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Contributing factors to the initial femoral stem migration in cementless total hip arthroplasty of postmenopausal women

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ABSTRACT

In cementless total hip arthroplasty (THA), femoral stems rely on the initial press-fit fixation against cortical bone to achieve osseointegration. Decreased bone mineral density (BMD) in postmenopausal women poses natural difficulties in achieving axial and rotational femoral stem stability. The present study examined contributing demographic, surgery-related and postoperative factors in determining the magnitude of early stem migration prior to osseointegration. A prospective cohort of 65 postmenopausal women with hip osteoarthritis (Dorr type A or B femur anatomy) underwent THA with implantation of an uncemented parallel-sided femoral component. Postoperative femoral stem translation and rotation were measured using model-based radiostereometric analysis. Based on analysis of covariance, which controlled for outliers and randomized antiresorptive treatment with denosumab or placebo, none of the analyzed demographics (including BMI) and surgery-related variables (including the stem-to-canal fil ratio) was associated with stem subsidence. Stem subsidence (mean 1.8 mm, 95% CI 1.2 to 2.4) occurred even in women with normal hip BMD. Total hip BMD and postoperative walking activity (measured three months after surgery) were significantly associated with stem rotation, and height acted as a confounding factor. The effect of walking activity on stem rotation was significant at 5 months ($p = 0.0083$) and at 11 months ($p = 0.0117$). This observation confirms the previous results of instrumented hip prostheses on torsional moments affecting stems during daily activities. High-resolution imaging modalities of local bone quality are needed to explore reasons for RSA-measurable stem subsidence even in women with normal hip BMD.

1. Introduction

Stability is the key factor for the biological osseointegration of implant components in cementless total hip arthroplasty (THA). Uncemented femoral stems rely on the initial press-fit fixation against cortical bone (Khanuja et al., 2011; Moritz et al., 2011). Optimal level of initial stability required for osseointegration remains unknown (Warth et al., 2020). Based on radiostereometric analyses (RSA), excellent primary stem stability with no or minimal stem migration ($\leq$1.0–1.5 mm) is achievable in middle-aged patients with good bone quality (Grant et al., 2005; Kärrholm et al., 1994; Klein et al., 2019). Clinical subsidence ($\geq$2 mm), measurable from plain radiographs, is a predictor of aseptic implant loosening and revision surgery (Grant et al., 2017; Streit et al., 2016, Warth et al., 2020).

Age-related postmenopausal changes of the cortical bone, including endosteal trabeculation and increased intracortical porosity (Zebaze et al., 2010), may pose natural difficulties in achieving axial and rotational stem stability. Indeed, the initial migration of uncemented femoral stems seems to be almost inevitable in postmenopausal women with decreased systemic bone mineral density (BMD) (Aro et al., 2018b, 2012; Nazari-Farsani et al., 2020). Despite the initial migration, the stems stabilize and stay osseointegrated (Aro et al., 2018a, 2018b).

Initial stem migration seems to be resistant to prevention with antiresorptive osteoporosis drugs. Denosumab is the most powerful inhibitor of osteoclastic activity with defined effects on the cortical bone of the proximal femur in postmenopausal women with low BMD (McClung et al., 2006; Zebaze et al., 2016), but in randomized clinical trials (RCTs), both denosumab (Aro et al., 2019) and bisphosphonates (Aro et al., 2018b; Sköldenberg et al., 2011)

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have failed to reduce the initial migration of uncemented femoral stems.

Different patient-related, surgery-related and postoperative factors may contribute to the magnitude of initial stem migration in postmenopausal women with low BMD. Therefore, we formulated two hypotheses: (1) certain demographics (such as body mass index) and surgery-related factors (such as stem-to-canal fill ratio) are associated with stem migration and (2) higher levels of postoperative walking activity have an influence on the direction and magnitude of stem migration. To investigate these hypotheses, we reanalyzed the data of our recent RCT (Aro et al., 2019). The trial protocol, designed to account for different potential confounding factors that might affect femoral stem migration, provided an ideal database for the current reanalysis.

2. Materials and methods

2.1. Study design

This is a prospective prognostic study based on the reanalyzed trial data. The original RCT was a single-center, randomized, double-blinded, placebo-controlled trial that evaluated the effects of denosumab in postmenopausal women undergoing cementless THA (Aro et al., 2019). The trial was registered with Clinicaltrials.gov (#NCT01926158) and approved by the Ethics Committee of the Hospital District of South-West Finland (decisions 105/2012 and 484/2017) and the Finnish Medicines Agency (decision 183/06.00.00/2012, EudraCT 2011-000628-14). All study participants provided written informed consent before enrollment.

2.2. Cohort and surgery

The cohort included postmenopausal women between 60 and 85 years of age, with primary hip osteoarthritis and Dorr type A or B proximal femur anatomy (Table 1). The exclusion criteria included diseases and prescribed drugs that affect bone metabolism or any condition that may affect the ability to perform the functional assessments required by the protocol. All subjects underwent cementless THA, using an anterolateral Hardinge approach. The procedure involved implantation of a parallel-sided femoral stem (Accolade II, Stryker Orthopaedics, Mahwah, NJ, USA) (Faizan et al., 2015; Grayson and Meneghini, 2017; Issa et al., 2014) with a 36-mm metallic head and a porous-coated, uncemented, acetabular cup with a polyethylene liner. Subjects with Dorr type C anatomy (Gordon et al., 2014), who frequently have osteoporosis (Mäkinen et al., 2007) and are prone to periprosthetic fractures (Gromov et al., 2017), were excluded from the cohort during the screening process. After surgery, the patients were mobilized with the use of standard physiotherapy, and unrestricted weight-bearing was encouraged with the aid of crutches. None of the analyzed subjects (n = 65) experienced periprosthetic infection, postoperative dislocation, or periprosthetic fracture. All subjects completed the one-year trial period. All stems were radiographically osseointegrated at two years. No revision surgery was performed during the three-year extension safety study.

2.3. Preoperative and postoperative assessments

The functional capacities of the enrolled subjects were evaluated before surgery and repeated at 3, 5, and 11 months after surgery (Table 2). Evaluation of functional recovery included the measurements of walking speed (Foucher, 2016), using a validated gait analysis system (RehaWatch, Hasomed GmbH, Germany) (Schwesig et al., 2011) that measured walking speed. The subjects were asked to walk at a self-selected comfortable walking speed (Foucher, 2016). The mean coefficient of the variation of the repeated measurements was 4.7%. Preoperative and postoperative assessment of inter-individual differences in daily walking activity was performed by means of digital pedometers. A total daily accounting of accumulated walking steps using digital pedometers is a valid approach for assessing physical activity (Schuna et al., 2013) and is reliable for the assessment of walking activity of arthroplasty patients (Schmalzried et al., 1998). The subjects were asked to wear a pedometer from the time that they got up in the

Table 1
Baseline characteristics of the patients.

Number of patients	65
Median age, yr. (range)	68 (60–84)
Mean BMI, kg/m^2 (SD)	28 (5)
ASA classification, n	
Class I	3
Class II	36
Class III	26
Allocated denosumab treatment, n	
active drug	33
placebo	32
Mean total hip BMD, g/cm^2 (SD)	0.91 (0.15)
Mean lumbar spine BMD, g/cm^2 (SD)	0.99 (0.17)
Mean distal radius BMD, g/cm^2 (SD)	0.66 (0.07)
Systemic BMD, n	
Normal BMD, T-score $\geq$ -1.0	31
Osteopenia, $-2.5 <$ T-score $<$ -1.0	32
Osteoporosis, T-score $\leq$ -2.5	2
Mean cortical thickness, mm (SD)	9.4 (1.6)
Mean canal flare index, CFI (SD)	3.8 (0.7)
Stovepipe (CFI < 3)	5
Normal (CFI 3.0–4.7)	55
Champagne flute (>4.7)	5
Median size of the femoral stem (range)	3 (1–6)
Model of the femoral stem, n	
132° offset	17
127° offset	48
Stem-to-canal fill ratio, %	
Proximal stem (SD)	97.8 (2.4)
Middle stem (SD)	85.8 (8.3)
Distal stem (SD)	84.6 (8.9)
Mean gluteus muscles size, cm^2 (SD)	45.7 (7.4)

SD = standard deviation.

Table 2
Clinical outcome of the patients.

Mean Harris hip score (SD)	
preoperative	48.2 (14.5)
3 months	73.5 (14.8)
5 months	77.7 (14.8)
11 months	77.9 (15.5)
Mean WOMAC score (SD)	
preoperative	47.9 (15.7)
3 months	16.8 (11.4)
5 months	15.8 (11.9)
11 months	15.9 (15.4)
Mean walking speed, m/s (SD)	
preoperative	0.91 (0.26)
3 months	0.97 (0.23)
5 months	1.10 (0.20)
11 months	1.15 (0.22)
Mean walking activity, steps/day (SD)	
preoperative	3080 (1910)
3 months	2800 (1580)
5 months	3510 (1980)
11 months	4120 (2140)

SD = standard deviation.

morning until they went to bed at night. Each patient recorded the number of steps per day as counted by the pedometer for seven days that were typical or representative of their usual activity. The median value of the number of steps measured each day was calculated and used as a measure of walking activity.

The preoperative and postoperative clinical assessments included recordings of standard patient-reported outcome measures, including the Harris hip score (HHS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Table 2).

2.4. Dual-energy X-ray absorptiometry and radiographic measurements

Before surgery, dual-energy X-ray absorptiometry (DXA) (Hologic, Discovery A, Hologic Inc., Marlborough, MA, USA) of local and systemic BMD (g/cm^2) was performed on the proximal femurs of both hips, the lumbar spine, and the distal radius of the nondominant hand. According to the official criteria of the International Society for Clinical Densitometry, the diagnosis of osteoporosis or osteopenia (Table 1) was based on the lowest T-score of the hips or the lumbar spine.

A computerized method (Rhinoceros software, version 3.0SR5b, Robert McNeel & Associates, Seattle, WA, USA) was used to measure various parameters from the anteroposterior preoperative and immediately postoperative (taken within three days after surgery) digital hip radiographs. The measured parameters were canal flare index (Noble et al., 1995), cortical bone thickness 15 mm below the lesser trochanter, preoperative and postoperative femoral and global offset (Mahmood et al., 2016), and stem-to-canal ratios of the implanted stems (Issa et al., 2014). The ratio of the stem width over the femoral canal width was measured medially 10 mm above the lesser trochanter (proximal stem), which corresponds to the site of proximal engagement against the calcar bone (Faizan et al., 2015). The stem-to-canal ratios were also measured 60 mm below the lesser trochanter (middle stem) and 25 mm above the distal tip (distal stem). Preoperatively, the subjects underwent computed tomography (CT) for preoperative measurement of the combined cross-sectional area of the gluteal medius and minimus muscles (Rasch et al., 2009), using ImageJ software (version 1.50i, https://imagej.nih.gov/ij/).

2.5. Radiostereometric analysis

The three-dimensional migration of the femoral stem was measured by model-based radiostereometric analysis (RSA) (Kaptein et al., 2006). The accuracy and precision of the applied model-based RSA technique was verified in a pretrial experiment, using a phantom model (Nazari-Farsani et al., 2016). RSA was performed according to the RSA guidelines (Derbyshire et al., 2009; Valstar et al., 2005). The implant manufacturer provided computer-aided design surface models of each stem size. The models were converted to the model-based format (Biomechanics and Imaging Group, Leiden University Medical Center, Leiden, the Netherlands) for calculation of stem 3D migration (MBRSA software version 3.34; Medis Specials BV, Leiden, The Netherlands). The calculation was performed using a combination of stem-head models (Prins et al., 2008). During surgery, multiple tantalum RSA markers were implanted in the trochanteric bone (Fig. 1). The stability and adequate distribution of bone markers were assessed by calculating the mean error of the rigid body fitting (upper limit ≤ 0.35) and the condition number (upper limit ≤ 150).

Baseline RSA imaging was performed within three days after surgery and repeated at 3, 5 and 11 months. At each time point,

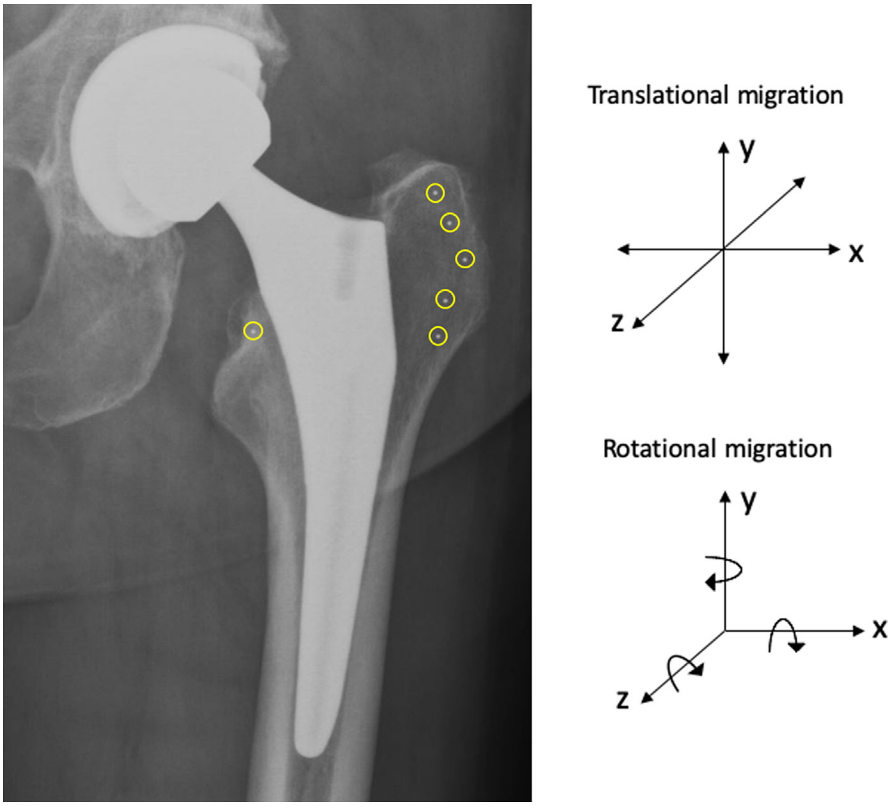

Fig. 1. Total hip arthroplasty with parallel-sided femoral component and tantalum RSA bone markers in the trochanteric region (yellow circles). The coordinate system, applied with an external calibration cage during imaging (not shown), for model-based RSA analysis of 3-D stem migration. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

stem translations and rotations along and around ×, y, and z axes were determined in relation to the baseline position as parameters of stem migration (Fig. 1). Translation along the y-axis (stem subsidence) and rotation around the y-axis (anteversion-retroversion) represent the two principle directions of postoperative stem migration and were selected as the outcome measures. The selected time period was five months. It covers the settling period of femoral stem migration prior to osseointegration and was defined to represent the initial stem migration. As recommended (Derbyshire et al., 2009), clinical precision was calculated for each axis based on double examinations of 58 trial subjects (Aro et al., 2019). For the measurement of stem subsidence, the accuracy of the model-based RSA (determined with the phantom model) was 30 μm, and the clinical precision was 110 μm. For the measurement of stem rotation around the y-axis, the accuracy of the model-based RSA was 0.39°, and the clinical precision was 1.04°. The RSA data from two subjects at five months, whose three-month RSA data was inputted into the analysis, was missing.

2.6. Statistical analysis

The original RCT was conducted according to the intention-to-treat principle (the full analysis set) without any exclusions or exploration of outliers. The treatment effect on the magnitude of femoral stem subsidence was a prespecified outcome measure. The two randomized treatment groups of the trial (denosumab-versus placebo-treated subjects) did not differ in stem subsidence and rotation. Therefore, the treatment groups were combined in the current reanalysis (Table 1). The influence of outliers was taken into account in the reanalysis.

The outliers were first detected in the visual, blinded inspection of the data by the study statistician. Seven outliers with excessive subsidence and/or y-axis rotation (Fig. 2) were confirmed in the applied statistical software, which defined the outliers as $X_i \geq Q3 + (1.5 \times IQR)$ and $X_i \leq Q1 - (1.5 \times IQR)$, where Q1 and Q3 represent the first and third quartile limits, respectively, and the interquartile range (IQR) represents the difference between Q1 and the Q3 limit. The calculation gave the following cutoff values of excessive migration (Nazari-Farsani et al., 2020): stem subsidence > 5.44 mm and/or stem rotation > 5.52° of internal rotation (retroversion) or > 4.32° of external rotation. In the cohort without outliers (n = 58), the subsidence and rotation values showed a normal distribution (Shapiro-Wilk normality test).

The main approach in the search for significant confounding factors in stem migration was analysis of covariance (ANCOVA) controlled for the randomized treatment group of the original trial and outliers as covariates in every analysis. The following 12 confounding factors from six domains (demographics, comorbidities, bone quality, hip biomechanics, implant sizing, physical condition and activity) were added to the model one factor at a time: age and body mass index (BMI)(Campbell et al., 2011; Grant et al., 2017; Stihsen et al., 2012), preoperative fitness classified according to the American Society of Anesthesiologists (ASA) class (Gordon et al., 2014), total hip BMD, femoral cortical bone thickness and canal flare index (Aro et al., 2018b; Mulliken et al., 1996; Noble et al., 1995), normal or high-offset model of the femoral component and femoral offset (Mahmood et al., 2016), stem-to-canal fill ratio (Warth et al., 2020), gluteus muscle size, preoperative walking speed, and preoperative walking activity (Foucher, 2016; Rasch et al., 2009; Schmalzried et al., 1998).

To evaluate the effect of postoperative physical activity on stem migration, the cohort was divided into two groups based on the median value (2600 steps/day) of daily walking activity measured three months after surgery. Linear mixed-effects models for repeated measures were applied to compare stem migration in subjects with walking activity < or ≥ 2600 steps/day in the cohort with and without outliers. The models were adjusted for potential confounding factors, including age, height, body weight, BMI, total hip BMD, stem-to-canal fill ratio, and antiresorptive treatment. When a significant effect was noticed, the difference was studied for every time-point in the same model.

The analyses were performed using SAS System, version 9.4 (SAS Institute, Cary, NC, USA) and IBM SPSS Statistics, version 25.0 (IBM Corp, Armonk, NY, USA). Significance was set to $P < 0.05$.

3. Results

3.1. Effect of total hip BMD

Women with normal total hip BMD had significantly less stem subsidence and rotation than did women with low total hip BMD (Table 3). The statistical significance of the differences disappeared when the outliers (n = 7) were not included in the analysis (Table 3), demonstrating the need to control for outliers. The total hip BMD of the outliers (0.81 g/m^2) (SD 0.16) was lower than that of non-outliers (0.93 g/m^2) (SD 0.14) (mean difference 0.11 g/cm^2, 95% confidence interval [CI] –0.23 to 0.01) (p = 0.034).

3.2. Effects of demographics and surgery-related factors

In the ANCOVA analysis (Table 4), which controlled for outliers and the treatment group of the original RCT, total hip BMD (p = 0.027) was associated with stem rotation (rotation around the y-axis). None of the analyzed preoperative or surgery-related variables showed a significant effect on stem subsidence (translation along the y-axis). Three factors showed a trend (p < 0.1)

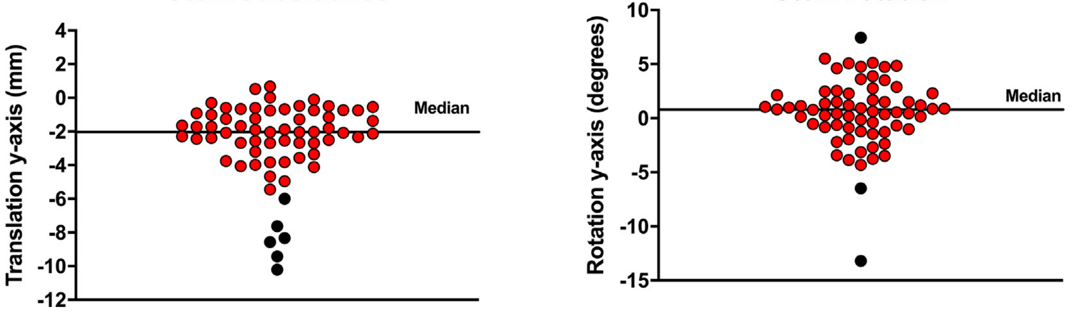

Fig. 2. Individual values of femoral stem subsidence and rotation measured five months after surgery in the cohort (n = 65). Data of outlier subjects (n = 7) are marked with black dots (n = 9). Four outliers had excessive stem subsidence, two outliers had both excessive stem subsidence and rotation, and one outlier had excessive stem rotation only.

Table 3
Comparison of femoral stem migration in patients with normal or low total hip BMD[†]

	Normal total hip BMD	Low total hip BMD	Difference (95% CI)	p value[*]
Subsidence (mm)[††]				
Cohort (n = 65)	-2.0 (1.9)	-3.8 (3.0)	1.8 (0.5 to 3.0)	0.006
Without outliers	-1.8 (1.5)	-2.1 (1.3)	0.3 (-0.6 to 1.2)	0.48
Rotation (degrees)[††]				
Cohort (n = 65)	1.4 (2.4)	-1.5 (3.9)	2.9 (1.3 to 4.5)	0.001
Without outliers	1.3 (2.3)	-0.1 (2.3)	1.3 (-0.1 to 2.8)	0.07

[*] Independent samples two-tailed *t*-test.
CI = confidence interval.
[††] Values are given as the mean (standard deviation) for the measurement of y-axis translation (subsidence) and y-axis rotation 5 months after surgery.
[†] Categorized according to the World Health Organization classification of normal (T-score ≥ –1.0) or low (T-score < –1.0) BMD.

Table 4
Demographics and surgery-related factors in initial femoral stem migration (ANCOVA).

	Translation	Rotation
	(F_{df}) p value	(F_{df}) p value
Age (yr)	(0.86_1) 0.359	(0.34_1) 0.564
BMI (kg/m^2)	(1.50_1) 0.225	(1.12_1) 0.294
ASA score	(2.51_2) 0.090	(0.15_2) 0.864
Total hip BMD (g/cm^2)	(3.29_1) 0.075	(5.17_1) 0.027
Femur cortical bone thickness *(*mm*)*	(0.00_1) 0.967	(1.13_1) 0.292
Canal flare index	(2.84_1) 0.097	(0.18_1) 0.676
Offset of the femoral stem (normal/high)	(1.69_1) 0.199	(0.22_1) 0.642
Stem-to-canal fill ratio (middle stem)	(2.05_1) 0.158	(0.16_1) 0.693
Preoperative femoral offset (mm)	(0.31_1) 0.578	(0.22_1) 0.638
Preoperative gluteus muscle size (mm^2)	(0.41_1) 0.527	(0.15_1) 0.698
Preoperative walking speed (m/s)	(0.70_1) 0.405	(0.01_1) 0.931
Preoperative walking activity (steps/day)	(0.18_1) 0.676	(1.39_1) 0.243

ANCOVA = analysis of covariance; Translation = subsidence along y-axis 5 months after surgery; Rotation = rotation around y-axis 5 months after surgery; F = F-ratio adjusted for the covariates; df = degrees of freedom.

toward an impact on stem subsidence. These factors included total hip BMD (p = 0.075), canal flare index (p = 0.097), and ASA (p = 0.090). However, when these three factors were included into a single model, none of them showed a significant effect on stem subsidence.

Stem subsidence did not significantly differ in the subgroups of subjects categorized into quartiles of body weight, body height, BMI and stem-to-canal fill ratio (middle stem). There was a positive correlation between BMI and local total hip BMD (Pearson correlation r = 0.439, p = 0.001).

3.3. Effect of postoperative walking activity

There was a significant association between postoperative walking activity (measured three months after surgery) and stem rotation. Stem subsidence did not differ between patients with walking activity below 2600 steps per day or equal to or above the cohort median (≥2600 steps/day), but there was a clear difference between the two groups in femoral stem rotation (Fig. 3). Patients with a higher walking activity (≥2600 steps/day) showed retroversion of stem (the mean difference compared with the baseline position 1.52°, 95% CI 0.50 to 2.53), and subjects with low walking activity (<2600 steps/day) maintained the original rotational position (–0.24°, 95% CI –1.08 to 0.60). The difference of stem rotation between the two groups was statistically significant in the cohort with and without outliers (p = 0.015 and p = 0.019, respectively). The effect of walking activity on stem rotation was highly significant both at 5 months (p = 0.0083) and at 11 months (p = 0.0117) (Fig. 3). The two groups did not show any significant differences in stem rotation around other axes, nor did translations along other axes show significant intergroup differences (Table 5).

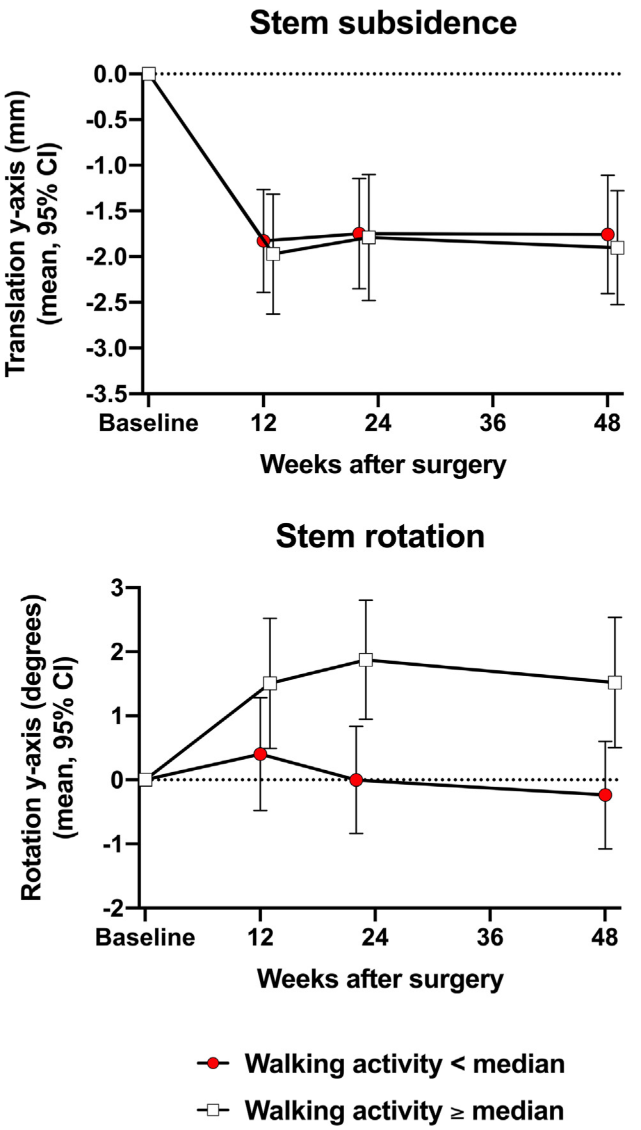

Fig. 3. Femoral stem migration as a function of time after total hip arthroplasty in patients with postoperative (three months) walking activity below or equal/above the cohort median (2600 steps/day). The values represent y-axis translation (mm) and y-axis rotation (degrees) (mean, 95% CI).

In linear mixed-effects models for repeated measures, height and total hip BMD (but not other tested factors) were significant

Table 5
The comparison of femoral stem migration in patients with postoperative walking activity below or above the cohort median.

	Walking activity				
	<2600 steps/day	≥2600 steps/day	Mean diff	95% CI	p value*
Translation† (mm)					
x-axis	0.09 (0.48)	0.03 (0.39)	0.06	-0.18 to 0.30	0.62
y-axis	-1.76 (1.60)	-1.90 (1.51)	0.15	-0.73 to 1.02	0.74
z-axis	-0.22 (1.08)	-0.55 (0.74)	0.33	-0.19 to 0.86	0.21
Rotation† (degrees)					
x-axis	-0.16 (1.21)	-0.59 (0.73)	0.42	-0.14 to 0.99	0.14
y-axis	-0.24 (2.08)	1.52 (2.46)	-1.75	-3.03 to -0.47	0.008
z-axis	0.36 (1.03)	0.10 (0.71)	0.26	-0.24 to 0.76	0.31

CI = confidence interval.

* Independent samples two-tailed *t*-test.

† Values are given as the mean (standard deviation) for the measurement of stem translation and rotation along and around different axes 11 months after surgery.

confounding factors for the effect of postoperative walking activity on stem rotation ($p = 0.042$ and $p = 0.015$, respectively). The confounding effect of total hip BMD was not significant in the cohort without outliers. These analyses were performed because patients with low walking activity had a higher body weight (79.9 kg [SD 14.1] vs. 71.8 kg [SD 9.7 kg]) and a higher BMI (29.5 kg/m^2 [SD 5.1] vs. 26.0 kg/m^2 [SD 3.8]) compared with subjects with walking activity of $\geq$ 2600 steps/day.

4. Discussion

Adequate initial femoral component stability is necessary for clinical success in cementless THA. Postoperative migration of uncemented femoral stems seems to be almost inevitable in postmenopausal women with low BMD. It is meaningful to explore clinical confounding factors that may contribute in stem migration. Against our hypothesis, none of the analyzed demographic and surgery-related factors was associated with stem subsidence. Stem subsidence occurred even in women with normal hip BMD. Our second hypothesis was correct. Postoperative walking activity was associated with rotational femoral stem migration. This observation is in line with results of clinical studies of hip arthroplasty patients with instrumented femoral stems (Bergmann et al., 2016, 2001; Heller et al., 2001), which have predicted the influence of loading on the initial torsional stability of cementless stems. In line with patient-specific hip loading conditions (Cilla et al., 2017), height, as a representative of body dimensions, and total hip BMD, as a parameter of bone quality, acted as confounding factors for the effect of walking activity on stem rotation. Body weight and BMI were not independent predictors of stem rotation, but were associated with the individual level of walking activity.

When controlling for outliers, demographics, radiographic parameters of local bone quality, DXA values, and surgery-related factors showed no association with stem subsidence. This result does not exclude the possibility that subsidence was due to impaired bone quality. In postmenopausal women, stem subsidence is probably due to endosteal changes of the cortical bone, but the applied methods of the current study (including DXA) are insensitive for detection of such changes. High-resolution CT techniques of the proximal femur (Genant et al., 2013; Zebaze et al., 2013) would be the best method in characterization of local bone quality and in prediction of stem subsidence.

BMI determines the level of contact forces and torsional moments affecting femoral stems during daily activities (Bergmann et al., 2001). Therefore, high BMI may trigger stem subsidence. The implant manufacturer warned of the use of this femoral stem in overweight patients (Stryker, 2012). High body weight has been linked to stem subsidence in men (Ries et al., 2019). However, we found no significant association between BMI and initial stem subsidence or rotation in postmenopausal women. A recent study, based on measurements of stem subsidence from clinical radiographs, also suggested that the stem is resistant to initial subsidence (defined as $\geq$ 2 mm) irrespective of BMI (Grant et al., 2017).

The subjects with walking activity equal to or above the cohort median exhibited limited internal rotation of the stem, which corroborates observations on the typical direction and degree of rotation of different femoral stem designs (Aro et al., 2018b; Ström et al., 2007; Weber et al., 2014). In contrast, the femoral stems tended to stay in the original rotational position in subjects with low walking activity. These subjects were characterized also by low walking speed. This result corroborates the expectations of lower torsional moments in these patients. These results should not be interpreted as suggesting that moderate walking activity is harmful for implant healing. The observed limited (mean 1.5°) retroversion of the stem is by no means an adverse event. It is important to note that all subjects experienced successful THA with good or excellent clinical outcome, independently on the magnitude of stem rotation and the level of postoperative walking activity. As an inherent feature, BMI of subjects with low walking activity was relatively high, and they had already exhibited low walking activity before surgery.

The parallel-sided femoral stem was designed to engage the metaphyseal cortical bone in the medial-lateral plane (Faizan et al., 2015; Issa et al., 2014). Compared with the original stem, the redesigned stem showed reduced retroversion and subsidence in preclinical testing (Faizan et al., 2015) and better proximal and distal engagement in a clinical fit and fill analysis (Issa et al., 2014). These studies offered no specific comments on the appropriateness of the use of this stem in postmenopausal women. The stem is currently in global use, and no adverse reports of implant survival have been issued from national implant registers. Based on a recommendation (Grayson and Meneghini, 2017), the use of the stem requires adequate bone stock and unaltered femoral geometry, but no exact definition for adequate bone stock was given. We excluded women with Dorr C femur morphology. In the presence of adequate bone stock (i.e., normal preoperative BMD) and unaltered femoral geometry (Dorr type A or B with canal flare index $\geq$ 3.0), the amount of subsidence and rotation was 1.8 mm (95% CI 1.2 to 2.4) and 1.1° (95% CI 0.3 to 1.9), respectively. The measured subsidence is in the upper end of ranges reported for different stem designs in RSA studies of female and male patients of different ages (Campbell et al., 2011; Rutherford et al., 2019; Ström et al., 2007). In our previous studies, women with normal systemic BMD exhibited minimal stem subsidence (0.5 mm – 0.7 mm) independently of the femoral stem design, including an anatomically designed stem (Aro et al., 2012) and a double-wedged straight femoral stem (Aro et al., 2018b).

Reporting RSA results in a universal way, including identification and interpretation of the outliers, can improve the potential of RSA in prediction of implant survival (de Vries et al., 2014;

Frazer and Tanzer, 2020). However, no clear definitions have been defined for RSA outliers. The present study reconfirms the importance of performing data analysis with and without outliers. The outliers seemed to form a separate, albeit not homogeneous, group of their own with low total hip BMD. The dichotomous presentation of excessive subsidence has been observed previously (Nebergall et al., 2016). Because the demographics of the outliers differed from those of the non-outliers, it is unlikely that the outliers occurred by chance or were due to measurement errors.

5. Limitations of our study

Only one femoral stem design was tested, and only one subgroup of patients undergoing cementless THA (postmenopausal women) was included. Therefore, the generalizability of our results remains unproven. A reference group of premenopausal women or male middle-aged patients with good bone quality would provide an important perspective for the interpretation of the current results. Uncemented femoral stems tend to show limited subsidence during the first months after surgery. However, the acceptable level of RSA-measured stem subsidence or rotation is still unknown (van der Voort et al., 2015). In the reanalysis of the trial data, the sample size was not tested for the power to assess relationships between stem migration and different patient-related and surgery-related factors. The sample size was, however, at a level recommended for RSA studies of arthroplasty patients (Derbyshire et al., 2009). A posthoc power analysis was performed to evaluate the required number of subjects to detect a clinically significant stem subsidence between two treatment groups at one time point. The clinically meaningful mean difference was set to 2 mm, adopted from clinical studies (Grant et al., 2017; Warth et al., 2020). Statistical power was set to 80% and significance level to 0.05 (two-tailed). Using the current data, standard deviation was calculated for each time point and treatment group, and the largest standard deviation (2.88 mm) was used. With these settings, the required number of subjects would be 68 (i.e. 34 subjects per group). As a further limitation, we had no established cutoff value for the expected walking activity of postmenopausal women during the first postoperative months.

6. Conclusions

Femoral component stability is critical for osseointegration and clinical success in cementless THA. This analysis examined contributing factors for the initial migration of a parallel-sided femoral stem in postmenopausal women with Dorr type A or B femurs. The rotational migration of the stem was associated with preoperative hip BMD and postoperative walking activity. After controlling for outliers, none of the analyzed factors was found to contribute in stem subsidence. High-resolution imaging modalities are needed to explore reasons for RSA-measurable stem subsidence in postmenopausal women with adequate bone stock and unaltered femoral geometry.

Declaration of Competing Interest

HTA has received institutional research grants (Amgen) and has served as a member of an advisory scientific board (Amgen). All other authors state that they have no conflicts of interest.

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