-up. Secondary functional outcomes measured with Knee Society Score (KSS) and Oxford Knee Score (OKS) were also evaluated.

Materials and methods

Study design and patients

This study is a randomized controlled trial with a 1:1 allocation. Patients scheduled for primary TKA due to OA at Gentofte Hospital, Denmark in the period from September 2018 to October 2019 were eligible for inclusion.

We included patients who were listed for a TKA due to OA, age 40-70 years. Exclusion criteria were diseases that could affect bone metabolism, expected use of a standard cruciate retaining implant, and inability to give informed consent for language or mental reasons.

The surgeries were performed according to guidelines from the manufacturer by 5 experienced consultant orthopaedic surgeons subspecialized in knee replacement surgery.

Overall, 66 patients were included for randomization. Subsequently to the randomization procedure two patients were excluded because they did not get the allocated treatment and 1 patient withdrew consent at the beginning of the study.

In total, 63 patients (M/F = 22/41, mean age 62.4 years (range: 50.3-70.8 years)) were included in this study and followed for 1 year while subsequently 2 more patients prematurely ended there follow-up schedule due to revision and change of the prosthesis leaving 61 patients (M/F= 21/40) to complete the 2-year follow-up. During this study 5 revision surgeries were performed in 4 patients (change of polyethylene insert (instability: n=2 and infection: n=1) and revision of the TKA (instability n=1 and infection n=1)), figure 1 illustrates the flowchart of enrolment, and table 1 the demographics of the patients included in this study.

RSA and follow-up

Perioperatively tantalum beads (0.8 mm, Tilly Medical Products, Lund, Sweden) were positioned with an inserter (Wennbergs Finsmark AB) by the first author in all cases to minimize variations and aiming for the widest non-linear distribution in the femur, polyethylene insert and, in the tibia.

A total of 18-20 beads were used. The beads placed in the polyethylene insert were not used for further analyses because CAD models [26] produced in Leiden (RSAcore Department of orthopaedics Leiden University Medical Centre) from the information by the prosthesis company were used with MBRSA software [26, 27] (Model-based RSA 4.1, 2003-2014 RSAcore Department of orthopaedics Leiden University Medical Centre) to evaluate migration and segmental motion. All RSA analyses were performed by the first author at the RSA laboratory in Lund, Sweden. The condition number (CN) and mean error (ME) were estimated by the MBRSA software and represent the distribution and stability of the tantalum markers respectively, and the maximum values were set as 150 and 0.35 mm according to guidelines [17], this is important due to MTPM being extremely sensitive for loose markers. Maximal Total Point Motion (MTPM) represents the highest motion and was the main parameter for migration, whereas segmental motion was represented as translation and rotation along the X, Y, and Z axes.

Patients had the baseline RSA examination performed on average 7 days (range: 4-16 days) postoperatively, further follow-up was conducted 3, 6, 12 and 24 months after the baseline examination. All RSA examinations were performed by the first author.

Patients were placed supine with the examined knee positioned in the biplane plexiglass calibration cage (Calibration cage 21; Tilly Medical Products, Lund, Sweden), at a 90°-degree angle created by two moveable ceiling-fixed X-ray tubes (Arcoma Precision T3, Siemens, 0.7mmAI/75kV, filtration 1.5mm), and with 100 cm to each detector, an anterior-posterior and medial-lateral view were created simultaneously. The intensity was set at 50 kV and 25 milliamperes seconds (mAs). The images, with a resolution of 10 pixels per mm in Digital Imaging and Communications in Medicine (DICOM) format, were stored in the Picture Archiving and Communication System (PACS).

At 12 months follow-up double examinations were performed. After the initial RSA measurement, the patient was requested to stand up and walk around for 5 minutes, and afterwards was repositioned and a new RSA measurement was obtained, to enable the calculation of the PE.

Knee function

OKS and KSS were obtained preoperatively and postoperatively at 6-, 12-, and 24-months follow-up. OKS is a patient-reported questionnaire containing 12 items evaluating knee function and scored from 0 (poor) to 48 (excellent) [28].

KSS was completed by the principal investigator and consists of a clinical and functional part, a total score below 60 is considered poor, 60-69 fair, 70-79 good, and 80-100 excellent [29].

Sample size

Sample size calculations were performed for the femoral and tibial components using mean MTPM after 2 years as the primary effect parameter. MTPM is found to be the best predictor of late ase ptic loosening and revision [11]. The sample size calculation was based on data from previous RSA studies [30, 31], and resulted in 24 patients per group using an SD=0.35 mm, minimum relevant difference=0.03 mm, α=5%, and statistical power =85%. To make allowance for dropouts an inclusion of 30 patients in each group was intended, but because of some early dropouts at the beginning of the inclusion period, we included 66 patients.

Randomization and blinding

Block randomization of 10 in each block with 1:1 allocation was performed. A digital randomization sequence was created and distributed in envelopes by an impartial person.

A theatre nurse (non-related to the study) selected an envelope in the surgery room after the patients were sedated and prior to skin incision to randomize the patients in group A (uncemented Trabecular Metal coated Persona® TKA, Zimmer Biomet, Warsaw, Indiana) or group B (cemented Persona® TKA, Zimmer Biomet, Warsaw, Indiana). All patients received a cruciate-retaining (CR) polyethylene insert and the patella was resurfaced with cemented Zimmer Biomet 3-Peg all-polyethylene patella component.

Due to differences in prosthesis design and fixation methods the surgeons could not be blinded, but the patients were kept blinded for the 2-year follow-up.

Statistical analysis and ethical statements

MTPM is a vector and statistical analyses were performed with the assumption of non-normal distribution. Comparison between groups was performed with a non-parametric t-test (Mann–Whitney U-test). The statistical significance level was set at $p<0.05$ and confidence intervals were

reported at 95% (95CI). Migration was visualized with plots and expressed as mean with 95CI as recommended by Valstar et al. [17]. Up until the point of exclusion, all data were collected on the patients who were used in the analysis. Segmental data are reported in table 2 with mean, range and 95CI.

Precision was defined as the standard deviation of the difference (SD_{diff}) and precision error was expressed as 1.96 x SD_{diff} [17].

Prior initiation of the study approval from the regional scientific ethical committee (case no. H-16035883), and the Danish Data Protection Agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264) was obtained. The study was registered at clinicaltrial.gov (NCT03563131) prior to enrolment [32].

The primary outcome measures of this clinical trial were the implant migration assessed by MBRSA and the most important measure of migration was MTPM. Knee function evaluated with the OKS and KSS was secondary/other outcome measures.
According to the Helsinki Declaration, the primary investigator provided oral and written information to every patient and written informed consent was obtained before inclusion.
All statistical analyses were performed in Rstudio® (Version 1.2.1335 © 2009-2019 RStudio, inc.).

Results

RSA femoral component
The precision error for MTPM was 0.5 mm, and for the translational segmental motion it was 0.29 mm, 0.07 mm, and 0.16 mm for X, Y, and Z-translation respectively. The precision error for the rotational segmental motion for X, Y, and Z-rotation was 0.25˚, 0.33˚, and 0.31˚ respectively.
All femoral component precision error calculations were based on double examinations in 55 patients.

The majority of the overall 2-year migration, expressed as mean MTPM, was observed within the first 3 months postoperatively for both the cemented 0.41 mm (95CI 0.398-0.482) and the uncemented trabecular metal 0.65 mm (95CI 0.623-677) femoral components. Subsequently, a stabilization occurred, and after 24 months a mean MTPM for the cemented and uncemented

components were respectively 0.51 mm (95CI 0.495-0.531) and 0.83 mm (95CI 0.8-0.868) (figure 2 and table 2).

A significant difference between the cemented and uncemented femoral component group was reported at 3 months (p=0.04), 6 months (p=0.03), 12 months (p=0.02), and 24 months (p=0.02) (table 2).

Heigh migration defined as migration above 2 mm was only observed in a single patient, no. 29 (uncemented) with an MTPM of 2.19 mm after 24 months. This patient did not undergo any revision and reported 80 in KSS clinical, 90 in KSS function, and 42 in OKS.

Eleven patients had an increase in MTPM above 0.1mm between 12 and 24 months ranging from 0.11 to 0.6 mm.

The highest translation after 24 months was along the Y-axis (superior) for both cemented (0.06 mm) and uncemented (0.13 mm) components. The highest rotation was observed around the X-axis (anterior tilt) with 0.16° for the cemented component and around the Y-axis (external rotation) with 0.097° for the uncemented component.

No statistically significant differences between cemented and uncemented components were found for translation or rotation axis.

RSA tibial component

The PE for MTPM was 0.33 mm, and for the translational segmental motion, PE was 0.12 mm, 0.07 mm, and 0.16 mm for the X, Y, and Z-translation respectively. The PE for the corresponding rotational segmental motion for X, Y, and Z-rotation was 0.18°, 0.51° , and 0.19°. All calculations of PE were based on 55 femoral double examinations.

The highest increase in MTPM for the tibial components was observed within the first 3 months, for the cemented 0.7 mm (95CI 0.669-0.731) and uncemented 0.76 mm (95CI 0.733-0.787). Afterward, a stabilization pattern was observed, and migration for the cemented components after 24 months was 0.72 mm (95CI 0.689-0.751) and for the uncemented components 0.78 mm (95CI 0.755-0.805) respectively (table 2).

There were no statistically significant differences in MTPM between the two groups.

Four patients were observed with migration above 1.6 mm after 12 months, one of these patients was revised and excluded after 12 months of follow-up due to revision surgery with the removal of the

prosthesis. When looking into patients with migration of more than 0.2 mm yearly, 7 patients were identified and none of these were revised. At 6 months of follow-up, 22 patients were identified with a migration below 0.5 mm.

The highest translation after 24 months was observed along the Y-axis (superior) with 0.09 mm and -0.24 mm for cemented and uncemented correspondingly and the rotation along the X-axis (posterior tilt) was -0.15° and -0.42° for the cemented and uncemented tibial components.

Statistically significant differences between cemented and uncemented components for the segmental motion were only found for Y-translation at all follow-ups and X-translation at 3-, and 6-months of follow-up.

Functional score

Mean preoperative clinical KSS was 48 (range: 15-90) for cemented knees and 56 (18-90) for the uncemented. The corresponding values after 24 months were 92 (range: 54-100) and 95 (range: 56-100), and the increase was statistical in both groups ($p<0.001$).

Mean preoperative functional KSS was 42 (range: 25-80) for the cemented knees and 45 (25-80) for uncemented. The corresponding values after 24 months were 91 (range: 54-100) and 95 (range: 56-100), with a notable increase in both groups which was statistically significant ($p<0.001$).

The functional outcome of OKS preoperative to 24 months follow-up showed a significant increase ($p<0.001$) in both the cemented and uncemented group with a mean increase from 26 (range: 13-32) to 44 (range: 30-48) for the cemented group and 22 (range: 13-28) to 46 (range: 36-48) in the uncemented group.

Discussion

This study is an RCT comparing cemented and uncemented trabecular metal fixation of femoral and asymmetrical tibial components using MBRSA with 2 years of follow-up. The majority of MTPM regardless of fixations mode was observed within the first 3 months followed by a stabilisation for both components and fixation types.

The translation was mainly observed along the Y-axis for both components and rotation along the X- and Z-axis. A statistically significant difference in MTPM between cemented and uncemented femoral components was identified after 6, 12, and 24 months.

Fixation with and without cement has been a major discussion topic regarding TKA. A study by Prudhan et al. [33] evaluated 200 cases with TKA comparing cemented and uncemented fixation and found aseptic loosening in six cemented cases compared with two cases in the uncemented group, with no significant difference between the two groups, however, the lack of statistical significance was mainly due a to low sample-size. Fricka et al [34] found no difference in all-cause revision between cemented and uncemented TKA in an RCT study from 2015. In this study, no patients were revised due to aseptic loosening, although revisions due to instability and infection were performed. Henricson et al [35] did not asses any difference in long-term migration between cemented and uncemented femoral components. Several previous studies did not show significant differences regarding cemented and uncemented fixation of femoral and tibial components [30, 36-43].
The risk of late revision due to aseptic loosening can be evaluated with RSA [16]. To our knowledge, no studies comparing cemented and uncemented femoral and asymmetrical tibial components in an RCT setup have previously been performed.

Few RSA studies on femoral components have been conducted. One main reason could be the low risk of revision due to failure [22, 35] and furthermore because tantalum beads attached to the implant are required in analyses using the conventional marker-based RSA. Henricson et al [35] suggest an annual migration of 0.09 – 0.10 mm for the femoral component to be associated with good long-term outcomes.
Previous studies found a median MTPM of 0.87 mm after 24 months [43] and a mean MTPM of 0.89 ± 0.08 mm [30]. In our study, we found a mean MTPM of 0.51 mm for the cemented and 0.83 mm for the uncemented group after 24 months which corresponds well with findings in previous studies [30, 35, 43, 44]. Furthermore, the mean increase from 12 to 24 months were 0.02 mm for the cemented and 0.04 mm for the uncemented components which fit well with the recommendation from Henricson et al [35] to expect a good long-term outcome.

Tibial component migration is well documented and several RSA studies have been performed on both design and fixation [12, 13, 44-46].
Pijls et al. [12] demonstrated that early migration evaluated with MTPM at 12 months was associated with late revision when prosthesis survival after 5 years was assessed.
The acceptable rate of migration was defined as 0.54 mm MTPM after 12 months, whereas migration over 1.6 mm was defined as unacceptable and values in between were considered as components at

risk. Furthermore, MTPM below 0.5 mm at 6 months was associated with good clinical outcomes [12].
Additionally, according to Ryd et al [11], MTPM migration of more than 0.2 mm from 1-2 years was a good predictive factor for the risk of later component aseptic loosening.
In our study, we found a mean migration MTPM after 6 months of 0.66 mm for the cemented and 0.8 mm for the uncemented components.

Our findings were larger than the threshold of 0.5 mm which according to Pijls et al [12] is associated with being a prognostic factor of good clinical outcomes, however still below the upper threshold of 1.6 mm after 12 months which indicates an unacceptable migration. The migration of the cemented and uncemented tibial components in our study corresponds well with findings in previous studies [12, 13, 44-46]. A newly published study by Christensson et al [47] compared the Persona® prosthesis regarding their polyethylene insert and found migration expressed as mean MTPM similar to this study.

Due to the severe symptomatic OA preoperatively, the functional outcome is typically better after TKA surgery, and we detect a statistically significant improvement in function.

Limitations
Sample calculations in this study were made for RSA and to calculate migration, expressed as mean MTPM, which was our primary endpoint and for this reason, it is under-sampled to conclude on functional outcome.

The baseline RSA measurement is executed mean of 7 days postoperative, we know that the initial migration is highest and must assume some migration in these 7 days has occurred and not registered.

Conclusion
Both the cemented and the uncemented Persona® TKA showed migratory patterns for both the femoral and the tibial components, comparable with other well-functioning TKAs. Thus, the statistically significant differences in mean MTPM between the femoral components and in segmental motion for the tibial components are not considered to be of any clinical relevance.

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Figure 1: Enrolment

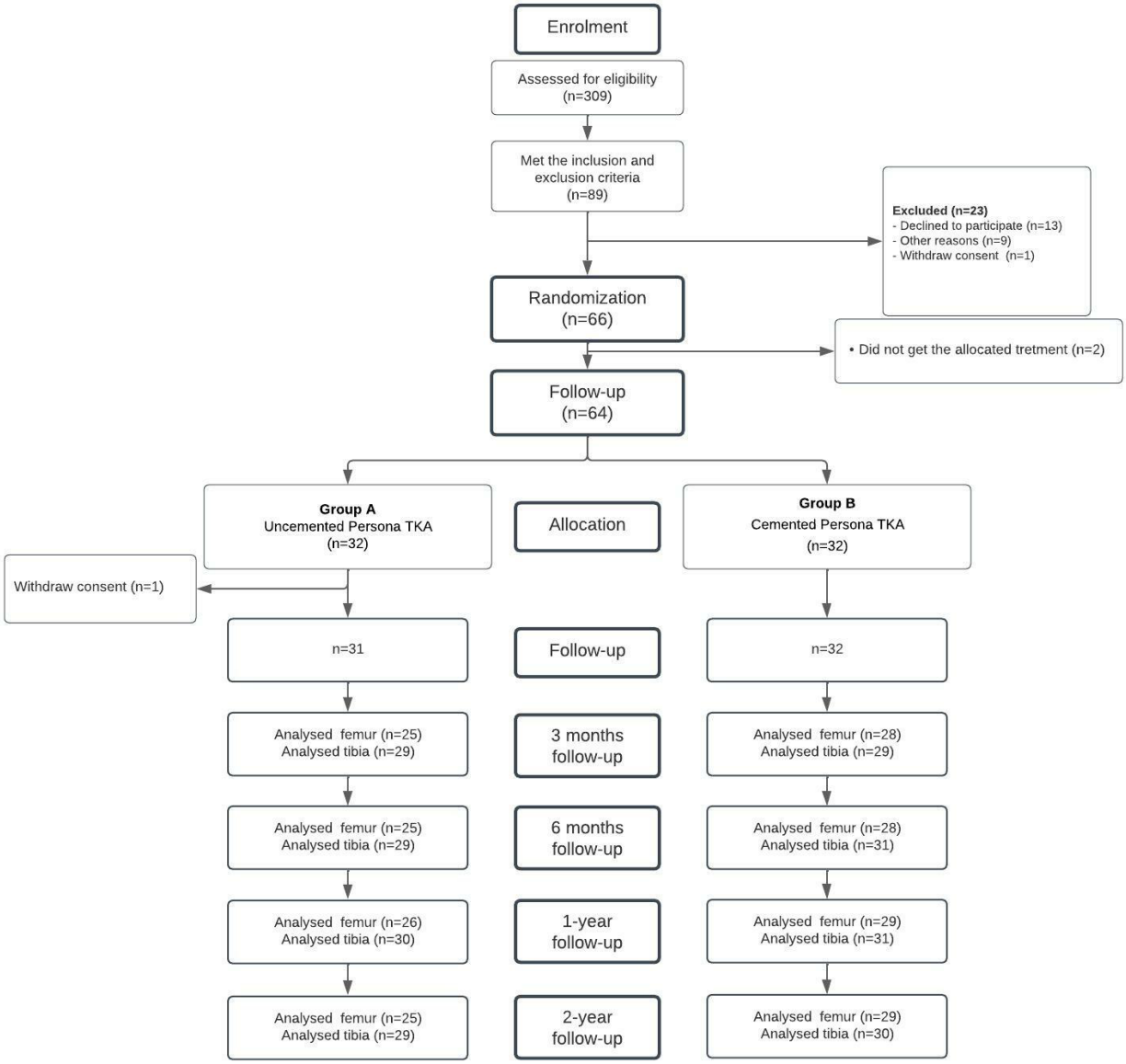

Figure 2: Mean MTPM for the cemented and uncemented trabecular metal femoral component. Whiskers indicate 95CI.

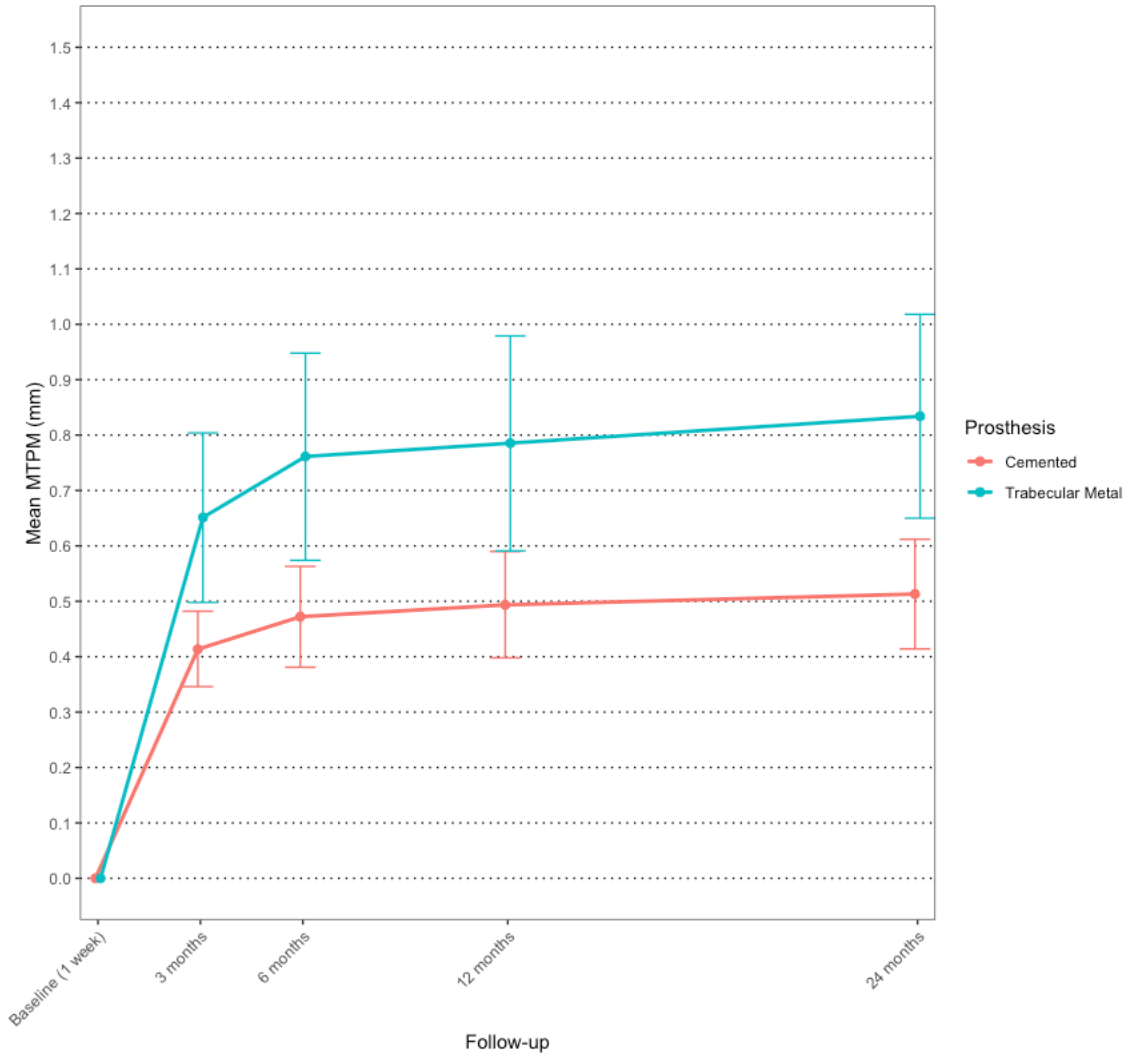

Figure 3: Mean MTPM for the cemented and uncemented trabecular metal tibial component. Whiskers indicate 95CI.

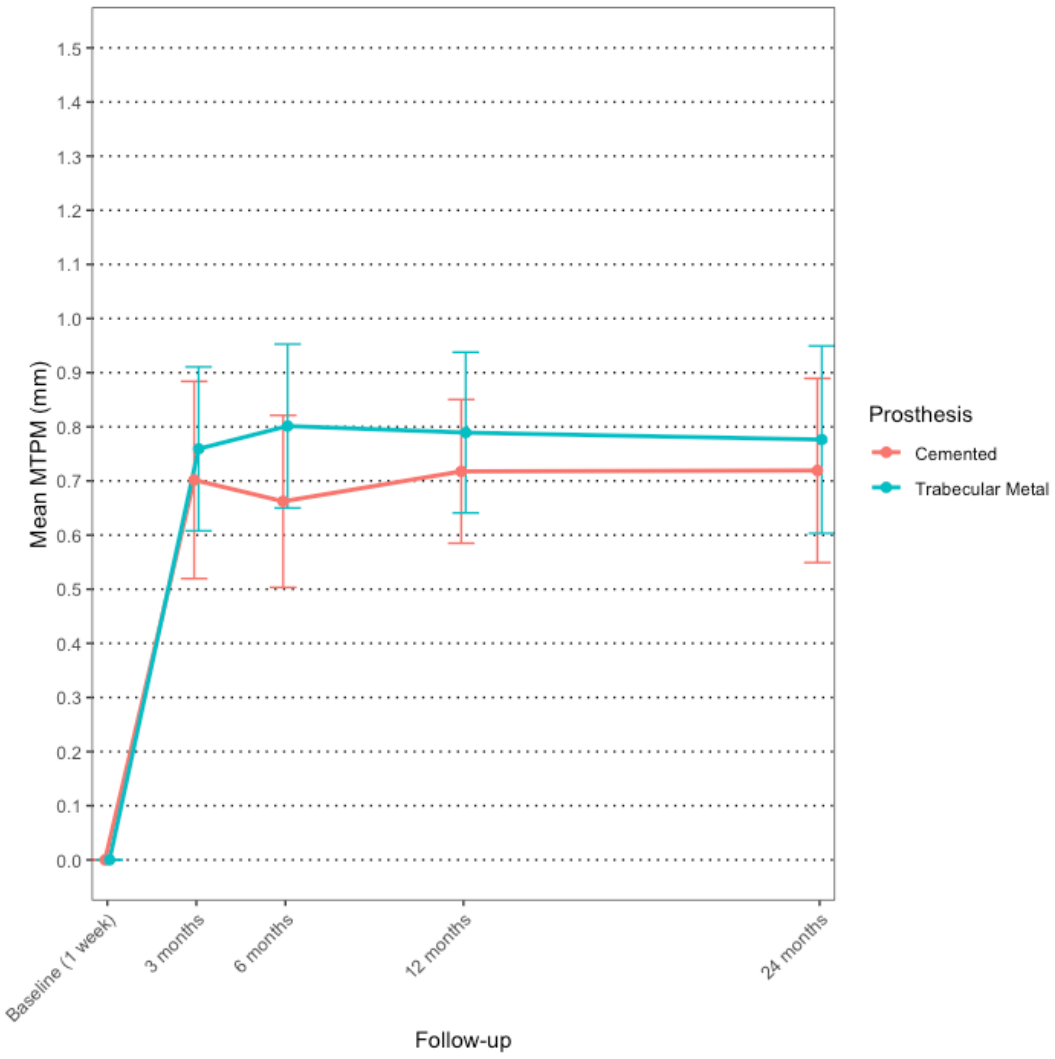

Table 1: Demography of the cohort

	Total (n=63)	Female (n=41)	Male (n=22)
Mean age at surgery (range)	62.4 (50.3 to 70.8)	62.1 (50.3 to 70.5)	62.8 (54.0 to 70.8)
BMI (range)	30.2 (21.6 to 46.1)	30.3 (21.6 to 43.7)	29.9 (23.5 to 46.1)
Smoking			
Never	31	20	11
Current	8	5	3
Former	24	16	8
ASA			
1	15	12	3
2	46	28	18
3	2	1	1
Anaesthesia			
General	27	17	10
Spinal	36	24	12
Surgery extremity			
Left	28	20	8
Right	35	21	14
Cemented	32	22	10
Uncemented	31	19	12
Prosthesis components			
Femoral size			
4	2	2	0
5	2	2	0
6	9	9	0
7	12	12	0
8	17	9	8
9	11	5	6
10	6	2	4
11	2	0	2
12	2	0	2
Standard	37	15	22
Narrow	26	26	0
Tibial size			
C	1	1	0
D	18	17	1
E	15	15	0
F	17	7	10
G	7	1	6
H	5	0	5
Insert	12 (10 to 18)	12 (10 to 18)	12 (10 to 14)
Patella	34 (29 to 41)	34 (29 to 41)	36 (32 to 41)

Table 2: Migration data represented as mean, (range), and [95CI], p-values marked with * are significant. P-values calculated with Mann-Whitney U test.

		3 months	p-value	6 months	p-value	12 months	p-value	24 months	p-value
Femur									
MTPM	Cemented	0.414 (0.137 to 0.911) [0.346 to 0.482]	0.04*	0.472 (0.137 to 1.18) [0.381 to 0.563]	0.03*	0.494 (0.119 to 1.05) [0.398 to 0.590]	0.02*	0.513 (0.207 to 1.03) [0.414 to 0.612]	0.02*
	Uncemented	0.651 (0.134 to 1.89) [0.498 to 0.804]		0.761 (0.201 to 2.66) [0.574 to 0.948]		0.785 (0.106 to 2.75) [0.591 to 0.979]		0.834 (0.252 to 2.19) [0.650 to 1.018]	
X-translation	Cemented	-0.066 (-0.541 to 0.171) [-0.122 to -0.010]	0.70	-0.035 (-0.558 to 0.321) [-0.093 to 0.023]	0.18	-0.041 (-0.803 to 0.242) [-0.109 to 0.027]	0.34	-0.026 (-0.405 to 0.415) [-0.087 to 0.035]	0.35
	Uncemented	-0.035 (-0.56 to 0.428) [-0.111 to 0.041]		0.351 (-0.543 to 0.516) [0.254 to 0.448]		0.034 (-0.419 to 0.433) [-0.044 to 0.112]		0.034 (-0.392 to 0.439) [-0.052 to 0.120]	
Y-translation	Cemented	0.002 (-0.387 to 0.215) [-0.042 to 0.046]	0.27	0.025 (-0.411 to 0.222) [-0.026 to 0.076]	0.37	0.033 (-0.321 to 0.29) [-0.015 to 0.081]	0.13	0.061 (-0.191 to 0.294) [0.017 to 0.105]	0.14
	Uncemented	0.053 (-0.174 to 0.436) [-0.004 to 0.110]		0.091 (-0.178 to 0.492) [0.022 to 0.160]		0.106 (-0.139 to 0.51) [0.041 to 0.171]		0.129 (-0.151 to 0.495) [0.063 to 0.195]	
Z-translation	Cemented	0.021 (-0.281 to 0.399) [-0.041 to 0.083]	0.71	0.033 (-0.365 to 0.944) [-0..063 to 0.129]	0.74	0.017 (-0369 to 0.539) [-0.064 to 0.098]	0.94	-0.016 (-0.391 to 0.483) [-0.089 to 0.057]	0.61
	Uncemented	-0.033 (-0.281 to 0.399) [-0.173 to 0.107]		-0.019 (-1.22 to 0.637) [-0.165 to 0.127]		-0.043 (-1.109 to 0.0539) [-0.163 to 0.077]		-0.013 (-0.967 to 0.683) [-0.153 to 0.127]	
X-rotation	Cemented	0.091 (-0.569 to 0.722) [-0.0149 to 0.197]	0.06	0.086 (-1.094 to 0.926) [-0.074 to 0.246]	0.11	0.098 (-0.719 to 0.872) [-0.053 to 0.249]	0.23	0.161 (-0.817 to 0.989) [0.015 to 0.307]	0.14
	Uncemented	-0.078 (-1.039 to 1.254) [-0.286 to 0.130]		-0.043 (-0.979 to 2.597) [-0.334 to 0.248]		0.063 (-0.942 to 2.647) [-0.202 to 0.328]		0.027 (-0.97 to 2.282) [-0.254 to 0.308]	
Y-rotation	Cemented	-0.031 (-0.529 to 0.441) [-0.122 to 0.060]	0.22	0.004 (-0.265 to 0.487) [-0.073 to 0.081]	0.23	-0.008 (-0.592 to 0.479) [-0.103 to 0.087]	0.76	-0.035 (-1.436 to 0.494) [-0.176 to 0.106]	0.26
	Uncemented	0.021 (-0.927 to 0.742) [-0.098 to 0.140]		-0.097 (-1.042 to 0.756) [-0.240 to 0.046]		-0.033 (-1.056 to 0.704) [-0.208 to 0.142]		-0.085 (-1.568 to 1.119) [-0.286 to 0.116]	
Z-rotation	Cemented	-0.08 (-0.841 to 0.508) [-0.173 to 0.013]	0.16	-0.028 (-0.851 to 0.716) [-0.103 to 0.047]	0.39	-0.049 (-0.935 to 0.188) [-0.137 to 0.039]	0.16	-0.026 (-0.516 to 0.667) [-0.110 to 0.070]	0.23
	Uncemented	0.007 (-0.476 to 0.529) [-0.089 to 0.103]		0.026 (-0.556 to 0.735) [-0.087 to 0.139]		0.068 (-0.765 to 0.927) [-0.060 to 0.196]		0.032 (-0.722 to 0.572) [-0.093 to 0.157]	
Tibia									
MTPM	Cemented	0.702 (0.203 to 2.23) [0.526 to 0.878]	0.18	0.662 (0.157 to 2.28) [0.503 to 0.821]	0.06	0.718 (0.114 to 1.65) [0.585 to 0.851]	0.39	0.719 (0.114 to 2.03) [0.549 to 0.889]	0.21
	Uncemented	0.759 (0.194 to 2.23) [0.607 to 0.911]		0.801 (0.355 to 2.07) [0.652 to 0.950]		0.789 (0.218 to 1.89) [0.640 to 0.938]		0.776 (0.185 to 1.92) [0.637 to 0.915]	
X-translation	Cemented	-0.051 (-0.865 to 0.269) [-0.139 to 0.037]	0.48	-0.069 (-0.613 to 0.289) [-0.141 to 0.004]	0.33	-0.065 (-0.586 to 0.297) [-0.131 to 0.001]	0.19	-0.413 (-0.453 to 0.304) [-0469 to -0.357]	0.18
	Uncemented	0.007 (-0.186 to 0.260) [-0.046 to 0.032]		-0.158 (-0.473 to 0.205) [-0.211 to -0.105]		-0.004 (-0.326 to 0.288) [-0.055 to 0.047]		0.0016 (-0.362 to 0.316) [-0.055 to 0.058]	
Y-translation	Cemented	0.024 (-0.192 to 0.389) [-0.018 to 0.066]	<0.001*	0.064 (-0.154 to 0.493) [0.020 to 0.108]	<0.001*	0.075 (-0.185 to 0.485) [0.028 to 0.122]	<0.001*	0.088 (-0.184 to 0.381) [0.041 to 0.135]	<0.001*
	Uncemented	-0.263 (-1.457 to 0.129) [-0.374 to -0.152]		-0.266 (-1.385 to 0.105) [-0.370 to -0.162]		-0.243 (-1.393 to 0.398) [-0.354 to -0.132]		-0.241 (-1.388 to 0.282) [-0.352 to -0.130]	
Z-translation	Cemented	-0.099 (-0.845 to 0.743) [-0.208 to 0.010]	0.61	-0.11 (-0.855 to 0.308) [-0.212 to -0.008]	0.42	-0.083 (-0.928 to 0.384) [-0.188 to 0.022]	0.81	-0.063 (-0.915 to 0.404) [-0.173 to 0.047]	0.95
	Uncemented	-0.084 (-0.699 to 0.354) [-0.164 to -0.004]		-0.129 (-0.517 to 0.201) [-0.195 to -0.063]		-0.088 (-0.749 to 0.193) [-0.188 to 0.022]		-0.044 (-0.685 to 0.338) [-0.133 to 0.045]	
X-rotation	Cemented	-0.097 (-1.125 to 0.968) [-0.248 to 0.054]	0.009*	-0.162 (-1.06 to 0.491) [-0.299 to -0.024]	0.002*	-0.163 (-1.14 to -1.28) [-0.306 to -0.0191]	0.07	-0.153 (-1.559 to 0.883) [-0.314 to 0.0074]	0.08
	Uncemented	-0.401 (-1.515 to 0.293) [-0.559 to -0.243]		-0.519 (-1.76 to 0.491) [-0.694 to -0.345]		-0.459 (-1.69 to 0.139) [-0.064 to 0.282]		-0.421 (-1.97 to 0.924) [-0.644 to -0.199]	
Y-rotation	Cemented	-0.156 (-1.769 to 1.85) [-0.406 to 0.094]	0.02*	-0.231 (-1.663 to 0.874) [-0.423 to -0.039]	0.007*	-0.015 (-1.277 to 2.122) [-0.234 to 0.204]	0.39	0.068 (-1.559 to 2.169) [-0.176 to 0.312]	0.40
	Uncemented	0.151 (-0.561 to 1.425) [-0.027 to 0.329]		0.149 (-0.681 to 1.839) [-0.037 to 0.335]		0.109 (-0.88 to 1.536) [-0.068 to 0.286]		0.172 (-0.722 to 1.242) [0.023 to 0.321]	
Z-rotation	Cemented	0.066 (-0.552 to 0.769) [-0.033 to 0.165]	0.86	0.119 (-0.334 to 0.749) [0.031 to 0.207]	0.64	0.126 (-0.312 to 0.512) [0.048 to 0.204]	0.52	0.126 (-0.489 to 0.744) [0.029 to 0.223]	0.50
	Uncemented	0.048 (-0.929 to 1.011) [-0.099 to 0.195]		0.144 (-0.959 to 0.994) [-0.020 to 0.308]		0.067 (-1.014 to 0.769) [-0.071 to 0.205]		0.017 (-1.033 to 0.671) [-0.130 to 0.164]	

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Müjgan Yilmaz
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Name of principal supervisor	Michael Mørk Petersen
Title of the PhD thesis	Cemented and uncemented trabecular metal total knee arthroplasty with asymmetrical tibial design. Comparison using model-based radiostereometric analysis, dual-energy x-ray absorptiometry, and computed tomography.

2. The declaration applies to the following article	
Title of article	Implant migration in cemented and uncemented knee arthroplasty with an asymmetrical tibial component. A randomized controlled trial with a 2-year model-based RSA follow-up
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☒
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	C

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
3. Planning of the experiments and methodology design and development	C
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] The PhD student (Müjgan Yilmaz) provided to all stages of the research.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	-
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	-

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**
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6. Signature of the principal supervisor
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7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 27/12-22 PhD student: Müjgan Yilmaz

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Study III

Adaptive bone remodeling after cemented and uncemented knee arthroplasty with an asymmetrical tibial component. Results from a randomized study using dual-energy X-ray absorptiometry.

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Declarations

Disclosures:

Dr. Yilmaz has nothing to disclose.

Dr. Lind has nothing to disclose.

Dr. Flivik reports institutional grants from Zimmer-Biomet, outside the submitted work. Furthermore, reports institutional grants outside the submitted work from Stryker, Depuy Synthes, JRI Ltd, Materialize, and Ortoma.

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Ethics approval and consent to participate:

Approval from the local Ethical Committee (case no. H-16035883) and Danish Data Protection Agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264) were obtained.
All patients were informed orally and in writing by the principal investigator and before inclusion informed consent was obtained by following the Helsinki Declaration.
Before inclusion, the randomized controlled study was registered at clinicaltrial.gov (protocol ID: PERSONA-RH-18, clinicaltrial.gov ID: NCT03563131)

Consent for publication:

All authors give consent for publication.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interest:

The authors have no competing interests.

Funding:

Grants from Zimmer Biomet were given to Rigshospitalet during the conduct of the study.

Authors' contributions:

Müjgan Yilmaz: Conducted data analysis, authored the text, and created the figures.
Gunnar Flivik: Oversaw the text and assisted in the interpretation of the findings.
Thomas Lind was the principal surgeon for the total knee arthroplasty carried out in this study and performed and oversaw data collecting.
Anders Odgaard: Oversaw the text and assisted in the interpretation of the findings.
Michael M. Petersen: Oversaw the preparation of the report, helped interpret the findings and planned the study.
Each author contributed to the development of the research and manuscript by offering constructive criticism.

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Abbreviations

OA:	Osteoarthritis
TKA:	Total Knee Arthroplasty
BMD:	Bone Mineral Density
RSA:	Radiostereometric Analysis
DEXA:	Dual-energy X-ray absorptiometry
PE:	Precision error
RCT:	Randomized Controlled Trial
ROI:	Region of Interest
KSS:	Knee Society Score
OKS:	Oxford Knee Score
95CI:	95% Confidence Interval

Introduction

Symptomatic advanced osteoarthritis (OA) is successfully treated with total knee arthroplasty (TKA) and implant survival of more than 90% after 10 years have been reported [1, 2]. However, TKA affects the mechanical loading of the knee joint which is associated with changes in bone mineral density (BMD) [3-5]. Changes in BMD around the TKA prosthesis components are clinically important as several studies have demonstrated that a decrease in BMD is associated with the breaking strength of the bone [6-8]. A decrease in BMD is related to periprosthetic fractures as well as a higher migration of the prosthesis components which can cause later aseptic loosening [9].
Subsequently to a TKA surgery, a decrease in BMD is expected due to the surgical trauma and following immobilization [10-13]. Moreover, stress-shielding and foreign body reactions are related to a decrease in BMD [10-13].

Different factors can influence the changes in BMD, of which the prosthesis design and fixation are important components. An uncemented prosthesis is press-fitted and relies on bone ingrowth, therefore different surfaces and coating are used to enhance the ingrowth [14-16].

The femoral prosthesis component prevents pressure from the patella to the anterior part of the distal femur condyles and instead stress-shielding occurs causing osteopenia in the area [17, 18].
Whereas stress-shielding causes osteopenia, wear, and foreign body reaction cause osteolysis [17-20]. Previous studies indicate that the anterior part of the distal femur is the bone area where the majority of BMD decrease (up to 44%) is observed [18-25]. Theoretically, the decrease in BMD could clinically bring the femoral component at risk of periprosthetic supracondylar fractures or loosening of the component [8, 20, 22, 26-28].

The decrease in BMD near the tibial prosthesis components is located in the medial plateau and is mainly caused by stress-shielding [29-31]. Some previous studies reported a decrease in BMD of up to 41 % [3, 25, 31-33], while other studies have reported unchanged or decreased of BMD in the proximal tibia one year postoperative regardless of fixation mode [10, 24, 32-35].

Studies comparing adaptive bone remodeling after TKA with a focus on implant fixation mode (cemented versus uncemented) and evaluation of uncemented asymmetrical tibia components are to our knowledge lacking.

Dual-energy X-ray absorptiometry (DEXA) is a reliable method to assess changes in BMD [3-5]. This study aimed to evaluate the adaptive periprosthetic bone remodeling by measuring the BMD, using DEXA, of the bone related to the femoral and asymmetrical tibial components (cemented and uncemented) after TKA and compare the remodeling pattern of the two groups.

Material and methods

Study design and patients

Patients in this study were included as a part of a randomized controlled trial (RCT) [36]. Data were prospectively collected, and randomization was performed with 1:1 allocation to either fully cemented or uncemented fixation of TKA and block randomized in blocks of 10.

Inclusion criteria were TKA surgery due to OA performed at Gentofte Hospital Department of Orthopaedic Surgery between September 2018 to October 2019, age between 40-70 years, and cognitively fit to understand and sign an informed consent. Patients with bone metabolism affecting diseases were excluded (figure 1).

Preoperatively 66 patients were measured with DEXA. Subsequently, two patients did not get the allocated treatment as they did not meet the criteria for the cruciate retaining TKA and hence were excluded. One patient from the cemented group withdrew consent after the allocation and was excluded. A total of 63 patients were included for further follow-up (cemented: n=31 and uncemented: n=32) (figure 1).

The demographics of these patients have been reported in a previous study [36].

DEXA and follow-up

DEXA measurements of the distal femur and proximal tibia on the surgical limb as well as both ankles were performed preoperatively and 1 week, 3 months, 6 months, 12 months, and 24 months

postoperative. All measurements were performed at the Department of Orthopaedic Surgery at Rigshospitalet, Copenhagen, Denmark by an experienced research nurse.

A double examination was performed at the 12-month follow-up. Subsequently to the first examination, the patient was requested to stand up, walk around, and again placed in position and rescanned.

To obtain measurements of the proximal tibia and both ankles, the patient was placed in a standardized supine position, the ankles fixed with a block, and weights were placed over the anterior crus to minimize movements. A small internal rotation was applied to minimize overlayer of the proximal tibia and fibula.

To obtain measurements of the distal femur, the patient was placed on the side of the surgical limb, with a small flexion in the knee and with weights over the ankle.

All measurements were performed with a Norland XR-46 bone densitometer (Norland Corp, Fort Atkinson, WI, USA), with a scan speed of 45 mm/s and a pixel size of 0.5x0.5 mm.

Prior to DEXA measurements, a daily calibration was performed for quality control. For analyses customized software was used to regulate the threshold for metal exclusion, allowing measurements of the bone adjacent to the component.

The DEXA images were analysed in the region of interest (ROI). To enable and distinguish the analyses of the BMD in the bone related to the tibial and femoral components the images were divided into three different ROIs. The tibial component was divided into two equal halves and a 4 cm. vertical line was drawn from the proximal to the distal part of the component (figure 2). The medial half was named ROI I and the lateral part ROI II. A vertical line of 2 cm. drawn from the distal part of ROI I and II including the whole bone segment formed the last ROI III (figure 2).

Similarly, the femoral component was divided into an anterior and posterior part. A vertical line through the pegs (two small pins in the distal and middle of the component) was drawn and once meeting a horizontal line from the apex of the femoral component the top of ROI I and II was formed (figure 3). The anterior part was named ROI I, and the posterior part ROI II. A proximal part, ROI III, was located 2 cm proximal to ROI I and II and included the whole bone segment (figure 3). All BMD measurements were measured in g/cm^2.

Statistical analysis and ethical statements

The mean coefficient of variation (CV) (CV = (standard deviation (SD)/mean) 100%) expresses the precision error of the BMD analyses in the different ROI of the proximal tibia and the distal femur.

The BMD data were checked for distribution and statistical tests were applied accordingly. An unpaired t-test was used to evaluate differences in BMD between the cemented and uncemented group of femoral and tibial components after 24 months. A paired t-test was used to evaluate the change from the first postoperative measurement to the measurement at 24 months.

Time-related changes in groups were evaluated with ANOVA. Statistical significance was set to $p<0.05$ and 95% confidence intervals were reported as CI 95. Statistical analyses were performed in Rstudio® (Version 1.2.1335 © 2009-2019 RStudio, inc.).

A difference of 8% between groups was assessed to be clinically meaningful and to provide a sample size with a high enough statistical power when comparing two fixation techniques. The greatest change in BMD is seen in the first postoperative year. A 5% type I error, 90% statistical power, 8% MIREDIF, and 8.4% SD are estimated. Although the calculation calls for 25 patients in each group, it was done with 60 patients—30 in each group—due to expected dropouts. Early dropouts were observed in our trial; as a result, 66 people were randomly assigned, leaving 63 patients for further follow-up.

Approval from the regional scientific ethical committee (case no. H-16035883) and Danish Data Protection Agency (case no. 2012-58-0004, RH-2017-36 and I-Suite nr: 05264) was obtained and the study was registered at clinicaltrial.gov (NCT03563131).

Results

Precision error measurements

Femur

Precision error for ROI I (anterior) was 1.86% (95CI: 1.45 to 2.28), ROI II (posterior) was 1.6% (95CI: 1.23 to 1.97) and ROI III (proximal) was 1.39% (95CI: 1.06 to 1.72).

Tibia

Precision error for ROI I (medial) was 2.12% (95CI: 1.67 to 2.56), ROI II (lateral) was 2.5% (95CI: 1.84 to 3.17) and ROI III (distal) was 2.13% (95CI:1.5 to 2.77).

Femoral component

In ROI I of the uncemented group, a decrease in BMD of 33% ($p<0.001$) from baseline to the 2-year follow-up was registered, and correspondingly a decrease of 21% ($p<0.001$) was seen in the cemented group. We found statistically significant differences between the fixation types throughout all follow-up measurements, and at 2 years of follow-up we found a mean difference of 12% ($p=0.004$) between the two groups (table 1, figure 4a).

In ROI II we also found a progressive decrease in BMD of both study groups ending with a decrease in BMD of 19% ($p<0.001$) and 13% ($p<0.001$) for respectively uncemented and cemented fixation after 2 years of follow-up. We found no statistically significant difference in the changes between the fixation types throughout all follow-up measurements in ROI II (table 1, figure 4b).

In ROI III we found we found a less pronounced and almost identical decrease in BMD of both study groups ending with a decrease in BMD of 7% ($p<0.001$) and 6% ($p<0.001$) for respectively uncemented and cemented fixation after 2 years of follow-up (table 1, figure 4c).

Tibial component

The changes in BMD below the tibia component were limited and a decrease after 2 years of follow-up between 0.4% and 5.5% was seen. Statistically significant changes were found only in ROI I (uncemented group) and ROI II (cemented group) with a decrease in BMD from baseline to the 2-year follow-up of respectively 4.4% ($p=0.005$) and 2.2% ($p=0.02$).

We found no statistically significant difference in the changes between the fixation types throughout all follow-up measurements in all 3 ROI (table 1, figure 5a, b).

Ankles

No significant change in BMD was found when comparing the ankle of the surgical limb with the contra-lateral side as well as the same site with baseline and 24 months follow-up.

Discussion

In this study, we evaluated the adaptive bone remodeling related to the femoral and tibial components following TKA surgery. We aimed to compare the differences between cemented and uncemented fixation.

The bone area with the greatest change in BMD was observed to be ROI I – the anterior part of the femoral bone behind the anterior flange. A statistically significant difference between the fixation types was observed. The decrease at 24 months was reported to be 21% in the cemented group and 33% in the uncemented group. This area is of notable clinical interest as previous studies have shown the highest decrease in BMD subsequently to TKA surgery in this anatomical location, which can increase the risk of periprosthetic fractures that require revision surgery [8, 26-28]. Several factors can lead to revision surgery of which aseptic loosening is the leading cause [37-39]. The risk of aseptic loosening can be assessed with radiostereometric analyses (RSA) measurement where high and continuous migration indicates a high risk of aseptic loosening. One previous study has demonstrated a low preoperative BMD is associated with high migration of the tibial component [9] and one study did not find any association between preoperative BMD and migration of the tibial component [40]. Therefore, a decrease in BMD as an implicated in the process leading to aseptic loosening, due to high migration, should be in consideration. A study on the same group of patients [36] measured migration and compared the amount of migration between the two fixation types. The study indicated a higher migration for the uncemented femoral components, and we speculate that these micromovements could be related to the higher decrease in BMD seen in the uncemented group in this present study. Aseptic loosening is rarely observed in the femoral components, and for this reason, RSA migration data with a higher migration observed in the uncemented component is not considered to have clinical relevance. However, the risk of periprosthetic fractures has been demonstrated to be higher in the distal femur than the proximal tibia which could be associated with the higher decrease in BMD observed in relation to the femoral component. Additionally, a decrease in the BMD is related to the breaking strength of the bone [8, 20, 22] and therefore a difference between the cemented and uncemented components could be clinically relevant.

For this reason, is it important to follow this group of patients for a longer period of time to measure if the decrease in BMD continues beyond 2 years of follow-up and observe if the risk of periprosthetic

fractures is higher for the uncemented group or if the pattern will change and a higher decrease in BMD will be observed for the cemented group later.

In this study, we observed the highest decrease in BMD in the anterior part of the femoral component within the first three months postoperatively with a tendency of stabilization throughout the follow-up period but without reaching a steady state. Several factors can influence the decrease in BMD of which surgical trauma is considered to cause the majority of the initial decrease, whereas the subsequent decrease could be caused by immobilization, stress-shielding and foreign body reaction [17, 18]. Our results are in concordance with previous studies that have reported a mean decrease of up to 44% under the anterior flange of the distal femur after 2 years [18, 19, 21-23].

In our study, the highest decrease in BMD related to the tibial component was found in ROI I – the medial part of the component with a decrease of 5.5% in the cemented group and 4.4% in the uncemented group. We did not find any significant difference between the fixation types related to the tibial component. Our findings are lower than those reported in previous studies where a mean medial decrease of up to 41% has been reported [3, 25, 31-33].

We did not find any difference in the BMD when comparing the ankle on the surgical limb to the contra-lateral ankle which indicates that the decrease in BMD observed in the bone related to the femoral and tibial components is not likely to be caused by immobilization as it then would be expected to observe a similar decrease in the ankle region. Instead, the decrease in BMD can be assumed to be caused by local adapting and bone remodeling.

Limitations

The postoperative measurements were performed with a mean of 7 days after surgery and we do not know if the patient experienced any bone significant remodeling within this week.

An important consideration when interpreting results related to a decrease in BMD following TKA surgery is that local changes caused by the disease might have increased the preoperative BMD measurements [41]. Therefore, the decrease seen postoperatively can be a result of the BMD returning to “normal” condition rather than an actual low BMD caused by the surgery.

Conclusion

We measured quantitatively the adaptive bone remodeling related to the femoral and tibial components following cemented and uncemented TKA surgery and found significant bone loss around the femoral components and with a particularly high decrease in BMD anteriorly where the bone loss was higher in uncemented (22%) compared to cemented (33%) implants.

The changes in BMD below the tibia component were limited and a decrease after 2 years of follow-up between 0.4% and 5.5% was seen.

The decrease in BMD around the femoral components might be of clinical importance with a risk of implant rated fractures, while the very limited changes below the tibial components seem to be without clinical importance.

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Figure 1 Enrolment

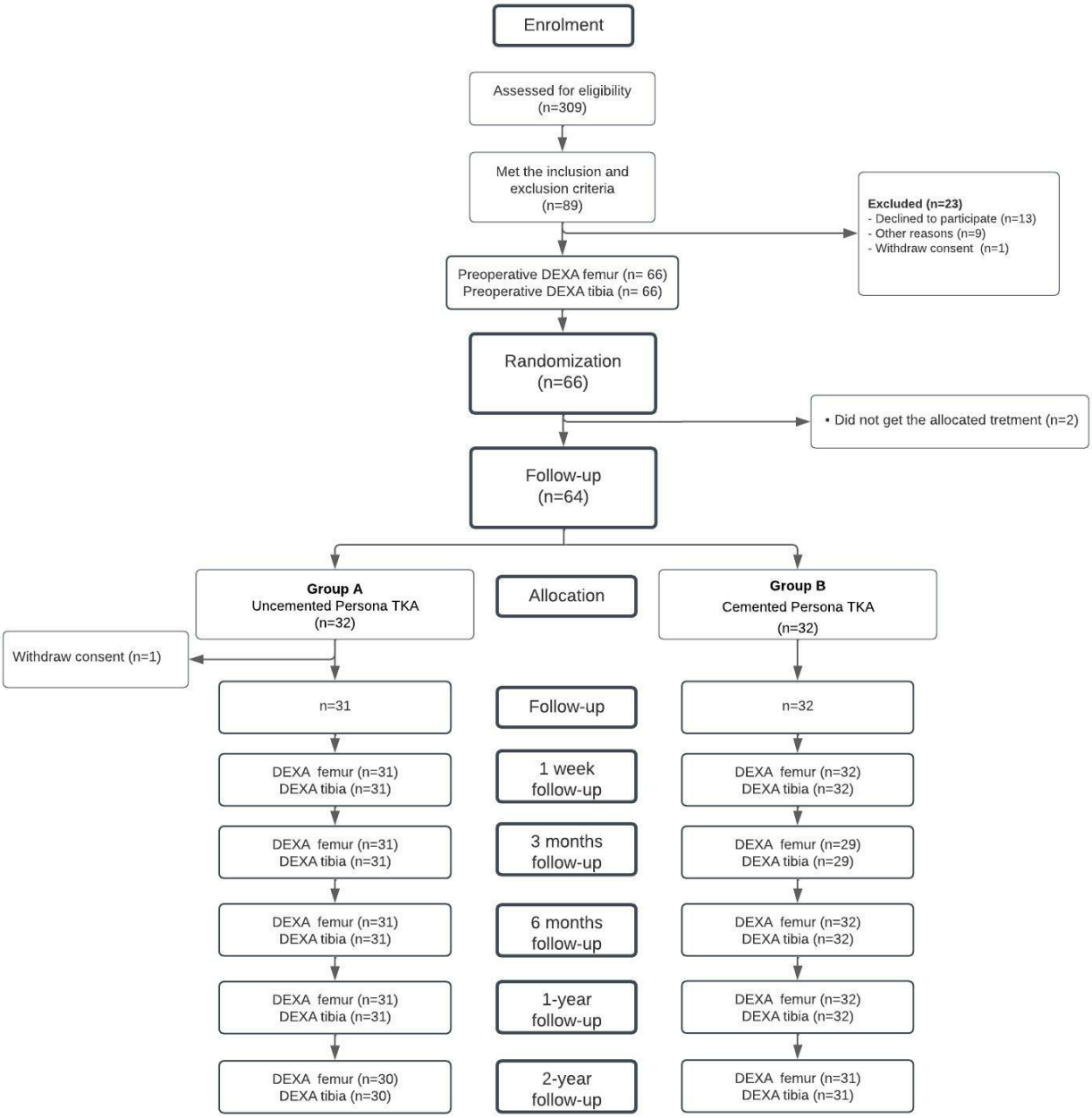


Figure 2 ROI in cemented (right) and uncemented (left) tibial components

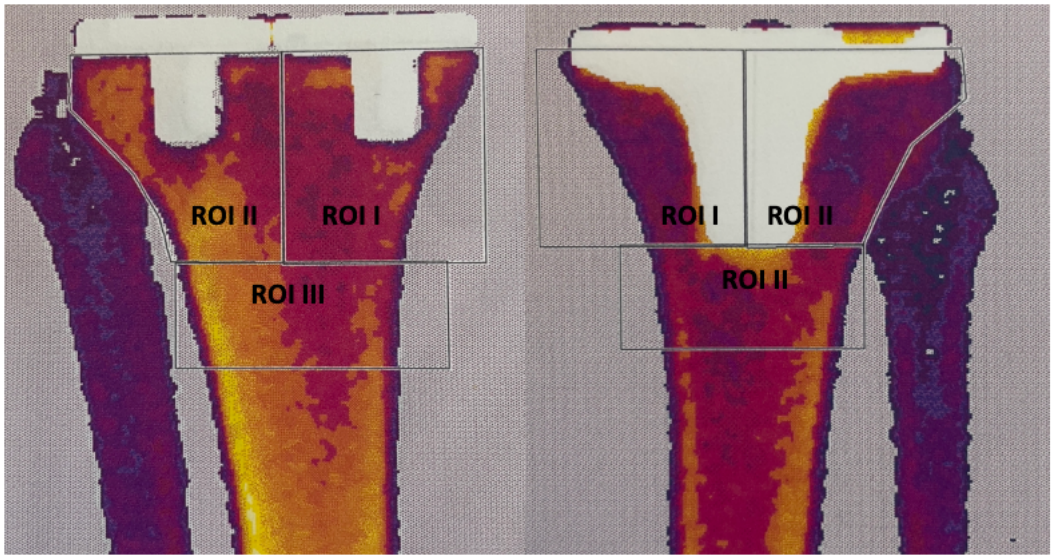


Figure 3 ROI in cemented (right) and uncemented (left) femoral components

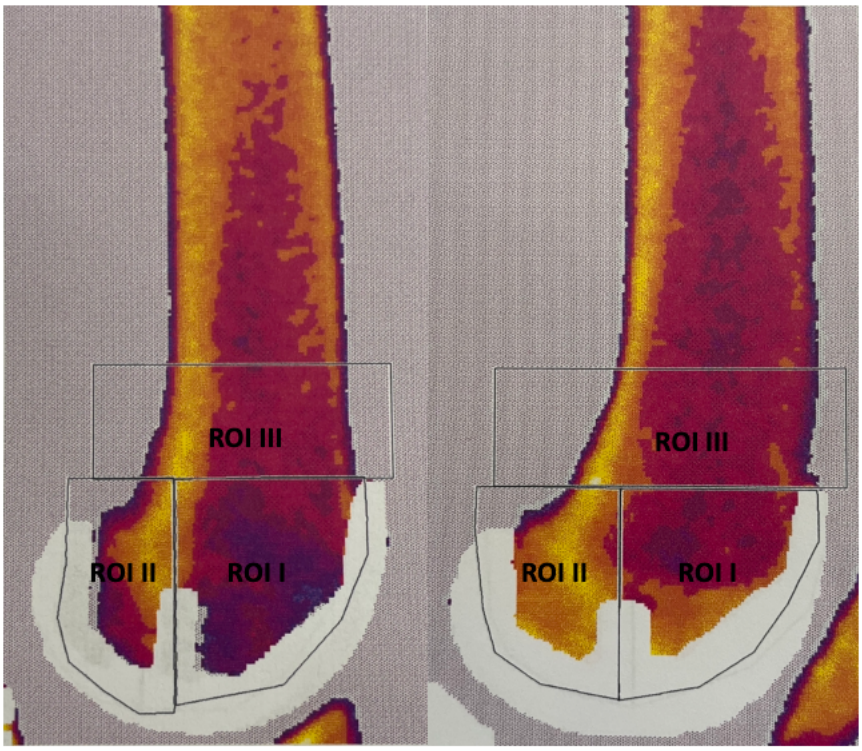
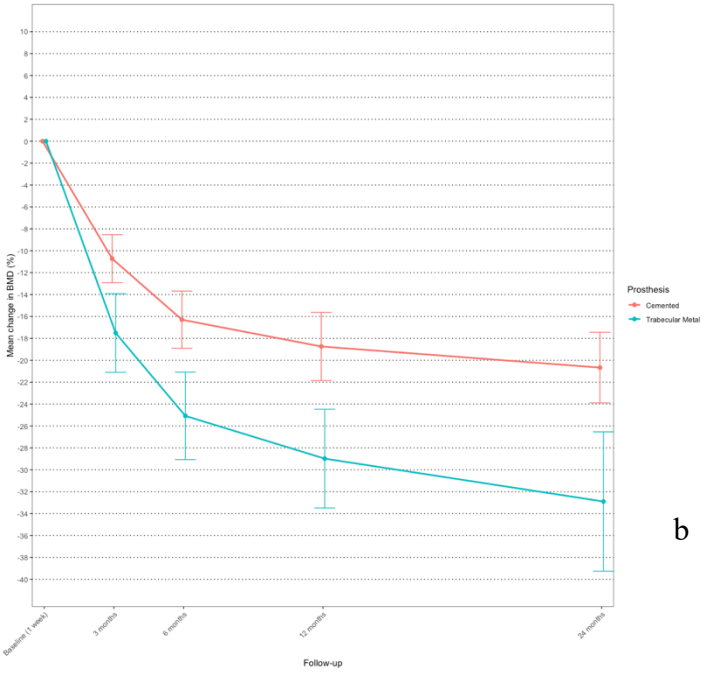


Figure 4 Changes in femoral component BMD for ROI I (upper), ROI II (middle) and ROI III (down), the whiskers indicate 95CI.

a



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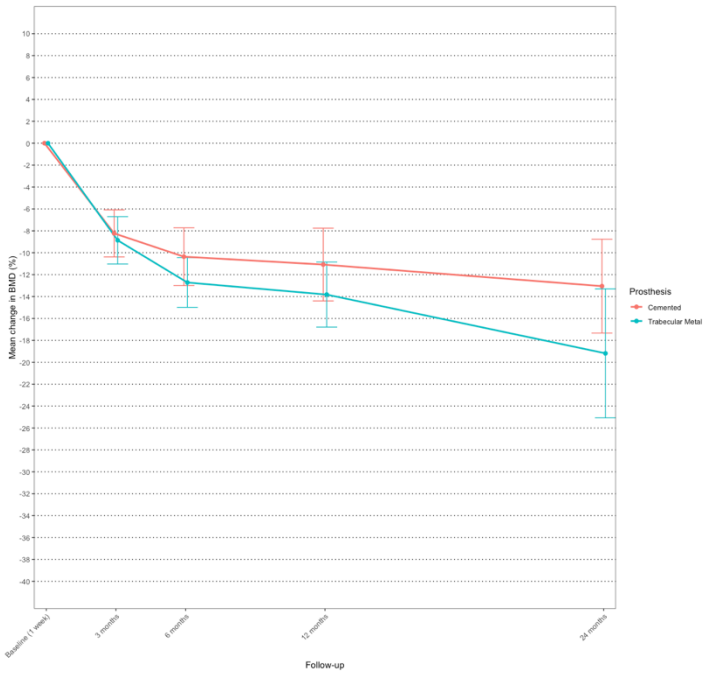

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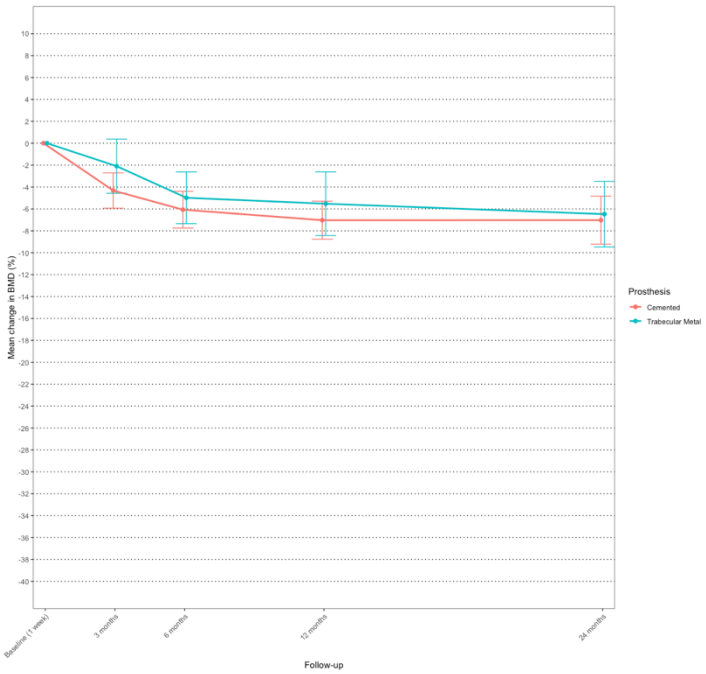
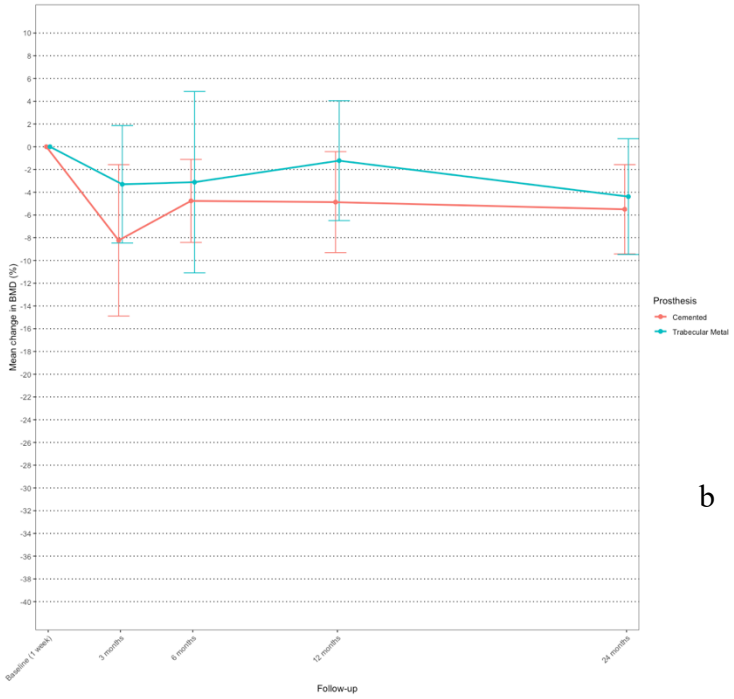
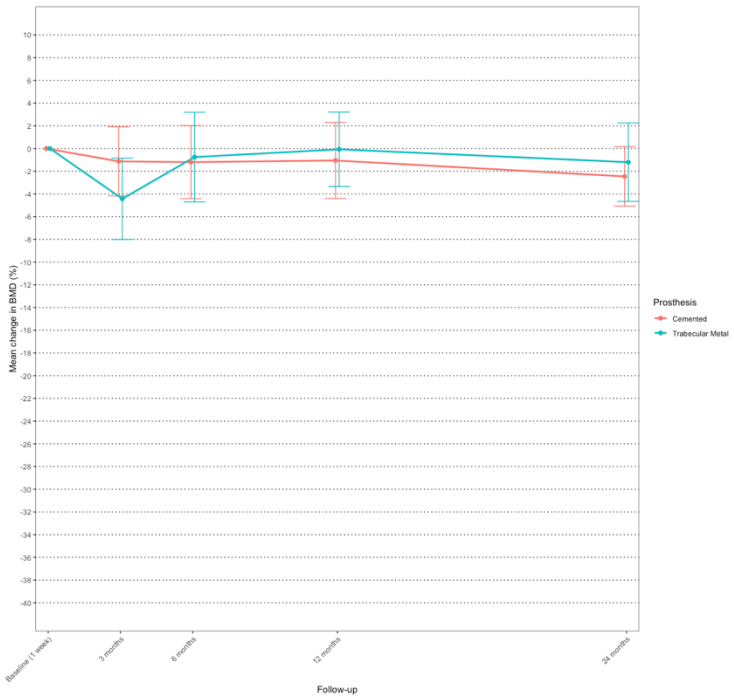


Figure 5: Changes in tibial component BMD for ROI I (upper), ROI II (middle) and ROI III (down), the whiskers indicate 95CI.

a



b



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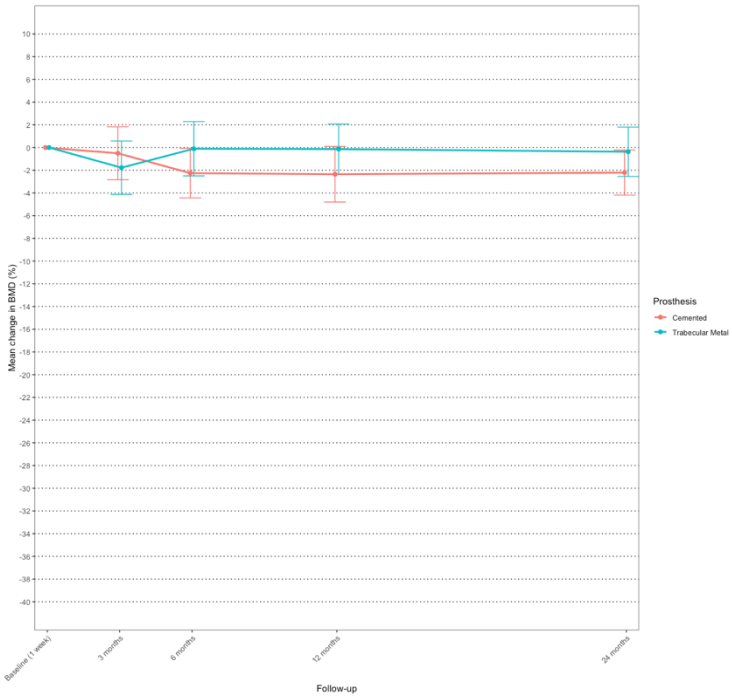


Table 1: Percentwise changes in BMD represented as mean and (95CI), p-values marked with * are significant.

		3 months	P-values	6 months	P-values	12 months	P-values	24 months	P-values	ANOVA	0-24 months
Femur											
ROI I	Cemented	-10.73 (-12.923 to -8.53)	0.029*	-16.29 (-18.91 to -13.68)	0.005*	-18.74 (-21.85 to -15.63)	0.001*	-20.67 (-23.89 to -17.44)	0.004*	0.0016*	<0.001*
	Uncemented	-17.51 (-21.10 to -13.92)		-25.08 (-29.07 to -21.08)		-28.98 (-33.48 to -24.47)		-32.89 (-39.26 to -26.53)		<0.001*	<0.001*
ROI II	Cemented	-8.23 (-10.38 to -6.08)	0.691	-10.36 (-13.00 to -7.72)	0.197	-11.08 (-14.40 to -7.72)	0.104	-13.05 (-17.33 to -8.77)	0.203	0.018*	<0.001*
	Uncemented	-8.86 (-11.02 to -6.70)		-12.72 (-14.99 to -10.44)		-13.82 (-16.79 to -10.85)		-19.18 (-25.07 to -13.30)		0.0115*	<0.001*
ROI III	Cemented	-4.32 (-5.93 to -2.71)	0.153	-6.07 (-7.74 to -4.39)	0.473	-7.03 (-8.76 to -5.30)	0.406	-7.03 (-9.22 to -4.84)	0.776	0.277	<0.001*
	Uncemented	-2.10 (-4.57 to 0.37)		-4.98 (-7.34 to -2.62)		-5.52 (-8.43 to -2.62)		-6.48 (-9.47 to -3.48)		0.466	<0.001*
Tibia											
ROI I	Cemented	-8.23 (-14.89 to -1.58)	0.190	-4.76 (-8.41 to -1.11)	0.205	-4.87 (-9.31 to -0.43)	0.111	-5.50 (-9.42 to -1.57)	0.247	0.518	0.005*
	Uncemented	-3.30 (-8.46 to 1.86)		-3.11 (-6.49 to 4.05)		-1.22 (-6.49 to 4.05)		-4.38 (-9.47 to 0.71)		0.535	0.0958
ROI II	Cemented	-1.13 (-4.17 to 1.92)	0.182	-1.19 (-4.41 to 2.03)	0.867	-1.05 (-4.39 to 2.30)	0.489	-2.45 (-5.08 to 0.17)	0.106	0.984	0.101
	Uncemented	-4.43 (-8.01 to -0.84)		-0.75 (-4.69 to 3.19)		-0.07 (-3.34 to 3.21)		-1.20 (-4.65 to 2.25)		0.768	0.291
ROI III	Cemented	-0.50 (-2.84 to 1.83)	0.203	-2.25 (-4.43 to -0.07)	0.163	-2.35 (-4.79 to 0.09)	0.298	-2.20 (-4.19 to -0.21)	0.883	0.679	0.0234
	Uncemented	-1.77 (-4.12 to 0.58)		-0.10 (-2.49 to 2.28)		-0.14 (-2.35 to 2.08)		-0.37 (-2.54 to 1.80)		0.955	0.5989

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

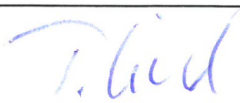
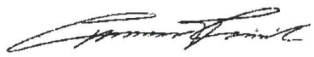
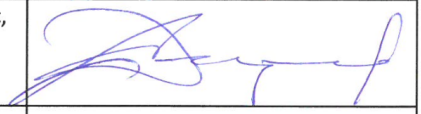
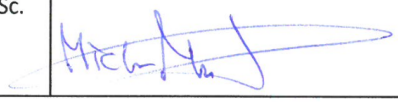
1. Declaration by	
Name of PhD student	Müjgan Yilmaz
E-mail	yilmaz_mujgan@hotmail.com
Name of principal supervisor	Michael Mørk Petersen
Title of the PhD thesis	Cemented and uncemented trabecular metal total knee arthroplasty with asymmetrical tibial design. Comparison using model-based radiostereometric analysis, dual-energy x-ray absorptiometry, and computed tomography.

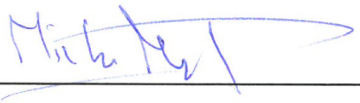
2. The declaration applies to the following article	
Title of article	Adaptive bone remodelling after cemented and uncemented knee arthroplasty with an asymmetrical tibial component. Results from a randomized study using dual-energy X-ray absorptiometry
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☒
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

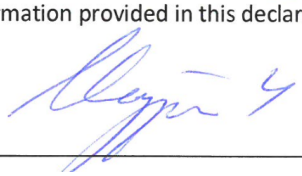
3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	C

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
3. Planning of the experiments and methodology design and development	C
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] The PhD student (Müjgan Yilmaz) provided to all stages of the research.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	-
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	-

5. Signatures of the co-authors[iii]				
	Date	**Name**	**Title**	**Signature**
1.	19/12-22	Thomas Lind	MD	
2.	21/12-22	Gunnar Flivik	Assoc. Prof. MD. PhD.	
3.	21/12-22	Anders Odgaard	Prof., DMSc, MD, FRCS	
4.	27/12-22	Michael Mørk Petersen	Prof. DMSc. MD	

6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 27/12-22 Principal supervisor: Michael Mørk Petersen 

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge. Date: 27/12-22 PhD student: Müjgan Yilmaz 

Please learn more about responsible conduct of research on the Faculty of Health and Medical Sciences' website.

[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

"Any articles included in the thesis may be written in cooperation with others, provided that each of the co-authors submits a written declaration stating the PhD student's or the author's contribution to the work."

Study IV

Influence of tibial component overhang and bone surface coverage on implant migration. Evaluation of a cemented asymmetrical tibial component using computed tomography and model-based RSA.

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Declarations

Disclosures:

Dr. Yilmaz has nothing to disclose.

Dr. Flivik reports institutional grants from Zimmer-Biomet, outside the submitted work. Furthermore, reports institutional grants outside the submitted work from Stryker, Depuy Synthes, JRI Ltd, Materialize, and Ortoma.

Dr. Lønstrup Harving: has nothing to disclose.

Dr. Lind has nothing to disclose.

Dr. Odgaard reports institutional grants from Zimmer-Biomet, outside the submitted work.

Dr. Christtensson: has nothing to disclose.

Dr. Petersen reports institutional grants from Zimmer Biomet, during the conduct of the study; institutional grants from Ethicon UK, and institutional grants from Zimmer Biomet, outside the submitted work.

Consent for publication:

All authors give consent for publication.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing interest:

The authors have no competing interests.

Funding:

Grants from Zimmer Biomet were given to Rigshospitalet during the conduct of the study.

Authors' contributions:

Müjgan Yilmaz: Performed data collection, analysed data, and drafted the manuscript.
Gunnar Flivik: Contributed to the interpretation of the results and supervised the manuscript.
Mette Lønstrup Harving: Analysed data.
Thomas Lind: Performed and supervised data collection and was the leading surgeon on the total knee arthroplasty performed in this study.
Anders Odgaard: Contributed to the interpretation of the results and supervised the manuscript.
Albin Christtensson: Contributed to the interpretation of the results and supervised the manuscript.
Michael Mørk Petersen: Planned the study, contributed to the interpretation of the results and supervised the manuscript.
All authors provided critical feedback and helped to develop the research and manuscript.

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Abbreviations

TKA:	Total Knee Arthroplasty
RSA:	Radiostereometric Analysis
OA:	Osteoarthritis
MTPM:	Maximal Total Point Motion
CT:	Computed tomography
SEMAR:	Single Energy Metal Artefact Reduction
CAD:	Computer-Aided Design
TM:	Trabecular metal
CR:	Cruciate retaining
MC:	Medial congruent
CN:	Condition number
ME:	Mean error
PE:	Precision error
95CI:	95% Confidence Interval
SE:	Sweden
DK:	Denmark
PACS:	Picture Archiving and Communication System

Introduction

Postoperative persistent pain is the main complaint from patients receiving a total knee arthroplasty (TKA) [1, 2]. The most common cause for patients to receive a TKA surgery is advanced symptomatic osteoarthritis (OA) and worldwide more than 250 million people are affected by OA [3]. Although a wide array of alternative treatments such as dietary intake, physical exercise, or weight loss might alleviate some of the symptoms [4, 5], the mainly used efficient treatment for advanced symptomatic end-stage OA is surgery [6, 7]. Depending on the severity and advancement of the OA the patient receives either a TKA or unilateral prosthesis in case of unicompartmental OA [4]. Postoperative pain is the main complaint from around 20% of patients receiving a TKA and is considered to be multifactorial [2]. However, studies have suggested that the rotation of the tibial component may be a part of the explanation of the persistent pain after TKA [8, 9]. An additional explanatory hypothesis is that the overhang and coverage of the symmetrical tibial components also contribute to the persistent postoperative pain [8, 10].

Asymmetrical tibial component have been developed to ensure a better anatomical fit with regards to both the positioning, good coverage, and minimal overhang of the tibial component. Due to the design of the asymmetrical component, the assumption was that it should alleviate and possibly eliminate some of the persistent postoperative pain. When introducing new orthopaedic implants – especially new designs in which the anatomical fit has been altered – it is of the highest importance to evaluate if the risk of aseptic loosening is affected.

Currently used TKA prostheses have demonstrated a very high implant survival of >90% [11, 12]. However, postoperative complications remain the leading cause of revision surgery of which aseptic loosening is an important contributor [13]. Components with segmental motion and/or high or continuous migration have an increased risk of aseptic loosening [14, 15].

The migration and segmental motion can be measured with radiostereometric analyses (RSA) and the measurements can provide information regarding components at risk of aseptic loosening [15]. Rotational alignment and coverage of the component can be evaluated using computed tomography (CT) which can assess the positioning of the component to the adjacent tibial plateau.

This study aimed to evaluate the coverage and rotational alignment of the asymmetrical tibial component. Additionally, the study aimed to evaluate if the positioning of the tibial component had an impact on the tibial component migration.

Material and methods

Patients

Patients included in this study were part of two separate completed RCT studies from Denmark [16] and Sweden (SE) [17] in which inclusion, exclusion, randomization, and demographic characteristics have been described. Flowcharts from the studies demonstrate the inclusion of n=66 [16] and n=60 [17] respectively.

All patients received a Persona® (Zimmer Biomet, Warsaw, Indiana, USA) TKA due to OA in both cohorts in which the tibial component had an asymmetrical design.
Procedures were performed by experienced surgeons specialized in arthroplasty surgery in accordance with the company's guidelines.

Overall, 126 patients were eligible post-randomization for this study (DK n=66 and SE n=60). To be included in this study patients had to have a CT scan performed postoperative onetime within the 2-year follow-up, and additionally have RSA measurements at baseline and at the 2-year follow-up. Patients who had revision surgery that resulted in exchange of the bone-anchored components within 2 years postoperatively were excluded.
A total of 111 patients (DK n=59 and SE n=52) were included in this study (figure 1) of which 29 patients from Denmark were uncemented and the remaining n=30 from Denmark and n=52 from Sweden were cemented tibial components.

Patients had a mean age of 65 years (SD 8, range: 51 to 86 years). Females (n=69) constituted 62.2%, and males (n=42) 37.8%.

RSA

The RSA setup, measurements, and intervals of follow-up are described in the original RCT studies from Denmark [16] and Sweden [17]. All measurements were performed according to RSA guidelines [14, 15, 18].

Software used for analysing the RSA results was model-based software (Model-Based RSA 4.1, 2003-2014 RSAcore Department of Orthopedics Leiden University Medical Centre) with this software Computer-Aided Design (CAD) models produced in Leiden (RSAcore Department of Orthopedics Leiden University Medical Centre) was used for analyses. All analyses were performed at Skane University Hospital, Lund, Department of Biomechanics.

The condition number (CN), representing the distribution of tantalum markers, and mean error (ME), representing the stability of tantalum markers, were both determined by the analysis program [18]. According to the guidelines for CN it is recommended to be 120-150 [18]. In the Danish RCT study [16] the CN was considered acceptable if below 150, whereas the Swedish RCT study used CN below 120 as an acceptable level [17]. For both RCT studies an acceptable ME was established as below 0.35 [18].

Migration of the component was expressed as Maximal Total Point Motion (MTPM) which represents the highest migration point.

The precision was calculated by double examination RSA measurements in both RCT studies and found acceptable [16, 17].

CT

During the 2-year follow-up period in the original RCT studies, all patients had a bilateral CT scan of the hip, knee, and ankle joints including one scout image of the pelvis and both extremities. All scans were performed according to an identical protocol describing the radiological setup.

All scans were performed using Single Energy Metal Artifact Reduction (SEMAR) technique.

The coverage of the tibial component and rotational alignment of the component was evaluated based on the CT scans.

All patients were pooled and anonymized by assigning a random numerical code to each patient in Picture Archiving and Communication System (PACS). Impax Client was used to analyse the CT scans. For each patient, four measurement sequences corrected for alignments in the axial and coronal plane were created to improve visualization of the tibial component.
To investigate the intratester reliability of the CT scans the principal investigator performed two measurement sequences using the same scan of each patient on coverage and rotation of the component. To investigate the intertester reliability one set of the measurements was sent to a blinded radiologist for evaluation whereas the other set was evaluated by the principal investigator.

Tibial coverage

The CT image in which the component was best visualized was used to template the border of the component (figure 2 – marker A). A line in the centre of the component from anterior to posterior divided the component into a medial and a lateral part (Figure 2 – line C). Subsequently, a line in the horizontal direction perpendicular to the anterior-posterior line divided the component into an anterior and posterior part (figure 2 – line D). Together, these two lines created four areas namely an anterior-medial (AM), anterior-lateral (AL), posterior-medial (PM), and posterior-lateral (PL) (figure 2). Secondly, the image in which the bone was clearly visualized was used to template the cortex of the tibial bone (figure 2 – marker B). If the component was cemented the first image free from cement was used to define the cortex of the tibial bone.

The software provided an instant calculation of the area of the component templated by the circumference marked A as well as the area of the tibial bone adjacent to the component marked B. The coverage in percentage was calculated by diving A/B x 100.

Tibial overhang

The overhang was measured individually in each of the four areas (AM, AL, PM, PL) by highlighting the difference in the circumferences of A and B (figure 2). The overhang was measured in mm^2 and presented as the percentual overhang by dividing the total overhang area by the total area of the component (A).

Tibial rotation

The image visualizing the tuberosity tibia was used to identify and mark the 1/3 medial of the tibial tuberosity (anterior). Subsequently, the image in which the PCL insertion was visualized was used to connect a line from the mark of 1/3 of the tibial tuberosity to the PCL insertion point (figure 3 – line E). The angle between line C and line E was calculated and used to express the rotation of the tibial component (figure 3).

Statistical analysis and ethical statements

Statistical analyses were performed in RStudio® (Version 1.2.1335 © 2009-2019 RStudio, inc.).

RSA results were reported with MTPM and segmental motion (translation/rotation along the X, Y, and Z axis). Statistical significance was set at $p < 0.05$ and confidence intervals were stated at 95% (95CI).

Inter- and intra-observer reliability was presented with interclass correlations coefficient (ICC), model 2, and 95CI, and the absolute reliability was visualized with a Bland Altman plot. Linear regression was used to predict the relationship between MTPM and coverage or MTPM and rotation.

Approval from the Danish local Ethical Committee (case no. H-4-2014-079)), Danish Data Protection Agency (case no. GEH-2015-079, I-Suite no. 03764), Swedish Regional Ethical Board at Lund University (Dnr 2017/73), as well as the local Swedish radiation committee was obtained.

This study is a part of two randomized studies registered at ClinicalTrials.gov with NCT02656771 and NCT03494348 [19].

In compliance with the Helsinki Declaration, oral and written information was provided to every patient, and informed consent was obtained before inclusion. Data are available on reasonable request.

Results

Inter- and intratester reliability

The inter – and intratester reliability for total coverage was ICC=0.98 and ICC= 0.99 respectively. The inter – and intratester reliability for rotation was ICC=0.95 and ICC=0.97 respectively.

Bland Altman plots were performed to visualize any systematic differences between two measurements performed by the investigator for coverage (figure 3 - A) and rotation (figure 3 – B) and between the investigator and the radiologist correspondingly (figure 4 – A and B).

Coverage and rotation

A total of 111 patients (SE=52 and DK=59) with complete CT scans were included. The mean total coverage percentage was 86.4% (SD 5.7) in the entire cohort. The total coverage among the cemented components was 87.2% (SD 5.2) and correspondingly 85.3% (SD 6.9) in the uncemented components.

The majority of the tibial components were placed in an external rotation (n=97) with a mean of 4.6° (SD 3.2), and a few components were placed in an internal rotation (n=9) with a mean of 3.6° (SD 1.9), the rest was in neutral. Mean total rotation was for the cemented group (n=82) and the uncemented group (n=29), the corresponding values were 4.1° (SD 3.0) and 5.4° (SD 3.5) in external rotation.

Overhang/under coverage

The tibial component was divided into four quadrants as described in the methods section (AM, AL, PM, PL – figure 2). The highest mean overhang was found in the posterior medial part of the component in 84 patients (mean 60.6 mm^2, 95CI: 49.1 to 71.8). In the anterior medial part, the mean overhang was 15.2 mm^2 (95CI: 10.8 to 19.6), anterior lateral 31.4 mm^2 (95CI: 24.3 to 38.6), and posterior lateral 34.3 (95CI: 25.6 to 42.9).

The highest mean under-coverage (207.6 mm^2, 95CI: 189.7 to 225.4) was observed in the posterior medial part. In the posterior-lateral part, a similar under-coverage was observed with a mean of 200.7 mm^2 (95CI: 181.8 to 219.7) (table 2).

Coverage and MTPM

Linear regression analysis stated that the coefficient of determination between MTPM and coverage percentage was low (R^2=1.5%) (figure 5 – A) thus indicating a poor relationship between the two variables, the same results were observed when divided into a cemented group (R^2=0.01%) (figure 5 – B) and an uncemented group R^2=15.6% (figure 5 – C).

Rotation and MTPM

Linear regression with the coefficient of determination between MTPM and rotation was calculated for all, cemented, and uncemented tibial components and we found correspondingly the following values for the coefficient of determination R^2=4.7%, R^2=5.4%, R^2=6.6%, (figure 5 – D, E, F).

Discussion

The objective of this study was to assess the rotational alignment and coverage of the asymmetrical tibial component. Additionally, this study evaluated whether implant migration was impacted by the positioning of the tibial component.
We found no relationship between either migration expressed as MTPM and coverage or between MTPM and rotation of the tibial component. However, we found a very high inter – and intratester reliability both on total coverage and rotational measurements.

Coverage of the tibial component is crucial for implant durability, patient satisfaction, postoperative pain, and function [20-23]. Several studies have demonstrated that asymmetrical tibial components have better coverage than symmetrical components when rotation also is accounted for [24-27]. It is assumed that better coverage will contribute to less migration which will lead to fewer revision surgeries due to aseptic loosening. Additionally, better coverage is thought to decrease postoperative pain and increase patient satisfaction and functional outcomes.
Previous studies have demonstrated that coverage >75% increases implant survival as well as decreases the risk of subsidence [21, 28-32]. Additionally, Klasan et al. [33] found that increased coverage was correlated with an increased KOOS (Knee injury and Osteoarthritis Outcome Score) indicating a higher functional outcome in the patient [33]. Moreover, increased tibial coverage might enhance fixation by boosting weight transmission from the implant to the proximal tibia and thereby prevent loosening [29, 34]. Although numerous studies have concluded the positive effects of increased coverage, there is a lack of conclusive evidence that evaluates the most advantageous percentual coverage to achieve the positive effects.

In our study, we found a total coverage of 86.4% of the tibial component. A very high coverage indicates that the risk of migration should be decreased. Although a small difference in the percentual coverage between the uncemented group (85.3 %) and cemented group (87.2%) was observed this is considered to be of no clinical relevance. Previous studies reported coverage of the tibial component ranging from 76% - 88% [26, 33, 35], thus the coverage percent obtained with persona TKA could be considered in the high end of the spectum for coverage percetages previously published.

The rotational alignment of the tibial component is also considered to be of great importance as misalignment of the tibial component is a major cause of revision surgery and also a contributing factor for other complications [20, 36].
Numerous studies have concluded that internal rotation of the component increases the risk of postoperative pain, extensor mechanism deficiency, patellar fractures and anterior knee pain leading to patient dissatisfaction [28, 37-39]. A systematic review by Panni et al. [40] concludes that an internal rotation >10° increases the risk of poor outcomes [40], whereas Bell et al. [39] finds that an internal rotation >5.8° is related to pain [39]. Only 9 out of 111 patients in our study demonstrated an internal rotation of the tibial component postoperative with a mean internal rotation of 3.6 (95CI: 2.3 to 4.8) which is below the acceptable threshold presented by the company, which aims for a rotation alignment within 5° [41].
Several studies endorse that a surgical compromise might be necessary to achieve the best rotational alignment causing a decrease in the coverage of the tibial component [22, 28, 34].

Due to the negative impact of internal rotation surgeons aim to place the tibial component in an external rotation. Bell et al. [39] conclude that excessive pain was not associated with excessive external rotation of the component, however, excessive values were not clearly defined [39]. Additionally, one study suggests that isolated external rotation can cause tissue impingement due to overhang [42]. To avoid this perioperative component downsizing is chosen which might decrease coverage of the tibial component [42]. A study by Kim et al. [43] suggests that external rotation of the tibial component of <2° increases the risk of failure of the tibial component and the recommended external rotation should be between 2-5° [43].
Maderbacher et al. [44] suggest that 6° external rotation is most optimal to restore a tibial rotation similar to the preoperative rotation indicating a well-balanced TKA [44].

Klasan et al. [33] suggest a “safe zone” between 7° internal and 3° external rotation from the axes as described in the study by Insall et al [45]. Klasan et al. [33] emphasize that the numbers should be considered as a “safe zone” rather than actual threshold values. Data from our study are in concordance with the safe zone described by Klasan et al. [33]. In our study, the majority of the tibial components (85.8%) were placed in an external rotation (mean: 4.6°).

The external validity of rotational alignment is compromised as there is a lack of agreement on measuring methodology. There is a consensus about using anatomical landmarks as guidelines for measurements and most studies use the description provided by Insall et al. [45]. The tibial tubercle and the posterior axis of the tibia are two different and less clearly defined bone markers for the asymmetric proximal tibia [27, 31, 36, 46-48]. However, there is individual variance in anatomical landmarks which can lead to unknown skewness of the results [46].

Strengths and limitations

The Danish and Swedish health care systems are based on universal health care enabling all patients to have TKA surgery if needed. By merging data from two cohorts, we increased our sample size thereby increasing both the internal and external validity of our results.

Conclusion

Asymmetrical tibial components show excellent coverage and rotational positioning when evaluated with CT scans with very high inter – and intra-reliability. The positioning of these components does not show high migration when evaluated with RSA.

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Figure 1: Enrolment

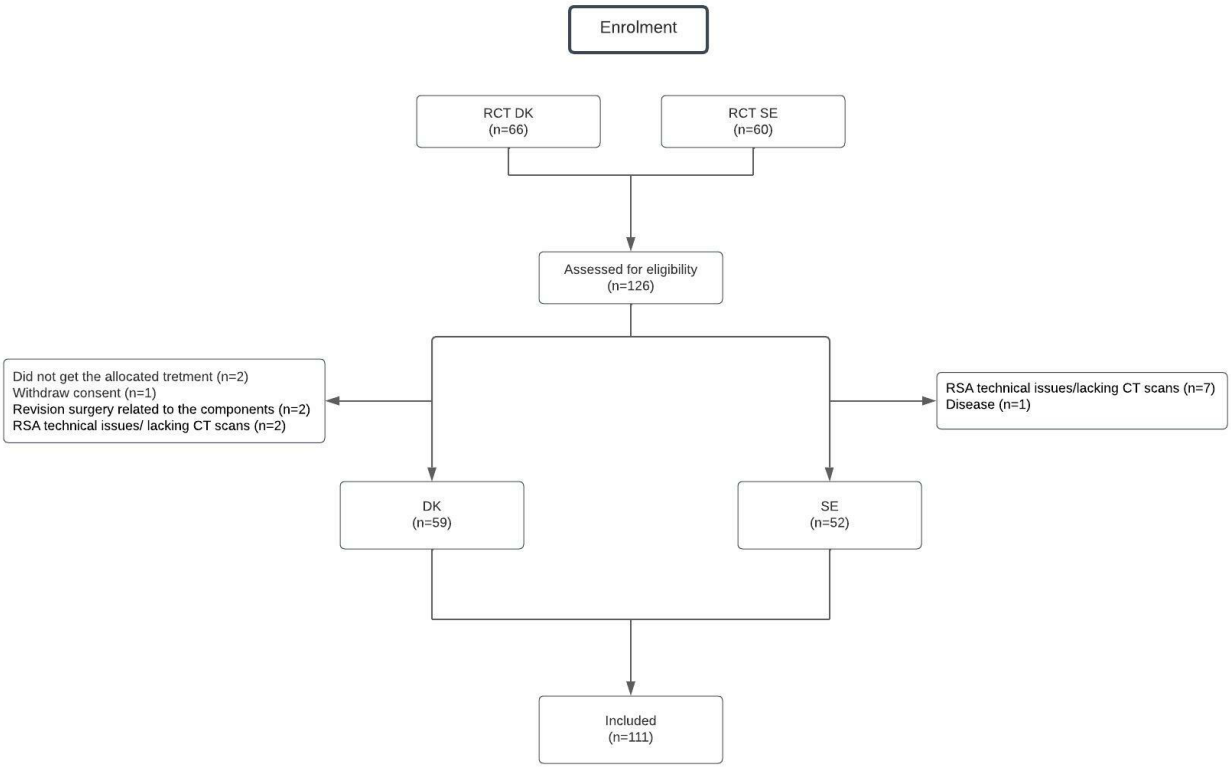
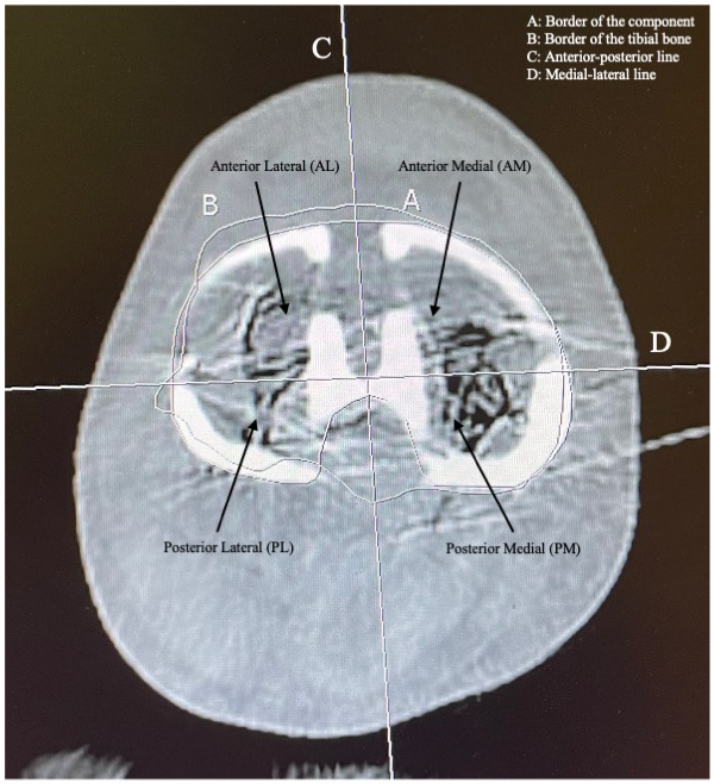


Figure 2: Coverage of the tibial bone and component. A: Border around the tibial component. B: Border around the tibial bone. C: Line dividing the component/bone into a medial and lateral side. D: Line dividing the component/bone into an anterior and posterior parts. AL: Anterior-lateral. AM: Anterior-medial. PL: Posterior-lateral and PM: Posterior-medial.

Figure 3: Rotation of the tibial component. Line E goes through 1/3 medial of the tuberosity tibia and PCL insertion. Rotation measured between lines E and C.



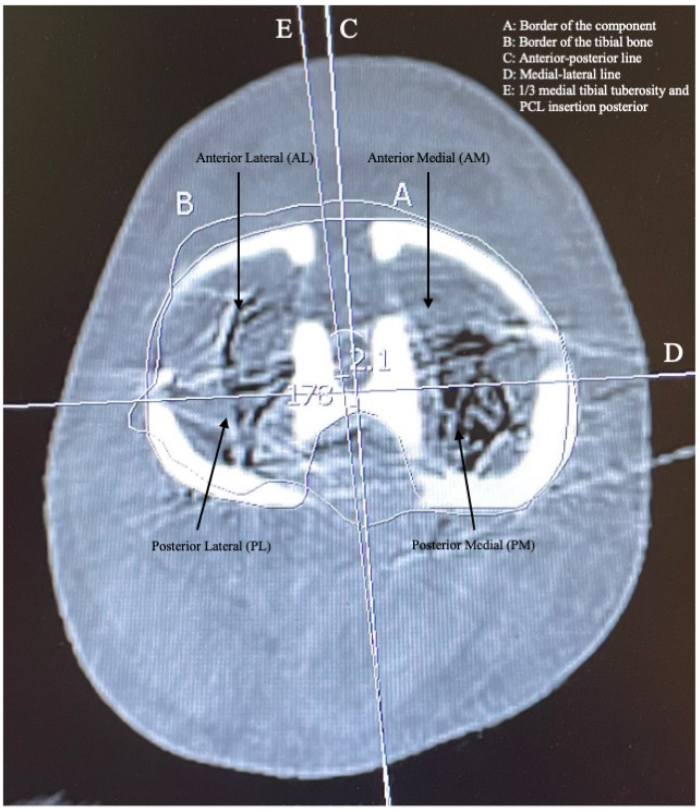


Figure 3: Bland Altman plot coverage. A: Intertester. B: Intratester.

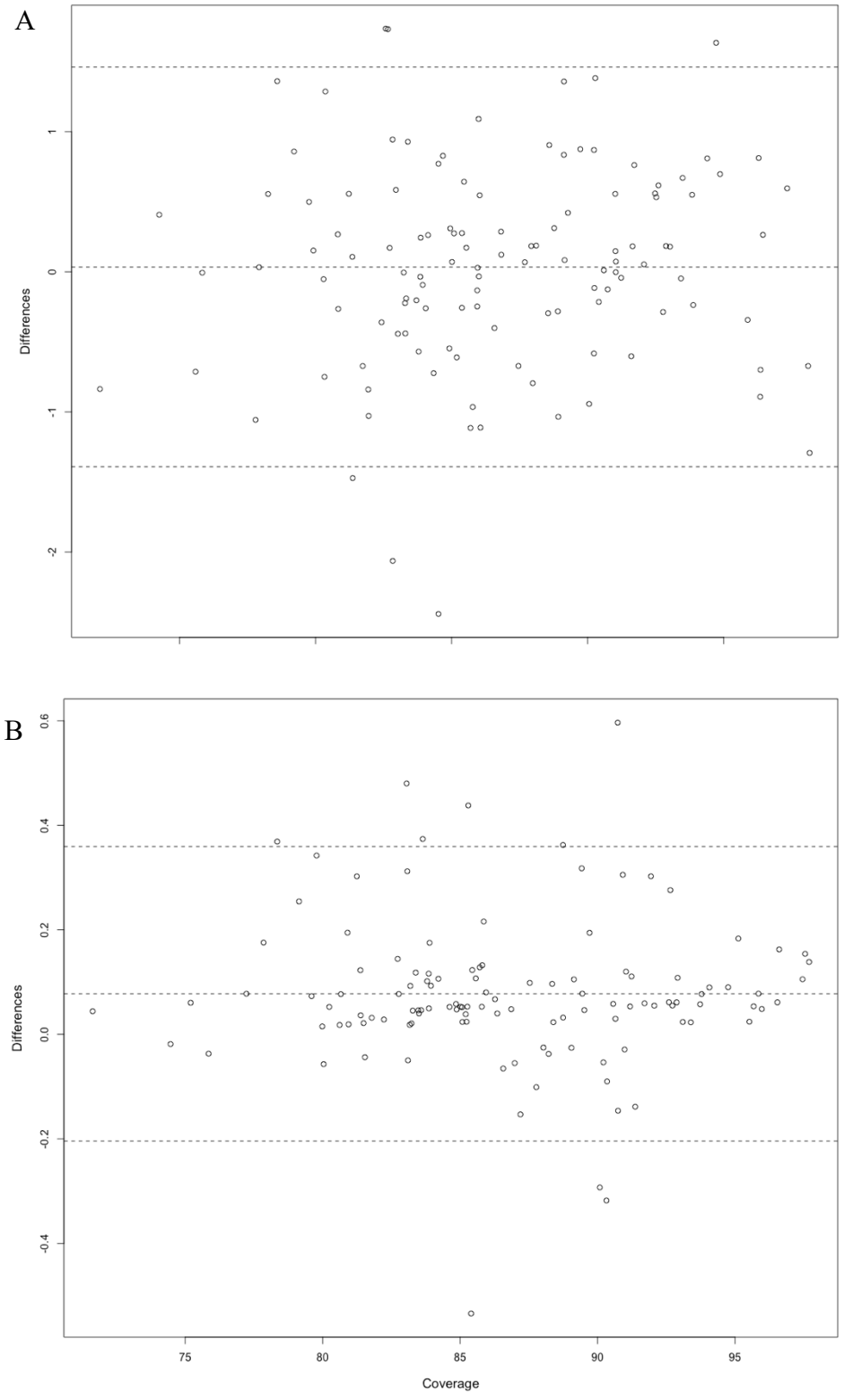


Figure 4: Bland Altman plot rotation. A: Intertester. B: Intratester.

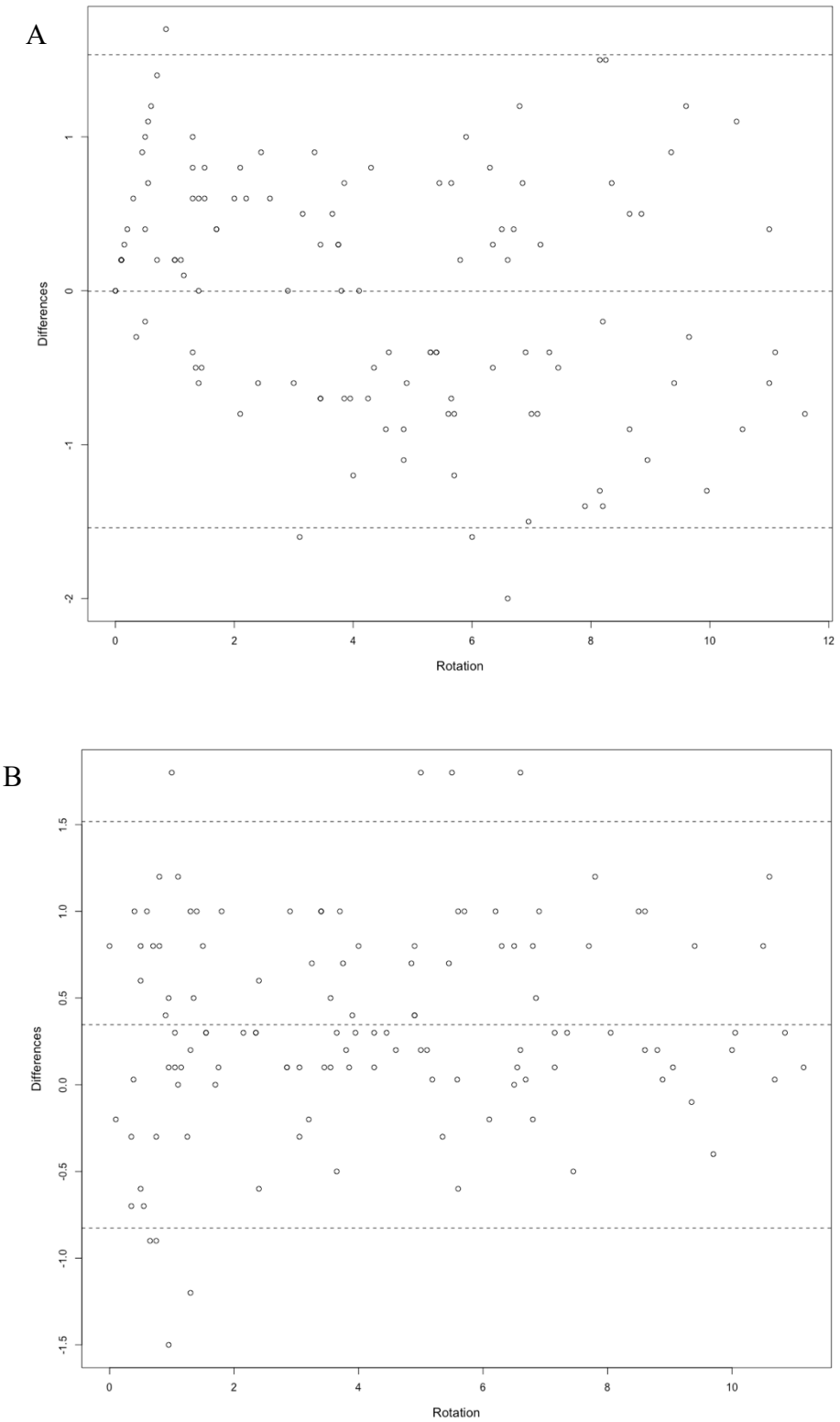


Figure 5: Linear regression model. MTPM and coverage (A: total cohort, B: cemented and C: uncemented). MTPM and rotation (A: total cohort, B: cemented and C: uncemented).

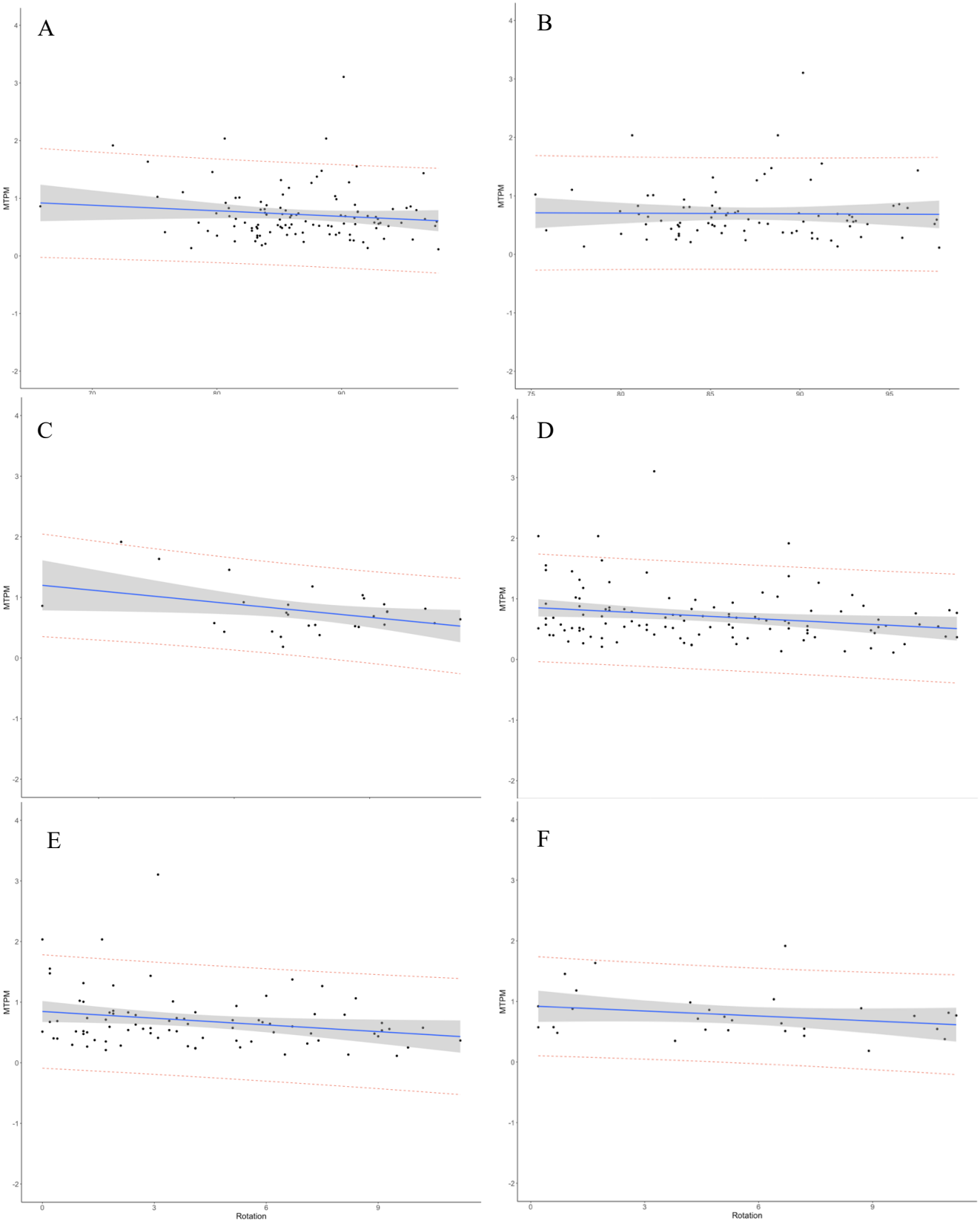


Table 1: Mean segmental MBRSA values.

Segment	Implant	Mean 3 months (CI95)	Mean 6 months (CI95)	Mean 12 months (CI95)	Mean 24 months (CI95)	P value
Sweden (SE)						
MTPM	CR	0.48 (0.37 to 0.58)	-	0.59 (0.48 to 0.70)	0.62 (0.50 to 0.73)	0.9[a]
	MC	0.56 (0.45 to 0.67)	-	0.61 (0.45 to 0.78)	0.73 (0.49 to 0.96)	
Denmark (DK)						
MTPM	Cemented	0.70 (0.52 to 0.88)	0.66 (0.50 to 0.82)	0.72 (0.58 to 0.85)	0.72 (0.55 to 0.89)	0.6[b]
	TM	0.76 (0.61 to 0.91)	0.80 (0.65 to 0.95)	0.79 (0.64 to 0.94)	0.78 (0.60 to 0.95)	

MTPM: Maximal Total Point Motion

CR: Cruciate retaining

MC: Medial congruent

TM: Trabecular metal

CI95: 95% confidence interval

a: P-values from Linear mixed-effect model comparing 3-24 months, adjusted for age, sex, BMI and ASA.

b: P-values from Mann-Whitney U test comparing 3-24 months.

Table 2: Overhang, under coverage and rotation reported by the investigator and the radiologist.

	Investigator Mean (Range)	Radiologist Mean (Range)
Overhang (mm^2)		
AM (n=47)	15.2 (1.10 to 63.3)	15.4 (0.9 to 65.6)
AL (n=55)	31.4 (1.8 to 151.4)	31.5 (1.8 to 151.4)
PM (n= 84)	60.6 (1.7 to 249.5)	60.7 (1.2 to 249.2)
PL (n=54)	34.25 (2.6 to 134.7)	34.4 (2.7 to 132.1)
Under coverage (mm^2)		
AM (n=106)	82.1 (1.7 to 294.6)	82.5 (1 to 296.6)
AL (n=105)	80.9 (2.1 to 211.2)	81.8 (2.1 to 209.6)
PM (n=119)	207.6 (18.9 to 504.9)	210.2 (18.4 to 503.8)
PL (n=118)	200.7 (42.7 to 511.2)	200.8 (39.1 to 506.3)
Rotation (°)		
Inward	4.2 (1 to 7.5) (n=9)	4.6 (1.2 to 8.9) (n=14)
Outward	4.6 (0.2 to 11.2) (n=97)	5.1 (0.2 to 12) (n=91)
Neutral	0 (n=5)	0 (n=6)

DECLARATION OF CO-AUTHORSHIP

The declaration is for PhD students and must be completed for each conjointly authored article. Please note that if a manuscript or published paper has ten or less co-authors, all co-authors must sign the declaration of co-authorship. If it has more than ten co-authors, declarations of co-authorship from the corresponding author(s), the senior author and the principal supervisor (if relevant) are a minimum requirement.

1. Declaration by	
Name of PhD student	Müjgan Yilmaz
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Name of principal supervisor	Michael Mørk Petersen
Title of the PhD thesis	Cemented and uncemented trabecular metal total knee arthroplasty with asymmetrical tibial design. Comparison using model-based radiostereometric analysis, dual-energy x-ray absorptiometry, and computed tomography.

2. The declaration applies to the following article	
Title of article	Influence of tibial component overhang and bone surface coverage on implant migration. Evaluation of a cemented asymmetrical tibial component using computed tomography and model-based RSA
Article status	
Published ☐ Date:	Accepted for publication ☐ Date:
Manuscript submitted ☐ Date:	Manuscript not submitted ☒
If the article is published or accepted for publication, please state the name of journal, year, volume, page and DOI (if you have the information).	

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
1. Formulation/identification of the scientific problem	C
2. Development of the key methods	C

3. The PhD student's contribution to the article ***(please use the scale A-F as benchmark)*** Benchmark scale of the PhD-student's contribution to the article **A**. Has essentially done all the work (> 90 %) **B**. Has done most of the work (60-90 %) **C**. Has contributed considerably (30-60 %) **D.** Has contributed (10-30 %) **E.** No or little contribution (<10 %) **F.** Not relevant	**A, B, C, D, E, F**
3. Planning of the experiments and methodology design and development	C
4. Conducting the experimental work/clinical studies/data collection/obtaining access to data	A
5. Conducting the analysis of data	A
6. Interpretation of the results	A
7. Writing of the first draft of the manuscript	A
8. Finalisation of the manuscript and submission	A
Provide a short description of the PhD student´s specific contribution to the article.[i] The PhD student (Müjgan Yilmaz) provided to all stages of the research.	

4. Material from another thesis / dissertation[ii]	
Does the article contain work which has also formed part of another thesis, e.g. master's thesis, PhD thesis or doctoral dissertation (the PhD student's or another person's)?	Yes: ☐ No: ☒
If yes, please state name of the author and title of thesis / dissertation.	-
If the article is part of another author's academic degree, please describe the PhD student´s and the author´s contributions to the article so that the individual contributions are clearly distinguishable from one another.	-

5. Signatures of the co-authors[ii]				
	Date	Name	Title	Signature
1.	21/12-22	Thomas Lind	MD	
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6. Signature of the principal supervisor
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 27/12-22
Principal supervisor: Michael Mørk Petersen

7. Signature of the PhD student
I solemnly declare that the information provided in this declaration is accurate to the best of my knowledge.
Date: 27/12-22
PhD student: Müjgan Yilmaz

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[i] This can be supplemented with an additional letter if needed.

[ii] Please see Ministerial Order on the PhD Programme at the Universities and Certain Higher Artistic Educational Institutions (PhD Order) § 12 (4):

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