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A long-lasting bisphosphonate partially protects periprosthetic bone, but does not enhance initial stability of uncemented femoral stems: A randomized placebo-controlled trial of women undergoing total hip arthroplasty

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ABSTRACT

Low bone quality may compromise the success of cementless total hip arthroplasty in high-risk patients such as elderly women. Zoledronic acid is a long-lasting antiresorptive agent, which is known to reduce short-term periprosthetic bone loss. However, its effect on femoral stem stability is not well known. Forty-nine female patients with a mean age of 68 years (range, 51–85 years) scheduled to undergo cementless total hip arthroplasty due to osteoarthritis were randomized in this double-blind, placebo-controlled trial to receive a single postoperative infusion of zoledronic acid or placebo. Patients were evaluated for up to four years postoperatively for femoral stem migration measured by radiostereometric analysis, bone mineral density (BMD) measured by dual X-ray absorptiometry, functional recovery, and patient-reported outcome scores. Implant survival was determined at nine years postoperatively. Zoledronic acid did not reduce the femoral stem migration that occurred predominantly during the settling period of the first 3–6 months. Subsequently, all femoral stems were radiographically osseointegrated. Zoledronic acid maintained periprosthetic BMD, while the expected loss of periprosthetic bone during the first 12 months was found in controls. Thereafter, periprosthetic BMD of Gruen zone 7 decreased even in the zoledronic acid group but remained 14.6% higher than that in the placebo group at four years postoperatively. Functional recovery was comparable across the groups. At nine years postoperatively, no revision arthroplasty had been performed. In conclusion, in women at high-risk for low BMD, zoledronic acid had a long-lasting, partially protective effect on periprosthetic bone loss, but the treatment did not enhance the initial femoral stem stability.

1. Introduction

Strain-adaptive bone resorption is an inevitable biological response around uncemented femoral stems in patients with total hip arthroplasty (Kerner et al., 1999; Sumner, 2015; Yamako et al., 2017). The baseline bone mineral density (BMD) value has been found to predict subsequent periprosthetic bone loss (Engh et al., 1992; Kerner et al., 1999; Sumner, 2015). The periprosthetic bone loss process is more likely to occur in women, patients with a low cortical index, and patients with larger stems (Engh et al., 2003). However, it is difficult to avoid strain shielding by changing the implant geometry and material properties (Cilla et al., 2017).

Radiostereometric analysis (RSA) is the benchmark for in vivo evaluation of implant migration (Valstar et al., 2005). Stability of uncemented femoral stems is essential to enable biologic osseointegration through bone ingrowth. Uncemented femoral stems should preferably not migrate at all, but many femoral stems still do and the maximum time limit for subsidence appears to be one year (Kärrholm, 2012). Early stem migration has been detected in patients with a low periprosthetic BMD (Sköldenberg et al., 2011b).

Bisphosphonates, such as zoledronic acid (Black et al., 2007), are effective for diseases characterized by increased osteoclast-mediated bone resorption. Cohort studies concerning the effects of bisphosphonates in patients with hip arthroplasty have also shown promising results (Bhandari et al., 2005). Clinical trials have

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shown beneficial short-term effects of bisphosphonates on periprosthetic BMD (Venesmaa et al., 2001; Sköldenberg et al., 2011a). Moreover, bisphosphonates use may even improve the implant survival (Prieto-Alhambra et al., 2012; Teng et al., 2015; Khatod et al., 2015).

Zoledronic acid may not only inhibit periprosthetic femoral bone resorption (Scott et al., 2013), but has been shown to reduce migration of acetabular components in patients with total hip arthroplasty treated for avascular necrosis of the femoral head (Friedl et al., 2009). In pre-clinical models, zoledronic acid has promoted bone ingrowth into porous tantalum implants as a potential method for enhancement of implant fixation (Bobyn, 2005; Bobyn et al., 2009).

No previous study on the effect of zoledronic acid on RSA-measured implant migration is currently available. Aging women are ideal subjects for a study on this effect, as they frequently have low BMD (Glowacki et al., 2003; Mäkinen et al., 2007), and are prone to early migration of both components of total hip arthroplasty (Aro et al., 2012; Finnilä et al., 2016) and periprosthetic femoral bone loss (Alm et al., 2009). This study evaluated whether zoledronic acid affects femoral stem stability in women with hip osteoarthritis. Our hypothesis was that zoledronic acid would reduce the osteoclast-mediated strain-adaptive periprosthetic bone resorption and thereby enhance the early stability of uncemented femoral stems measured by RSA.

2. Material and methods

This single-center randomized, double-blind, placebo-controlled clinical trial followed the CONSORT guidelines (Schulz et al., 2010), was conducted in accordance with the ethical principles of the Declaration of Helsinki (JAVA, 2013), and was registered at ClinicalTrials.gov (NCT01218035). The study was approved by the Ethics Committee of the Hospital District of South-West Finland (decisions 4/2006 §173 and 9/2012 §270) and the Finnish Medicines Agency (191/2006, EudraCT 2006-002557-68). All study participants provided written informed consent before enrollment.

2.1. Study participants and screening

The trial included postmenopausal women with advanced degenerative hip osteoarthritis. The exclusion criteria included any inflammatory arthritis, parathyroid dysfunction, current use of drugs for osteoporosis or corticosteroids, hepatic or renal disease, skeletal disorder such as Paget's disease, malignancy within the past five years, and a history of dental infections or impending dental surgery.

During the recruitment period between March 2008 and November 2009, all new admissions were prescreened for the eligibility and willingness to participate in the study. Sixty patients were assessed for eligibility (Fig. 1), which included laboratory

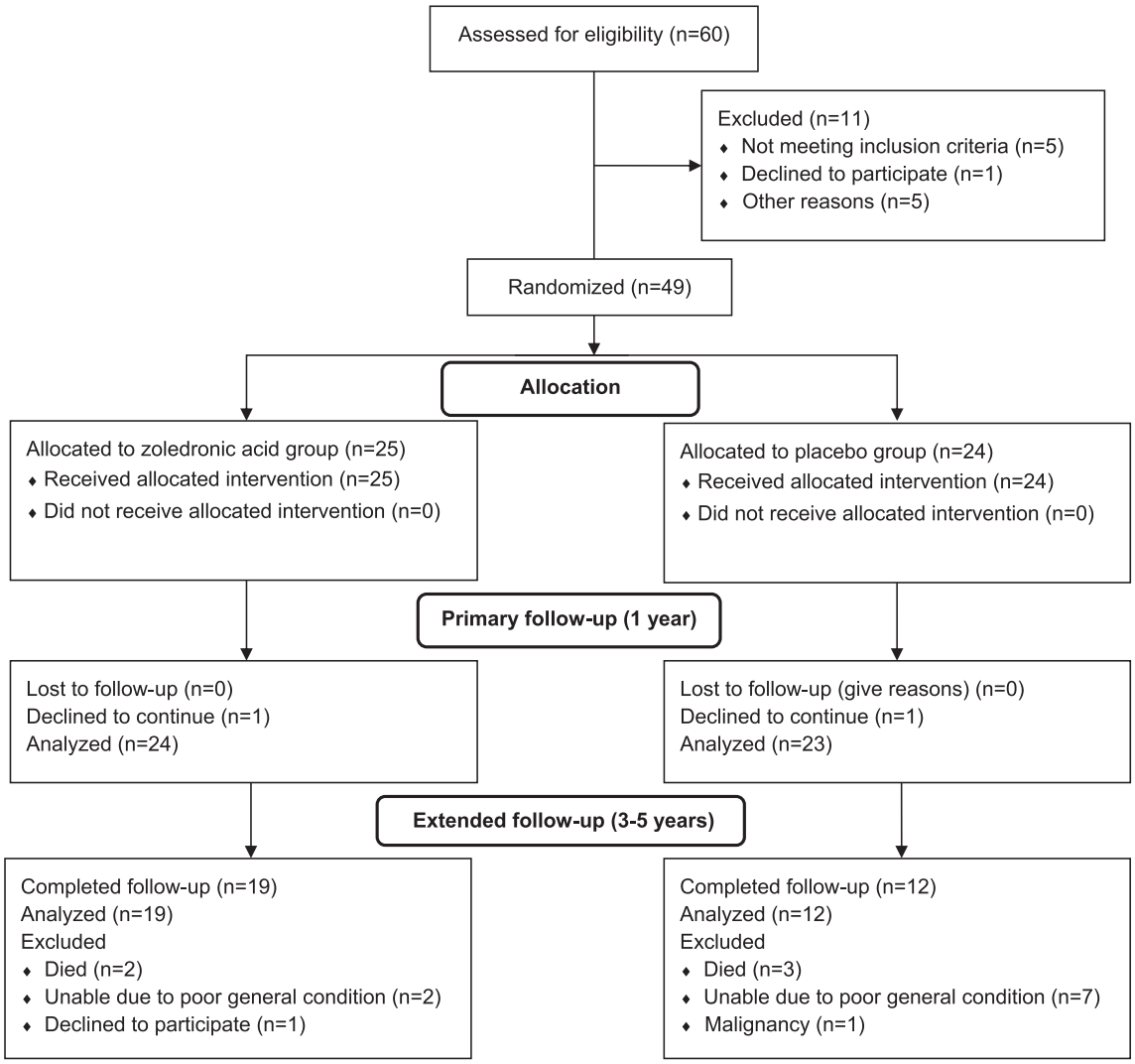

Fig. 1. Diagram of patient flow through the study.

screening tests (Mäkinen et al., 2007). The screened patients constituted 29.0% of 207 women who were scheduled and underwent cementless total hip arthroplasty during the recruitment period.

2.2. Surgery

The surgery was performed by a single orthopedic surgeon, and all patients received an uncemented stem composed of a Ti-6Al-4 V titanium alloy (Symax; Stryker Inc., Netherlands), a 36 mm chromium-cobalt head (LFIT; Stryker), an uncemented Ti-6Al-4 V press-fit cup (Trident; Stryker), and a 36 mm inner diameter polyethylene liner (Trident X3; Stryker). The straight double-wedge stem (type 2) (Khanuja et al., 2011) had a plasma-sprayed pure titanium and electrochemically deposited hydroxyapatite proximal coating (ten Broeke et al., 2011). The stem was marked for RSA by the manufacturer with three tantalum beads (1.0 mm) (Fig. 2). During surgery, 5–7 tantalum beads were implanted into the femur trochanter to serve as bone markers. After surgery, full-weight bearing with the use of crutches was encouraged.

2.3. Randomization, intervention, and blinding

Enrolled participants received calcium and D-vitamin supplementation. The participants were randomized to receive either a single infusion of 5 mg of zoledronic acid or placebo prior to the discharge from the hospital (with the median of five days post-surgery). The physically indistinguishable active and placebo infusion vials (Novartis Inc., Switzerland) were coded by the hospital pharmacy according to a computerized randomization list provided by a third party (4Pharma Ltd., Turku, Finland). Before the infusion, each participant was re-screened for the level of serum calcium. Compared with screening, the serum calcium had decreased by 5.1% (95% confidence interval [CI], 3.3–6.8%). Asymptomatic postoperative hypocalcemia (< 2.15 mmol/L) was found in 20 participants (40.8%). Their infusions were postponed for 24 days (range, 13–57 days). To prevent post-infusion fever reaction, all participants received prophylactic paracetamol medication. All patients, staff, and investigators were blinded to the treatment assignment. Investigators responsible for the image analyses remained blinded throughout the data analysis.

2.4. Treatment period and extension studies

The randomized treatment period was one year. Based on an amendment, the trial participants were recalled for a re-examination performed at four years (range, 3.0–5.4 years) after surgery (Fig. 1). Implant survival was evaluated based on the review of electronic medical records at a median of nine years (range, 3.0–10.3 years).

2.5. Follow-up methods

The trial end-points were the change of periprosthetic femoral BMD (Gruen zone 7) and the femoral stem migration. The baseline

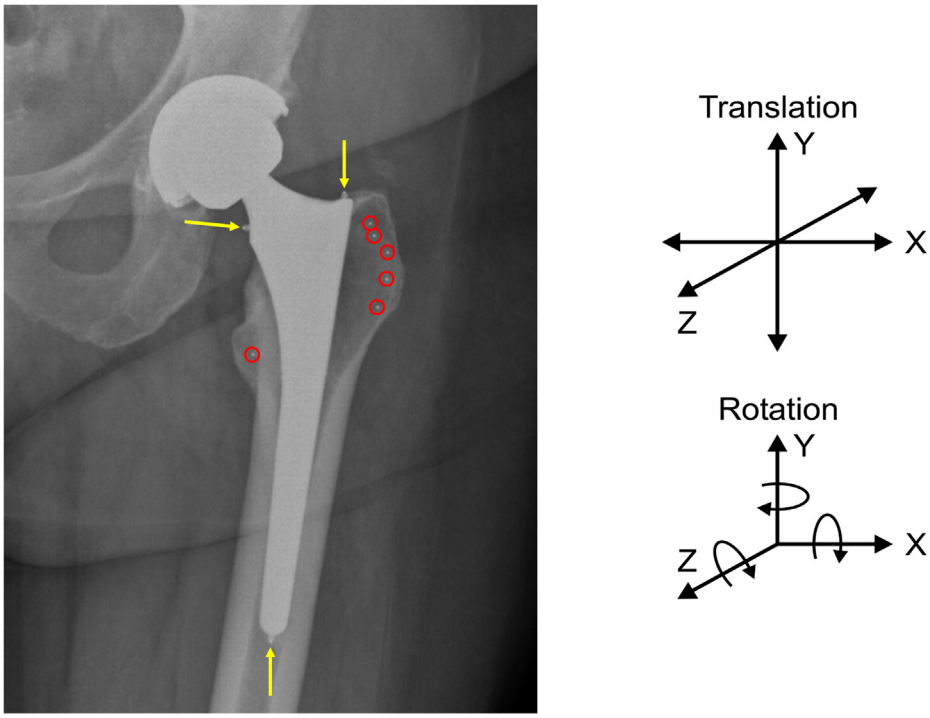

Fig. 2. The uncemented femoral stem marked with 3 RSA beads (yellow arrows) and 6 tantalum bone beads (red circles) in the trochanteric region. The coordinate system for RSA analysis of 3-D migration of the stem.

Table 1
Precision of radiostereometric analysis based on double-examinations.

	Translation x-axis (mm)	Translation y-axis (mm)	Translation z-axis (mm)	Rotation x-axis (°)	Rotation y-axis (°)	Rotation z-axis (°)
Clinical precision	0.15	0.07	0.33	0.22	0.71	0.09

Clinical precision = the mean difference between 2 examinations ± 1.96 × standard deviation.

measurements were performed within three days after surgery and repeated at three, six, and 12 months and four years. As exploratory end-points, we investigated functional outcome, bone turnover markers, systemic BMD, patient-reported outcome measures, implant survival, and occurrence of adverse events.

Systemic BMD was measured with the use of dual X-ray absorptiometry (DXA) from the proximal femurs, the lumbar spine (L1–L4), and the distal non-dominant radius during screening and at 12 months. Periprosthetic BMD was measured from 7 Gruen zones of the proximal femur. Each patient was measured with the same DXA device (Hologic QDR 4500C, Hologic Inc., USA or Osteocore III, Medilink, France) on all occasions during the treatment period. During the extension study, all measurements were performed using Hologic QDR 4500C. The two groups showed no imbalance in the use of the two devices, and the device effect was included in the statistical analysis as a covariate. The agreement between the two devices was confirmed by means of double examinations of six trial participants (r^2 = 0.879, two anatomical locations) and the equation of the linear correlation was applied to adjust measured BMDs.

Stem migration was measured with the use of marker-based RSA (UmRSA software 6.03.7, Biomedical Innovations AB, Sweden) (Aro et al., 2012; Valstar et al., 2005). The accuracy of the imaging set-up has been validated in phantom studies (Nazari-Farsani et al., 2016). Clinical precision was determined based on double examinations of 48 trial participants and calculated for each axis (Table 1), as previously recommended (Derbyshire et al., 2009). The mean error of rigid body fitting, as a measure of RSA marker stability, and the condition number, as an indicator of sufficient marker distribution, were calculated and the recommended cutoff points were adopted (Valstar et al., 2005).

A standard gait laboratory system of a 3.8-m electronic walkway (GAITRite, CIR Systems, Franklin, NJ, USA) was used to measure the self-selected walking velocity (Schwesig et al., 2011). Digital pedometers were used for the assessment of walking activity (Schmalzried et al., 1998). Each patient recorded the number of steps per day as counted by the pedometer for periods of 14 days. In addition to clinical assessment of range of motion and hip function, the participants completed the Harris Hip Score (HHS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the validated Finnish version of the Rand-36 as a general health survey. Stem fixation and stability were assessed on standard hip radiographs according to the criteria proposed by Engh et al. (Engh et al., 1990). Rapid response of serum bone-resorption markers to the administration of zoledronic acid (Delmas et al., 2009) was utilized to confirm the bone-resorption efficacy of the drug. Bone resorption markers, carboxy-terminal crosslinked telopeptide of type I collagen (CTX) (Serum CrossLaps®, IDS Ltd., Boldon, UK) and tartrate-resistant acid phosphatase 5b (TRACP-5b) (BoneTRAP®, IDS Ltd., Boldon, UK) and a bone formation marker, procollagen type I aminoterminal propeptide (PINP) (Orion Diagnostica, Espoo, Finland), were determined by a third party from serum-separated blood samples after morning fasting (Pharmatest Services Ltd., Turku, Finland). A serum marker for the rate of bone turnover, osteocalcin, was determined using an intra-institutional standard method.

Table 2
Baseline characteristics of the patients.

	Zoledronic acid (n = 25)	Placebo (n = 24)	P value‡
Age* (yr)	65.3 ± 8.0	71.0 ± 9.5	0.03
Height* (cm)	163.9 ± 6.1	162.8 ± 4.3	0.46
Weight* (kg)	76.9 ± 20.6	78.8 ± 12.6	0.70
Body mass index* (kg/m^2)	28.4 ± 6.5	29.8 ± 4.8	0.42
ASA classification			
1 or 2	12 (48)	10 (42)	0.39
3	13 (52)	14 (58)	
Bone mineral density* (g/cm^2), proximal femur			
Femoral neck	0.828 ± 0.121	0.790 ± 0.088	0.21
Total hip	0.932 ± 0.117	0.929 ± 0.127	0.95
Normal bone density (T-score > −1.0) §	16 (64)	16 (64)	
Osteopenia (−2.5 ≤ T-score ≥ −1.0) §	8 (32)	8 (36)	
Osteoporosis (T-score < −2.5) §	1 (4)	0 (0)	
Bone mineral density* (g/cm^2), L1-L4 vertebrae	1.058 ± 0.164	1.063 ± 0.229	0.91
Normal bone density (T-score > −1.0) §	14 (56)	18 (75)	
Osteopenia (−2.5 ≤ T-score ≥ −1.0) §	9 (36)	3 (12.5)	
Osteoporosis (T-score < −2.5) §	2 (8)	3 (12.5)	
Bone mineral density* (g/cm^2), distal radius	0.515 ± 0.061	0.495 ± 0.097	0.39
Normal bone density (T-score > −1.0) §	11 (44)	9 (38)	
Osteopenia (−2.5 ≤ T-score ≥ −1.0) §	11 (44)	8 (33)	
Osteoporosis (T-score < −2.5) §	3 (12)	7 (29)	
25(OH)D-vitamin* (nmol/l)	64.1 ± 21.1	57.0 ± 25.7	0.31
Parathyroid hormone* (PTH, ng/l)	53.0 ± 14.6	64.0 ± 29.5	0.11
PINP* (ng/ml)	44.3 ± 13.8	45.9 ± 17.9	0.67
CTX* (ng/ml)	0.45 ± 0.21	0.48 ± 0.29	0.88
TRACP-5b* (U/L)	3.26 ± 1.03	2.95 ± 1.53	0.42
Osteoclacin* (μg/l)	25.5 ± 10.0	26.1 ± 9.9	0.86
Harris hip score*	55.5 ± 18.8	43.2 ± 16.0	0.02
WOMAC score*	47.3 ± 21.1	50.6 ± 21.1	0.59
Walking speed* (m/s)	0.85 ± 30.8	0.81 ± 28.0	0.63
Walking activity* (steps/day)	2873 ± 2133	2717 ± 2710	0.84
Surgery			
Stem size 4/5/6	9/14/2	11/12/1	0.48
Surgery time* (min)	90 ± 16	87 ± 9	0.52

* Values are given as the mean and the standard deviation. § Values are given as the number of patients with the percentage in parentheses. ‡ Independent-samples *t* test or chi-square test. ASA = American Society of Anesthesiologists, PINP = procollagen type I N-terminal propeptide, CTX = C-terminal cross-linked telopeptide of type I collagen, TRACP-5b = tartrate-resistant acid phosphatase 5b.

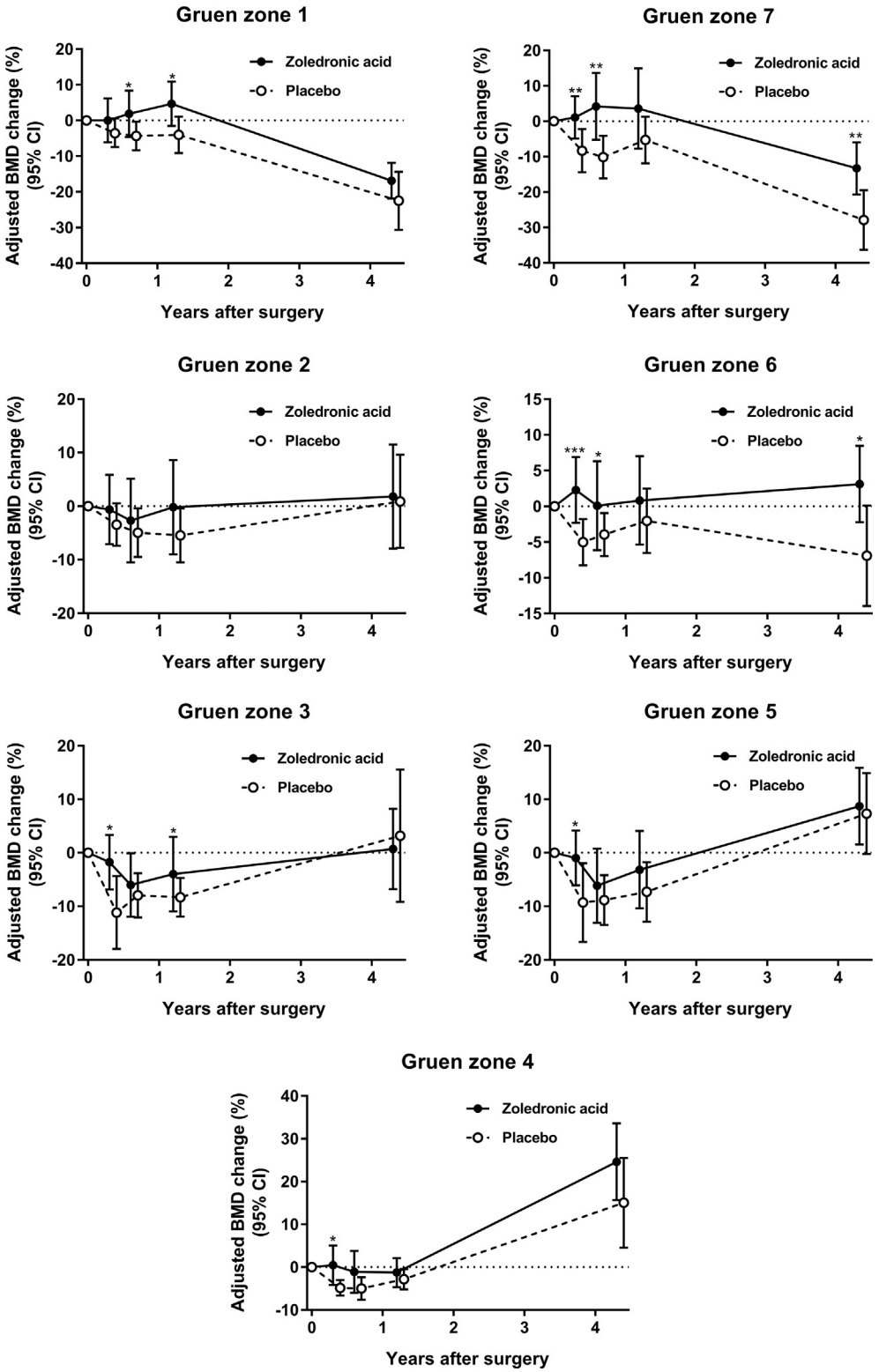

Fig. 3. The adjusted mean percentage change in BMD of femoral Gruen zones in patients receiving zoledronic acid (solid line) or placebo (dashed line). The error bars indicate 95% CI. The intergroup differences: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

2.6. Sample size and power analysis

Aging women have shown a 16–21% postoperative BMD decrease in Gruen zone 7 by 12 months (Alm et al., 2009). To be clinically relevant, zoledronic acid was expected to ameliorate this bone loss by at least 50% compared to placebo. With a power of 80% ($\alpha = 0.05$) and a standard deviation of 5%, it was calculated that 17 participants were needed in each group in order to detect the expected difference. Allowing for dropouts, 25 participants per group were enrolled, giving a total sample size of 50 patients. The sample size fulfilled the recommended minimum group size of 15–25 patients in RSA (Valstar et al., 2005).

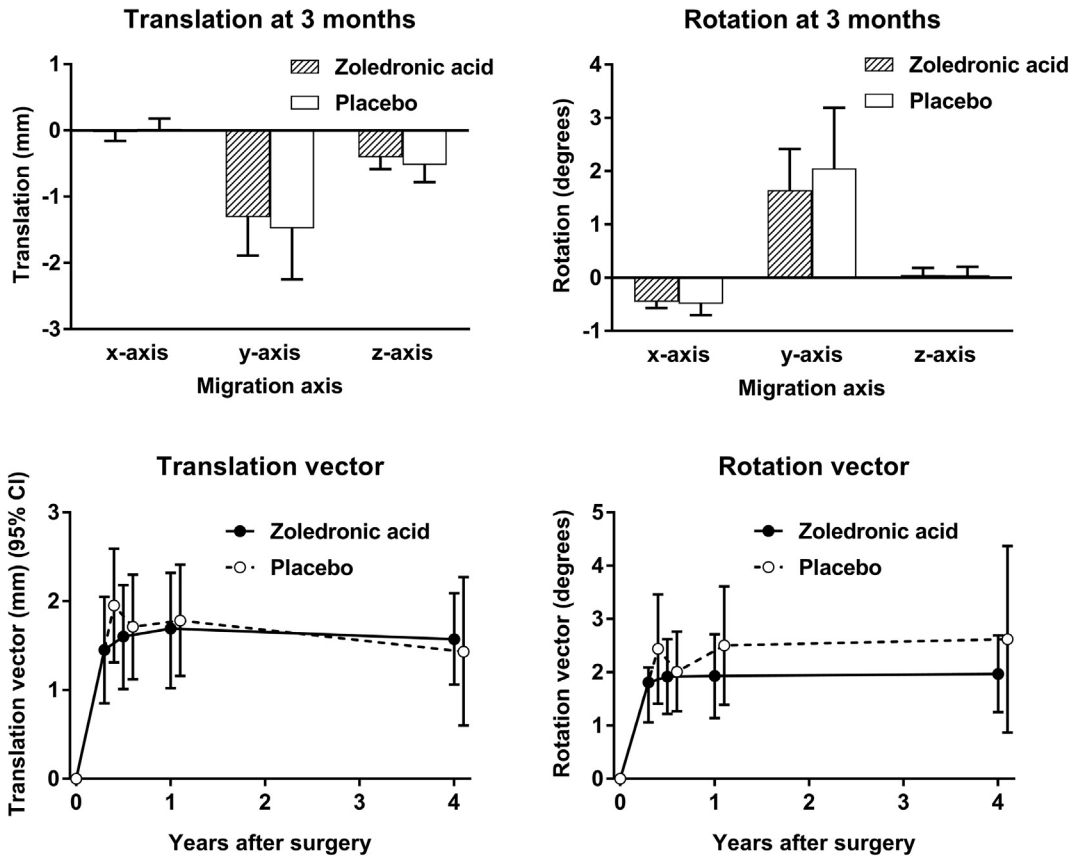

Fig. 4. Translation and rotation of femoral stems along and around individual axes (x, y, z) 3 months after surgery and the translation and rotation vectors through the 4-year period in the zoledronic acid group (solid line) and placebo group (dashed line). The intergroup differences were statistically insignificant. The error bars indicate 95% CI.

2.7. Statistical analysis

Statistical analysis was executed by a third party (4Pharma Group Ltd., Turku, Finland). The study end-points were analyzed using a repeated measurement analysis of covariance (RMANCOVA). In the analysis of periprosthetic BMD, the DXA device was modeled as a fixed effect with full interactions with treatment and clinic visit effects. Preoperative BMD, known to influence periprosthetic BMD and femoral stem migration in aging women (Alm et al., 2009; Aro et al., 2012), was applied as a covariate in the models for the analysis of periprosthetic BMD changes and stem migration. In a post-hoc analysis, the models were further adjusted for height and weight. The analysis was based on the intent-to-treat population. Results were presented as mean values with corresponding 95% CIs.

3. Results

3.1. Participants characteristics

The randomized groups showed statistical imbalances in the mean age, and Harris hip scores (Table 2). Sixteen patients (64%) in the zoledronic acid group and 19 patients (79%) in the placebo group had low BMD (osteopenia or osteoporosis) (Table 2).

3.2. Periprosthetic BMD

Zoledronic acid had a significant ($p = 0.006$, RMANCOVA) treatment-effect on the periprosthetic femoral BMD in zone 7 (Fig. 3). The treatment-effect was observed with both DXA devices. The adjusted BMD of zone 7 was 9.4% higher (CI, 1.1–17.7%) at three months, 14.3% higher (CI, 3.4–25.3%) at six months, 8.9% higher (CI, −4.0 to 21.7%) at 12 months, and 14.6% higher (CI, 3.8% to 25.3%) at four years postoperatively in the zoledronic acid group than in the placebo group. The periprosthetic BMD of zone 6 was 10.0% higher (CI, 1.8–18.3%) in the zoledronic acid group compared to the placebo group at four years postoperatively.

In the greater trochanteric region (zone 1), the adjusted BMD decreased by 16.9% (CI, 21.9–11.9%) in the zoledronic acid group, and by 22.5% (CI, 30.6–14.4%) in the placebo group ($p = 0.19$ for the intergroup difference) by four years postoperatively. Both groups showed increased periprosthetic BMD in the region of the distal stem (zone 4) reflecting distal cortical hypertrophy (Fig. 3).

In the post-hoc analysis, the adjustment for height and weight had only a slight effect on the treatment response. In a subgroup analysis, BMD changes of zone 1 and 7 in patients with delayed infusion of zoledronic acid ($n = 9$) did not differ from those of patients who received the infusion in time prior to the discharge from the hospital ($n = 16$).

3.3. Femoral stem migration

Zoledronic acid treatment had no significant effect ($p = 0.79$, RMANCOVA) on the femoral stem migration (Fig. 4). The differences in translation and rotation vectors between the zoledronic acid and placebo groups remained statistically insignificant even when adjusted for age ($p = 0.69$ for both) and for preoperative Harris hip score ($p = 0.85$ and $p = 0.51$). Translation occurred predominantly along the y-axis and rotation around the y-axis at three months (Fig. 4). Migration values after 3–6 months were within the precision thresholds (Fig. 5).

Baseline BMD had an effect on stem migration. This BMD effect showed no interaction with the zoledronic acid treatment. Participants with normal BMD (T-score >−1.0), independently of the

assigned treatment, had minimal vertical stem translation (−0.7 mm; CI, 0.2–1.2 mm) and rotation around the y-axis (0.8°; CI, 0.3–1.4°) at 12 months, while osteopenic and osteoporotic patients exhibited significantly more translation and rotation ($p = 0.024$ for translation vector and $p = 0.048$ for rotation vector, RMANCOVA).

The post-hoc adjustment for height and weight did not change the statistics of the RSA results. In the subgroup analysis, the postoperative stem migration did not differ in patients with delayed infusion of zoledronic acid compared to those who received the infusion without delay.

3.4. Functional recovery

No statistically significant differences were found between the groups regarding the walking speed ($p = 0.68$, RMANCOVA) and walking activity ($p = 0.89$, RMANCOVA) at any time point (Fig. 6). The Harris hip score, WOMAC global score (Fig. 6), and Rand-35 score did not differ between the groups at any time.

3.5. Radiographic evaluation

All femoral stems osseointegrated. According to previously established criteria (Engh et al., 1990), endosteal bone bridging (spot welds) was detected in 80.0% of the zoledronic acid group and in 87.5% in the placebo group. The zoledronic acid and placebo groups did not differ significantly in the number of patients with calcar atrophy (32.0% vs. 45.8%), stable distal stem with pedestal formation (72.0% vs. 58.3%), thin (<1–2 mm) radiodense lines surrounding the distal stem (32.0% vs. 29.2%), and distal cortical hypertrophy (40.0% vs. 29.2%).

3.6. Serum markers of bone turnover

Significant intergroup differences ($p < 0.001$) were detected in postoperative serum levels of bone turnover markers at all time points (Fig. 7). The zoledronic acid group showed a 85% decrease of CTX bone resorption marker (CI, 92–74%) ($p < 0.001$ compared with baseline) and a 28% decrease of the osteoclastic-specific enzyme TRACP-5b (CI, 39–18%) ($p < 0.001$) by three months postoperatively. Reflecting the coupled processes of bone resorption and formation, the serum levels of PINP and osteocalcin were lower in patients treated with zoledronic acid ($p < 0.001$ compared with the placebo group at all postoperative time points).

In the post-hoc subgroup analysis, patients with delayed infusion of zoledronic acid had a similar decrease of CTX by three months; however, they exhibited a slower decrease of PINP ($p = 0.04$) compared with those who received the infusion in time.

3.7. Systemic BMD

Vertebral BMD increased significantly by 2.2% (CI, 0.2–4.3%) ($p = 0.027$, paired *t* test) in the zoledronic acid group, but not in the placebo group ($p = 0.38$), at 12 months.

3.8. Implant survival

Five patients died of unrelated causes. For the surviving patients ($n = 44$), the mean follow-up time of implant survival ranged between eight and 10 years. No revision of any implant component was performed. One patient of the placebo group underwent internal fixation of a periprosthetic fracture occurring around a stable femoral stem at nine years. Two other patients in the placebo

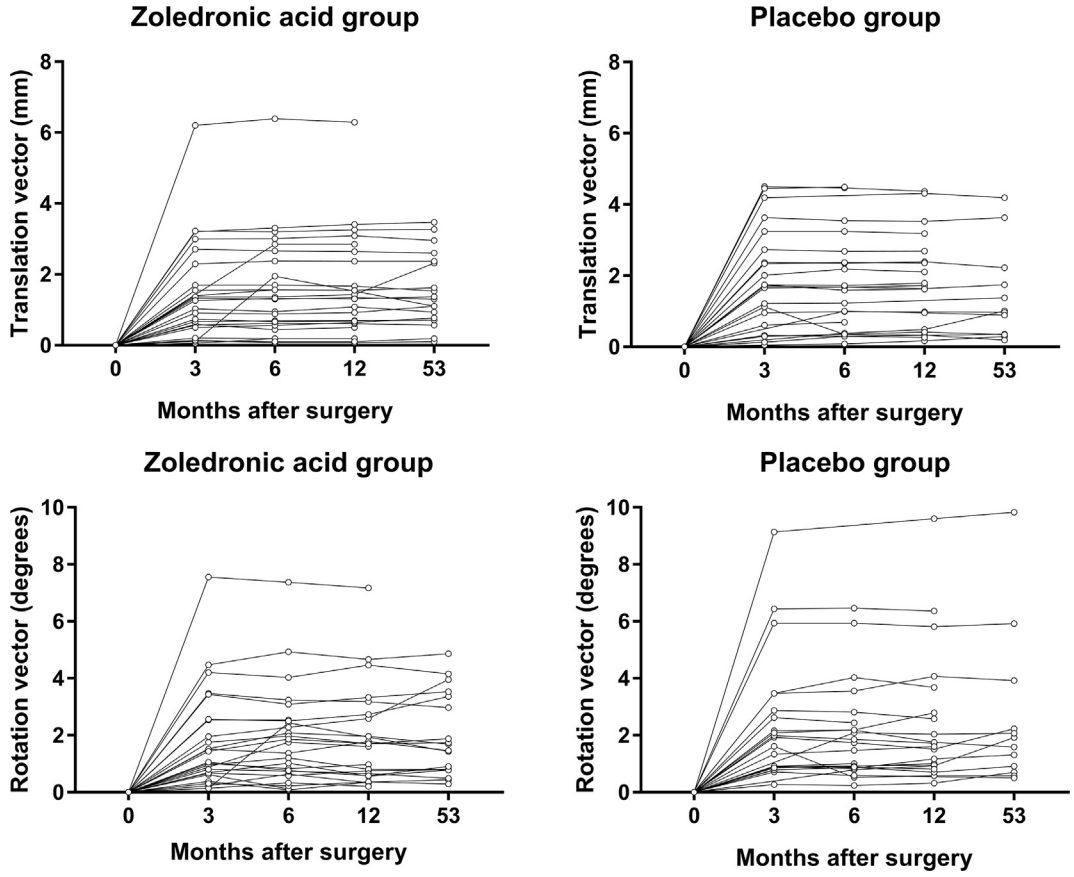

Fig. 5. Migration profiles of femoral stems in individual patients as a function of time after total hip arthroplasty. Migration occurred predominantly during the first 3–6 months.

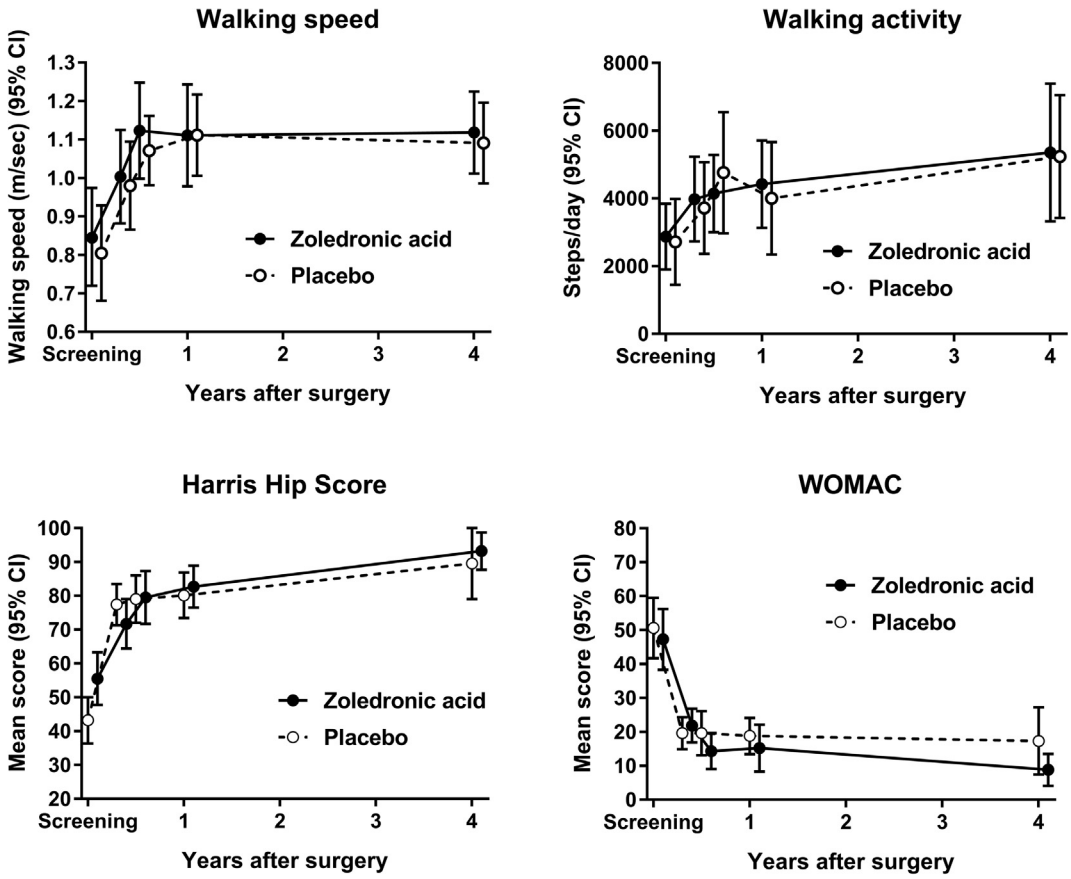

Fig. 6. The mean walking speed, walking activity, Harris Hip Score, and WOMAC global score in patients receiving zoledronic acid (solid line) or placebo (dashed line). The error bars indicate the 95% CI.

group suffered a fragility fracture, including a thoracic vertebral fracture at four years and a contralateral hip fracture at nine years. None of the patients treated with zoledronic acid experienced a fracture.

3.9. Adverse events

During the 1-year trial period, the number of participants with one or more adverse events was similar in the zoledronic acid and placebo groups (68.0% vs. 70.8%) and no significant differences were found in the incidence of serious adverse events (8.0% vs. 12.5%). The most common adverse event was low-back pain (28.0% vs. 37.5%). No event showed a causal relationship to the zoledronic acid. No cases of osteonecrosis of the jaw, atypical femur fractures, deep infections, or hip dislocations occurred.

4. Discussion

This study represents the first randomized RSA trial of zoledronic acid conducted on patients with cementless total hip arthroplasty. Our rationale was that if early stem migration is pronounced in patients with a low periprosthetic or systemic BMD (Sköldenberg et al., 2011b; Aro et al., 2012), it could be a potential target for zoledronic acid treatment. We expected that zoledronic acid could reduce early stem migration. The enhanced stability was expected to promote implant healing and functional recovery. Against our hypothesis, zoledronic acid did not reduce femoral stem migration in aging women, despite a partially protective effect against periprosthetic bone loss.

Our results are in line with a previous study on patients with hip avascular necrosis (Friedl et al., 2009); however, there are major differences between these two studies. First, our study showed early cessation of stem migration, while the previous study that used a two-dimensional digital method showed a continuous subsidence for up to three years (Friedl et al., 2009). In the current study, migration stopped after the settling period of 3–6 months, suggesting that the stems achieved mechanical stability and started osseointegration. In line with previous RSA studies (Kärrholm et al., 1994; Grant et al., 2005), translation occurred mainly along y-axis and rotation around the y-axis (Fig. 4).

What are the likely reasons that zoledronic acid may reduce migration of uncemented acetabular cups (Friedl et al., 2009), but not the migration of uncemented femoral stems? Current designs of uncemented femoral stems rely mostly on cortical contact for stability (Khanuja et al., 2011), and the quality of intertrochanteric cancellous bone has less impact on stem migration (Moritz et al., 2011). In aging women, endosteal trabeculation of the proximal femur (Zebaze et al., 2010) is probably one of the determinants for the initial stem migration. This fact would probably partly explain the observed drug inefficacy, because the treatment response of zoledronic acid is mostly seen in the trabecular bone and less in the cortical bone (Yang et al., 2013). On the other hand, the postoperative administration of zoledronic acid is probably too late, if the treatment goal is to fix any endosteal trabeculation of the femur.

The estimation of sample size was based on the prospective power analysis to detect a clinically meaningful difference in the periprosthetic BMD. We believe this goal was achieved. The

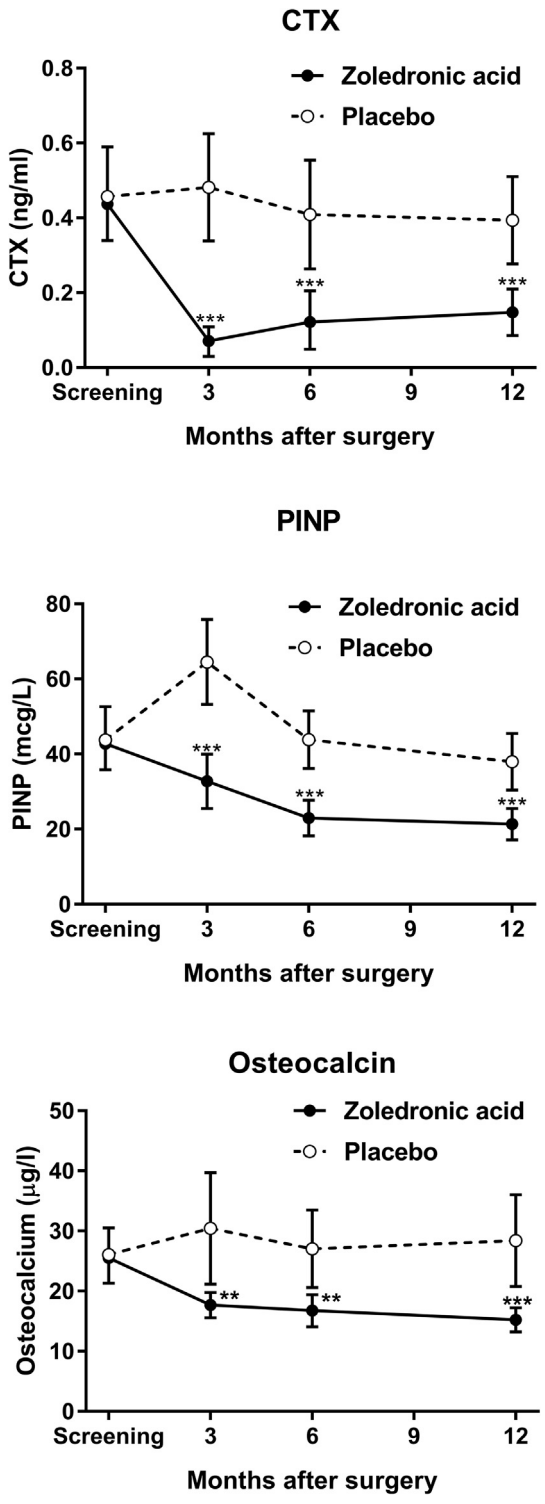

Fig. 7. The mean serum levels of bone-resorption (CTX), bone-formation (PINP) and bone turnover (osteocalcin) markers in patients receiving zoledronic acid (solid line) or placebo (dashed line). The postoperative differences between the groups were highly significant. The error bars indicate 95% CI. ***p < 0.001.

selected sample size fulfilled the recommended minimum group size for RSA (Valstar et al., 2005); however, no power analysis was performed for the RSA analysis. Therefore, a post-hoc power analysis ($\alpha = 0.05$, $\beta = 0.80$) of the two groups, using the actual data (standard deviations of y-axis translation at 12 months range 1.47–1.49), was performed. A difference of subsidence larger than 1.21 mm would have been recognized as being statistically significant at 12 months. This is a relevant difference of stem subsidence, albeit only detectable by RSA. As an illustration, the current trial would have shown a significant intergroup difference of stem subsidence, if the active-treatment group had shown a constant low subsidence similar to that reported in younger patients (Nysted et al., 2014).

The extension study was performed in response to studies that showed the loss of the beneficial effect within four years after discontinuation of postoperative risedronate therapy (Muren et al., 2015). The single postoperative dose of zoledronic acid appeared to have a long-lasting impact on periprosthetic BMD on the calcar and lesser trochanter regions of the proximal femur (Gruen zones 7 and 6). The observed response is in line with published data, which showed that a single infusion of zoledronic acid can have a skeletal influence and anti-fracture efficacy for up to five years (Reid et al., 2013; Grey et al., 2012). The regions of zones 7 and 6 are critical for the outcome. Zone 7 shows the fastest bone resorption by three months (Kröger et al., 1998) and bone loss continues beyond 10 years (Bodén et al., 2006). Periprosthetic fractures tend to occur in the calcar and lesser trochanter regions and have a particular pattern (Capello et al., 2014).

Femoral stem migration was minimal in women with normal BMD, similar to the results of previous RSA studies performed on middle-aged patients (Kärrholm et al., 1994; Grant et al., 2005). An encouraging result for women with low BMD was that initial stem migration neither affected stem migration nor clinical outcome. Thus, one can question the relevance of efforts to prevent early stem migration detectable by RSA. Unlike cemented femoral stems, the safe level of migration is still unknown for uncemented femoral stem (van der Voort et al., 2015). Without doubt, major subsidence carries a risk for failure of osseointegration (White et al., 2012).

As a limitation, two DXA devices were used in the treatment period. This confounding factor was incorporated in the statistical model. The treatment response was observed with both devices. Additionally, a relatively low participation rate (n = 31/49, 63%) was detected at the 4-year visit, reflecting the aging study population. Despite the small group size, the intergroup differences of the two treatment groups remained unchanged at four years, and the implant survival could be traced for all participants.

In conclusion, zoledronic acid did not enhance the initial stability of uncemented femoral stems. However, stem migration was temporary even in women with low BMD and did not interfere with osseointegration and implant survival. Zoledronic acid had a long-lasting, partially protective effect on periprosthetic BMD. Further large-scale prospective studies are warranted to evaluate the effects of antiresorptives on clinically relevant outcome measures, such as periprosthetic anti-fracture efficacy and implant survival, in patients with impaired bone quality. This applies both for cementless and cemented total hip arthroplasties.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Inc., and the hospital purchased the implants without extra charge. The sponsors had no further role in the study.

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