Denosumab prevents acetabular bone loss around an uncemented cup: analysis of secondary outcomes in a randomized controlled trial

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Background and purpose — Uncemented total hip arthroplasty (THA) is associated with periprosthetic bone loss. In a secondary outcome analysis from a randomized controlled trial, we studied whether denosumab can prevent loss of acetabular periprosthetic bone mineral density (pBMD) in patients who received a trabecular metal cup during uncemented THA.

Patients and methods — 64 patients (aged 35–65 years) with unilateral osteoarthritis of the hip were randomized to 2 subcutaneous injections with denosumab or placebo, given 1–3 days post-surgery and 6 months post-surgery. Acetabular pBMD was measured in 5 regions of interest (ROIs) by dual-energy X-ray absorptiometry. Serum markers for bone metabolism were analyzed. Periprosthetic osteoblastic activity, measured as standardized uptake values (SUVs) by [18F] positron emission tomography/computed tomography, was evaluated in 32 of the 64 study patients.

Results — After 12 months, patients treated with denosumab had higher pBMD compared with the placebo-treated patients in 4 of 5 ROIs and in sum of ROIs 1–5. After 24 months, the effect on pBMD for patients treated with denosumab declined. Serum markers declined pronouncedly up to 12 months in patients treated with denosumab, but rebounded above baseline levels after 24 months. Patients treated with denosumab had statistically significantly lower SUVs in all ROIs, except ROI 5, after 6 months.

Interpretation — Based on this exploratory analysis of secondary endpoints the application of denosumab seems associated with preserved acetabular pBMD, reduced bone metabolism and attenuated periprosthetic osteoblastic activity. However, given the known rebound affects after discontinuation of denosumab treatment, these effects cannot be expected to persist. If prolonged treatment or shift to other regimes would be beneficial to reduce the risk of cup loosening is yet to be investigated.

Implant loosening is the most common cause for total hip arthroplasty (THA) revision (1). Periprosthetic bone mineral density (pBMD) loss around the acetabular cup and the femoral stem has been reported (2,3) and is mediated by osteoclast activation, stress shielding, polyethylene wear, implant material, and stiffness (4,5).

Regimes to overcome pBMD loss have included treatment with antiresorptive drugs, but none of these preserved periprosthetic bone in the long term (6,7). Denosumab, a human monoclonal antibody directed against receptor activator of nuclear factor Kappa-B ligand (RANK-L), inhibits osteoclast recruitment and activation (8). Treatment with denosumab depresses bone metabolism markers (9), increases BMD, and attenuates the risk of fractures in patients with osteoporosis (10). Reports on the effects of denosumab treatment on periprosthetic bone are sparse, and we are unaware of studies on its impact on acetabular pBMD (11,12).

Acetabular cups with a trabecular surface are used in primary and revision THA. The dynamics around such implants are unknown, but studies indicate a reduction of pBMD (3,13). Few studies on pBMD around acetabular cups are designed as randomized controlled trials (RCTs), and no studies evaluating the effect of drugs have included [18F]-sodium fluoride positron emission tomography/computed tomography (F-PET) to measure osteoblast activity, periprosthetic standardized uptake value, pSUV (14,15).

We hypothesized that denosumab would inhibit pBMD loss after THA. We have performed an RCT on patients with unilateral osteoarthritis of the hip (OAH) who received an uncemented THA. The primary outcome variable, femoral pBMD, has been published (11). Denosumab prevented periprosthetic bone loss 1 year after insertion of an uncemented THA stem. Denosumab also decreased periprosthetic [18F] uptake locally as an indirect measure of bone metabolism and a prompt, systemic decrease in biochemical markers of bone resorption was
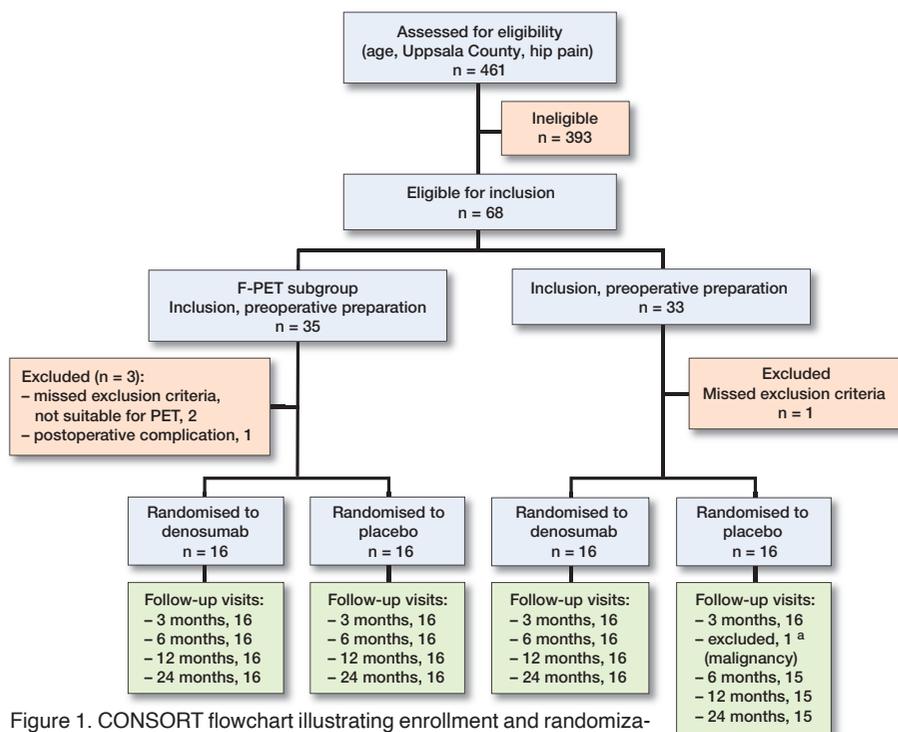
Figure 1. CONSORT flowchart illustrating enrollment and randomization process. Numbers represent patients available for analysis for the secondary outcomes. [a] HHS and biomarkers at 6 months.

Figure 2. A DXA scan showing the 5 ROIs according to Digas.

observed. However, the effect declined after discontinuation of denosumab treatment.

Here, we report the effects of denosumab treatment on acetabular pBMD and pSUV, secondary outcomes of the previously referred RCT.

Patients and methods

Trial design

The study was performed as a double-blind placebo RCT at the University Hospital of Uppsala (11). The effect of denosumab on systemic and local bone metabolism was evaluated by (i) assessing periprosthetic, contralateral hip, and vertebral BMD by dual-energy X-ray absorptiometry (DXA), (ii) measuring biochemical markers of bone turnover, and (iii) performing F-PET to measure pSUV in half of the study population (n = 32). Clinical outcome was assessed using the Harris Hip Score (HHS).

Participants

Patients were recruited from August 2012 to January 2015. All patients 35 to 65 years of age living in the Uppsala region and referred to the Department of Orthopedics, Uppsala University Hospital with unilateral OAH (Kellgren–Lawrence grade 3–4 for the affected hip and 0–1 for the unaffected hip) and with a BMI < 35 were eligible for inclusion (16) (Figure 1 and Table 1, see Supplementary data).
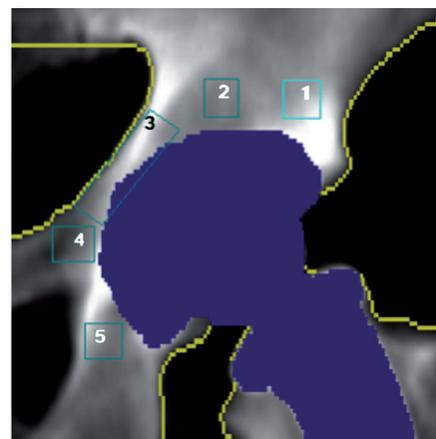
Drugs and randomization

7 to 14 days before surgery, morning fasting blood samples were drawn. At the same time, the patients started a daily oral regimen of calcium (500 mg) and vitamin D3 (800 IE) over a 1-year period. The patients were randomized in blocks of 4 to a subcutaneous injection of 1 mL containing 60 mg of denosumab or 1 mL of sodium chloride 0.9%. The study drug was given after baseline pBMD assessment along with DXA scans and fasting morning blood samples had been drawn 1–3 days postoperatively. The 2nd and final injection was delivered in the same way 6 months postoperatively. Half of the study population was also evaluated with F-PET, and the study drug was given after F-PET scans had been conducted.

Peri- and postoperative procedures and implants

All patients underwent surgery in a lateral decubitus position with an anterolateral approach using an uncemented CFP stem with a 28-mm CoCrMo head and an uncemented Continuum cup with a trabecular tantalum surface fitted with a highly cross-linked polyethylene elevated liner (see Supplementary data for details).

Bone mineral density

All scans were performed on a Prodigy Advance system (GE Healthcare, Chicago, IL, USA). Preoperatively, the lumbar spine and both proximal femora were scanned. Orthopedic hip implant scans were performed postoperatively and after 3, 6, 12, and 24 months and analyzed for acetabular pBMD in 5 ROIs and the sum of ROIs 1–5 according to Digas (3) (Figure 2). The precision of the periprosthetic acetabular DXA measurements, expressed as a coefficient variation (CV), is 2.99% for ROI 1 and 3.59% for ROI 3 (13).

Standardized uptake value

The 1st 32 patients were additionally investigated by F-PET to quantify regional mineral formation rates. F-PET scans were performed 7–14 days before surgery and 3 and 6 months post-surgery. The 5 volumes of interest VOIs, corresponding to the 5 ROIs by DXA, were chosen for analysis of acetabular pSUV and the VOIs are hereafter named ROIs (see Supplementary data for details). The inter- and intraobserver agreement of periprosthetic VOI with F-PET had an intraclass correlation coefficient of 0.86 and > 0.95, respectively.

Biochemical markers of bone metabolism

All blood samples were acquired fasting in the morning 7–14 days before surgery, 1–3 days post-surgery, and after 3, 6, 12, and 24 months. Carboxy-terminal telopeptide of type 1 collagen (CTX, β-CrossLaps, Cobas, Roche, Basel, Switzerland) was measured as a bone resorption marker and procollagen type 1 amino-terminal propeptide (P1NP, Cobas, Roche) as a bone formation marker.

Our laboratory is certified according to the international standard ISO 15189:201. The CV was 3% for P1NP and 6% for β-CrossLaps.

Patient-reported outcome measures

The HHS was used to assess patient-reported clinical efficacy of the operation, recorded 7–14 days pre-surgery and then 3, 6, 12, and 24 months post-surgery.

Conventional radiography

Hip and pelvic digital radiographs were obtained preoperatively. The degree of OAH was bilaterally classified according to the Kellgren and Lawrence system postoperatively and after 1 year.

All analyses were performed by investigators blinded to treatment assignment.

Statistics

The sample size calculations were performed for the primary outcome femoral pBMD and are described in detail in our previous publication (11).

Analyses of efficacy outcomes were based on all randomized patients who received the study drug and who had evaluable post-baseline data. Safety analyses were based on all patients who received any amount of study drug or placebo.

Descriptive statistics were used to compare baseline characteristics of the trial participants. Continuous variables were summarized using means (SD) or as medians (min–max). Categorical variables were described using frequencies. Treatment contrasts were expressed as model-based geometric mean ratios (with 95% confidence intervals [CIs]), estimated using analysis of covariance (ANCOVA) with randomized treatment and the baseline value for each corresponding outcome as independent variables. Continuous efficacy variables were transformed using natural logarithms before analysis. For the

HHS, a nonparametric ANCOVA (i.e., rank analysis of covariance combined with Mantel–Haenszel statistics) was used. No adjustment for multiplicity was undertaken, and all secondary endpoint analyses should be regarded as exploratory.

A 2-tailed p-value of < 0.05 was considered statistically significant.

Results

Characteristics of the study population

Of 461 assessed patients, 64 patients were included and randomized to treatment, of whom 32 were additionally investigated by F-PET (Figure 1). All patients received the designated cup. 1 patient diagnosed with rectal cancer chose to withdraw 3 months after enrollment into the study. Baseline characteristics were similar in the 2 treatment groups (Table 2) as well as for the study group investigated by F-PET (Table 3, see Supplementary data). None of the patients had osteoporosis according to the definition of WHO, i.e., a T-score < –2.5 (17).

Periprosthetic bone mineral density

Denosumab-treated patients had 10% higher pBMD (CI 1.1–1.2) in ROI 1 than placebo-treated patients after 3 months, and 17% (CI 1.1–1.2) higher pBMD after 12 months (Figure 3). Similar increases compared with placebo-treated patients were seen in ROI 2, ROI 3, ROI 4, and the sum of ROIs 1–5 up to 12 months after surgery. After 24 months, the effect on pBMD for patients treated with denosumab declined, although it was still statistically significantly higher in ROI 2 and the

Table 2. Baseline (preoperative) characteristics of the study participants. Values are mean (SD) or median (min–max) unless otherwise specified

Characteristic	Denosumab (n = 32)	Placebo (n = 32)
Age	58 (5)	59 (5)
Male, n (%)	12 (38)	13 (41)
Body mass index	27 (4)	27 (3)
Kellgren–Lawrence grading		
unaffected hip	1 (0–1)	1 (0–1)
affected hip	3 (3–4)	3 (3–4)
Harris Hip Score	58 (28–81)	51 (33–77)
CTX (μg/L)	0.44 (0.19) [a]	0.44 (0.18)
P1NP (μg/L)	46 (16) [a]	44 (15)
Z-score [b]		
total hip (unaffected hip)	0.58 (1.13)	0.65 (0.67)
total hip (affected hip)	0.33 (1.20)	0.33 (0.91)
L1–L4	0.91 (1.18)	0.83 (0.91)

[a] n = 31; because of incorrect handling, blood samples from 1 patient in the denosumab group were unavailable for analysis.
[b] Age- and sex-matched and weight-adjusted comparison with a White/Caucasian US reference population.

sum of ROIs 1–5 compared with patients treated with placebo (Table 4, see Supplementary data).

Compared with baseline, pBMD increased in all ROIs in patients treated with denosumab up to 12 months but then declined to the baseline level after 24 months in proximal and medial ROI 1, ROI 2, and ROI 3. In the distal ROI 4 and ROI 5 and the sum of ROIs 1–5, pBMD was still higher after 24 months (Table 4, see Supplementary data).

Compared with baseline, pBMD declined in ROI 1 and ROI 2 in patients treated with placebo at 12 and 24 months. In ROI 3 and the sum of ROIs 1–5, pBMD remained at baseline level at 12 and 24 months. In ROI 5 pBMD was higher at 12 and 24 months than baseline, and in ROI 4 pBMD was higher only at 24 months (Table 4, see Supplementary data).

Standardized uptake value

Patients treated with denosumab had reduced acetabular pSUV in all ROIs, including the sum of ROIs 1–5, after 3 and 6 months when compared with patients treated with placebo. However, the reduction in pSUV, varying from –21% to –34%, was statistically significant in ROI 1, ROI 2, ROI 3, ROI 4, and the sum of ROIs 1–5 only after 6 months (Figure 4 and Table 5, see Supplementary data).

Compared with baseline, pSUV was statistically significant reduced by 17–62% in all ROIs in patients treated with denosumab at 3 and 6 months. Compared with baseline, pSUV had less but similar decreases of 34–55% in ROI 2, ROI 3, ROI 4, ROI 5, and the sum of ROIs 1–5 in patients treated with placebo at 3 and 6 months (Table 5, see Supplementary data).
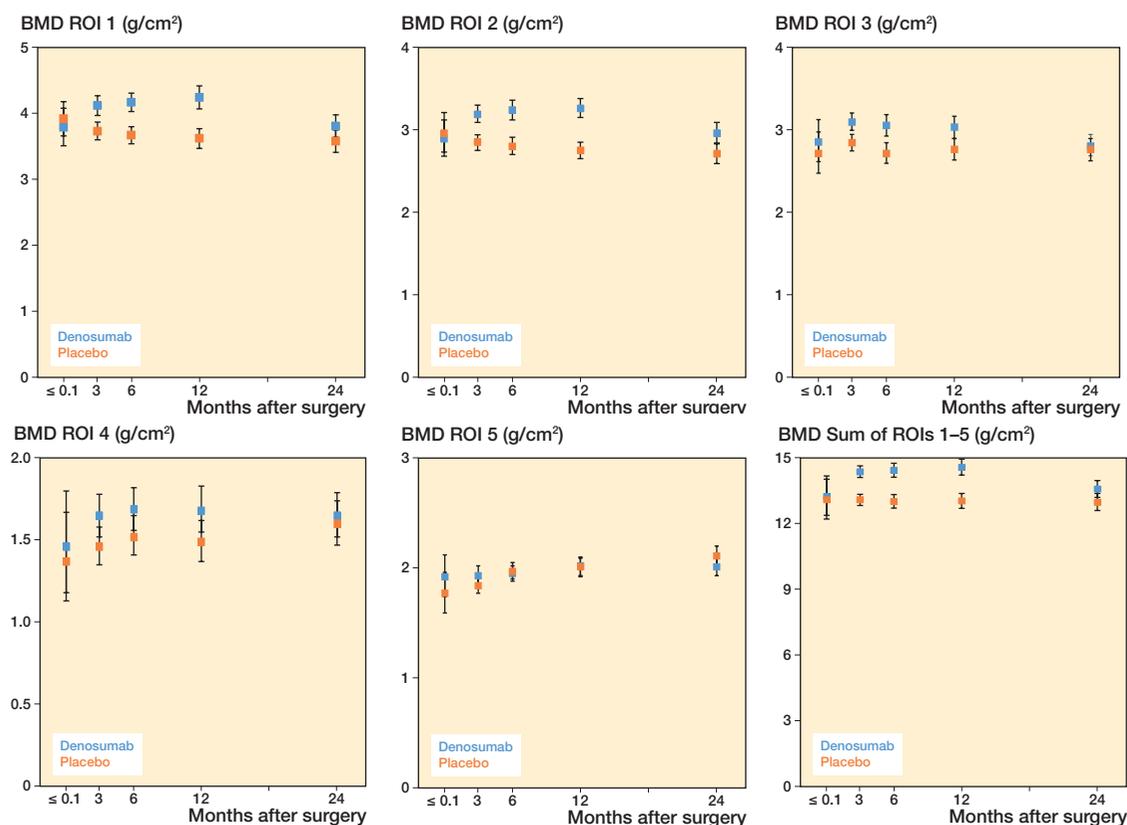
Figure 3. Periprosthetic BMD in ROI 1, ROI 2, ROI 3, ROI 4, ROI 5, and the sum of ROIs 1–5. For visits pre-randomization, descriptive geometric means with 95% confidence intervals are given. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1 to 3 days postoperatively.
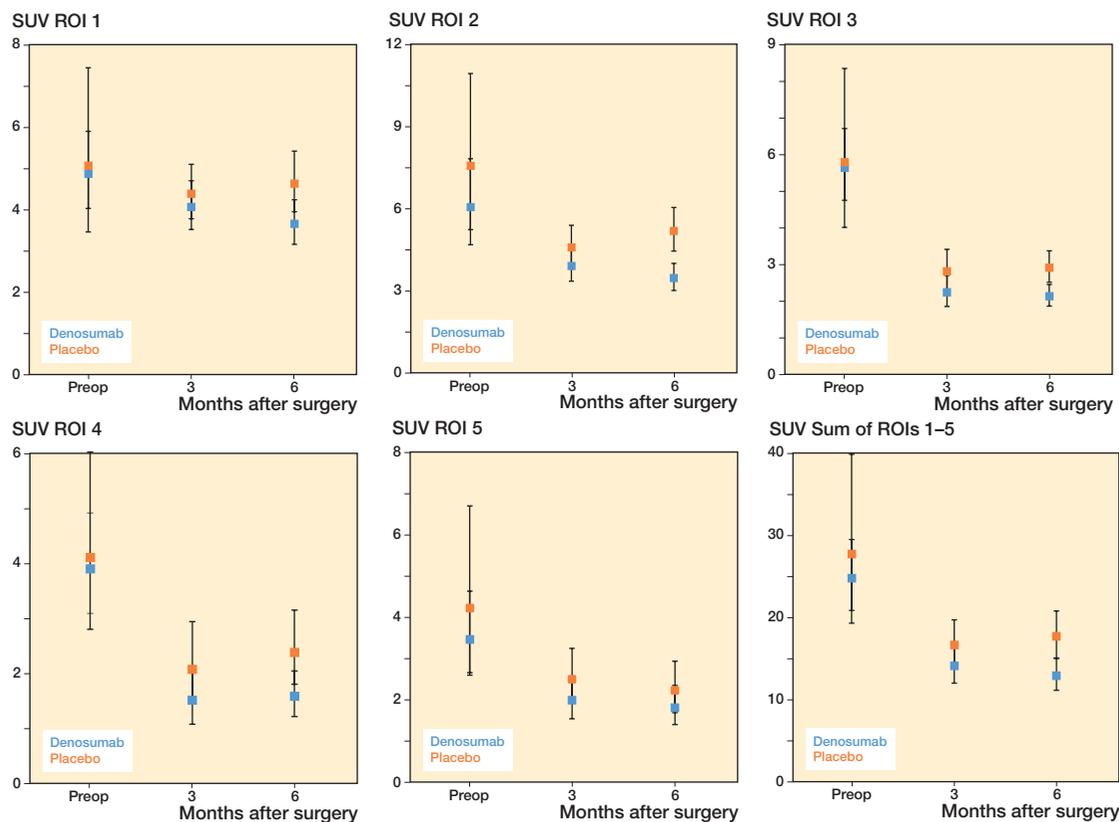
Figure 4. Periprosthetic SUV in ROI 1, ROI 2, ROI 3, ROI 4, ROI 5, and the sum of ROIs 1–5. For visits pre-randomization, descriptive geometric means with 95% confidence intervals are given. For visits post-randomization, model-based geometric means with confidence intervals are given. The drug was administered at 1 to 3 days postoperatively.

Biochemical markers

A pronounced reduction in blood concentrations of bone resorption and formation markers were registered in patients treated with denosumab after 3, 6, and 12 months. However, after 24 months, both marker levels were above baseline levels (Figures 5 and 6, see Supplementary data).

Patient-reported outcome measures

The placebo-treated patients had slightly higher HHS after 12 months than the patients treated with denosumab (100 vs. 94) (Table 6, see Supplementary data).

Adverse events

Serious adverse events and adverse events were equally distributed between patients treated with denosumab and placebo (Table 7, see Supplementary data).

Discussion

The main findings of this RCT are that 2 doses of denosumab prevent loss of acetabular pBMD after inserting an uncemented acetabular trabecular tantalum metal cup during the 1st year; however, pBMD declines in the 2nd year. Moreover,

and not previously reported, acetabular pSUV is potently reduced 6 months after the 1st dose of denosumab.

Acetabular periprosthetic bone mineral density

2 doses of denosumab prevented loss of acetabular pBMD compared with placebo and increased acetabular pBMD compared with baseline. Others have reported a loss of acetabular pBMD in proximal and central periacetabular ROI and increased pBMD in the distal ROI during the 1st year after inserting an uncemented THA cup ([3,13,14,18]). 1 RCT on the effects of a single IV injection of pamidronate reported a reduced loss of acetabular pBMD compared with placebo after 26 weeks ([19]). However, the effect disappeared after 2 years, and migration of the acetabular implant was not affected by pamidronate ([20]).

Only 1 previous RCT has evaluated the pharmacological effects of antiresorptive treatment on acetabular pBMD after a THA, and, to our knowledge, none has reported on the effects of denosumab in this setting ([19,20]). Yet, several RCTs that evaluated 1-year results of antiresorptive treatment on femoral pBMD indicate that the loss of pBMD can be attenuated or prevented after uncemented THA ([7,11,12]). However, the effects of antiresorptive treatment on femoral pBMD decline during the 2nd and 3rd year ([7,11,12]). Thus, the effect of 2

doses of denosumab on acetabular pBMD in the present study was similar to what has been reported for femoral pBMD.

Acetabular periprosthetic standardized uptake value

Few RCTs have investigated F-PET in bone. Increased bone turnover markers, osteoblastic activity by F-PET, and BMD in postmenopausal women with osteopenia have been reported 12 weeks after treatment with daily subcutaneous injections of teriparatide (21). In contrast, we found decreased bone turnover markers and acetabular pSUV but increased pBMD in patients treated with denosumab.

The reduced pSUV in patients treated with denosumab compared with placebo in both acetabular and femoral periprosthetic bone after 3 and 6 months is probably related to the biologic effect of the 1st dose of denosumab, with depressed osteoclast activity and insufficient coupling to osteoblast activity, reflected by the systemically depressed levels of CTX and P1NP (11). An experimental study suggests that uptake of [^{18}F] NaF and increased SUV can be the result of a mechanism other than the activity of the osteoblasts, such as affinity of [^{18}F] NaF to hydroxyapatite (22). However, that hypothesis is challenged by our results on acetabular pSUV as well as on femoral pSUV (11).

Theoretically, reduced bone metabolism, systemically and in periprosthetic bone, could negatively impact osteointegration, fixation, and stability of orthopedic implants.

Effects of antiresorptive treatment have shown that implant stability is achieved, femoral pBMD reached a plateau, and there were excellent patient-reported outcome measures 1 year after an uncemented THA (7,11). These findings indicate successful ingrowth and incorporation for an uncemented stem because of or despite antiresorptive drugs. 1 RCT that applied a 2-dose regime with denosumab 6 months apart and starting 1 month prior to surgery in elderly women reported increased femoral pBMD after 48 weeks that declined after 3 years. Implant stability after 48 weeks for an uncemented femoral stem was not affected by denosumab compared with placebo (12).

No data has been published for the effect of denosumab on cup stability by RSA. We did not perform any cup revisions during the 2-year study, indicating that denosumab is not harmful to the initial stability of an uncemented cup.

Compared with baseline, acetabular pSUV was reduced for both the placebo and denosumab treated patients. This is in contrast to increased levels of femur pSUV that we have reported previously (11).

An explanation for these differences in postoperative findings for pSUV of the acetabulum and proximal femur could be that the proximal part of the hip joint, the acetabulum, is close to bone affected by OAH, whereas the femoral head affected by OAH, the distal part of the OAH-affected hip joint, is resected and replaced (23,24). This implies that only extra-articular proximal femoral regions remain to be investigated for the pSUV after a THA, whereas the acetabular THA component is positioned in the previously affected subchondral bone.

Biochemical markers of bone metabolism

The present and an additional RCT investigating the antiresorptive effect of 2 doses of denosumab given in the first 6 months in connection with an uncemented THA reported distinct depressed CTX levels after 3 months and robust depressed levels at 6 and 12 months accompanied by similarly depressed levels of the bone formation marker P1NP (11,12). These findings could be interpreted as inadequate coupling between the osteoclasts and the osteoblasts, consistent with reports from large osteoporosis studies for denosumab (10). After the withdrawal of denosumab treatment, and in line with findings from osteoporosis studies, a rebound phenomenon with statistically significant above baseline serum levels for both bone resorption and formation markers was reported in the present RCT (25) (Figures 5 and 6, see Supplementary data).

Strength and limitations

The main strength of our study is that, to our knowledge, this is the first RCT that has included a pharmaceutical drug in the study protocol to evaluate the effect on acetabular pBMD and pSUV after a THA. Strict inclusion and exclusion criteria, defined radiological diagnosis of OAH, standardized surgical procedures, implants and postoperative care, carefully conducted case-report formulas, external monitoring, and a minimal number of patients lost to follow-up ensure that our study has excellent internal validity. In addition, the study was performed as an independent academic study without any support from the pharmaceutical industry.

Our study also has some limitations. The number of patients for the study was based on a power analysis for the primary outcome, femoral pBMD but not acetabular pBMD, 1 year after the 1st dose of denosumab or placebo. The secondary outcomes in the present report were planned and specified before the study start and followed according to the clinical trial protocol. However, secondary outcomes, while informative, should be interpreted cautiously.

Moreover, considering the width of the relevant CIs, the differences in effects between the treatment groups could be affected and should also be interpreted with caution.

The possibility to generalize the results to other implants (uncemented or cemented), age groups, anatomical sites, or diagnoses is not immediately evident. This is the 1st RCT to report effects of denosumab on acetabular pBMD, preceded by only 1 RCT that reported the effects of one IV dose of pamidronate (19,20). Thus, the external validity is limited.

Also, the importance of acetabular pBMD as a surrogate variable for implant loosening and unfavorable clinical results remains to be validated.

The positive effect on pBMD reported from RCTs during the 1-year anti-resorptive treatment on femur pBMD has been transient at a later follow-up (7,12). To preserve a sustainable

effect on pBMD, prolonged treatment with denosumab or switching to an alternative antiresorptive treatment could be considered but this remains to be determined.

Patients with osteoporosis on long-term treatment with denosumab have reported a rapid loss of gained BMD and have an increased risk of vertebral fractures when treatment is discontinued (26). However, no deleterious clinical effects of discontinuing only 2 doses of denosumab on orthopedic implant stability, revision rate, PROMs, and rates of adverse or serious adverse events have been reported from RCTs (12,27). Although not included in the study protocol, estimation of serum calcium levels could be of importance for safety reasons.

Conclusions

Our findings on this exploratory analysis of secondary endpoints indicate that denosumab seems to attenuate loss of acetabular pBMD, most probably by preventing periprosthetic osteoclast activation. However, this effect almost disappears after discontinuation of treatment. Further research is needed to determine whether inhibition of osteoclast recruitment by RANK-L inhibitors can reduce the need for subsequent acetabular revision surgery.

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Supplementary data

Peri- and postoperative procedures and implants

Preoperative digital radiographic planning for implant size, positioning, and inclination was performed before all procedures. Patients underwent surgery in a lateral decubitus position with an anterolateral approach by one of 2 surgeons (JM, NH) in regional spinal anesthesia or general anesthesia. Thereafter, an uncemented femoral neck-preserving stem (CFP, LINK, Hamburg, Germany) with a 28-mm CoCrMo head was implanted in the femur. However, for technical reasons, one patient was provided with an uncemented Cone stem with a 28-mm head. The acetabular implant, a uni-hole Continuum cup (Zimmer, Warsaw, IN, USA), is a press-fit hemispheric cup made of Tivanium, a titanium alloy, to which a surface of Trabecular Metal, a highly porous biomaterial made from elemental tantalum is bonded. The surface offers a high coefficient of friction and scratch fit that reduces micromotion and supposedly allows for rapid bone ingrowth. The acetabular bed was reamed line to line and the implant was anchored in

the acetabular bed according to the manufacturer's manual. The Continuum cup was fitted with a highly cross-linked polyethylene elevated liner with an inner diameter of 28 mm. Operative infection prophylaxis with cefuroxime 1.5 g x 3 (or clindamycin 600 mg x 2 in cases of penicillin allergy) was given intravenously, with the first dose administered < 60 minutes before surgery. Tranexamic acid (10 mg/kg bodyweight) was injected as an intravenous infusion before the start of surgery to reduce blood loss, provided no contraindications were present. Perioperative local infiltration anesthesia consisting of 150 ml of 0.2% ropivacaine and 1 mg adrenaline was administered, but no ketorolac was added to avoid potential effects on bone formation. Non-steroidal anti-inflammatory drugs were not prescribed, and patients were instructed not to use them after discharge. 0.4 ml enoxaparin (100 mg/ml) as thromboprophylaxis was given subcutaneously daily for 4 weeks postoperatively. The average operating time was 54 minutes (range 33–75).

Figure 5. CTX-Crosslaps. For visits pre-randomization, descriptive geometric means with confidence intervals are given. For visits post-randomization, model-based geometric means with confidence intervals are provided. The drug was administered 1–3 days postoperatively.

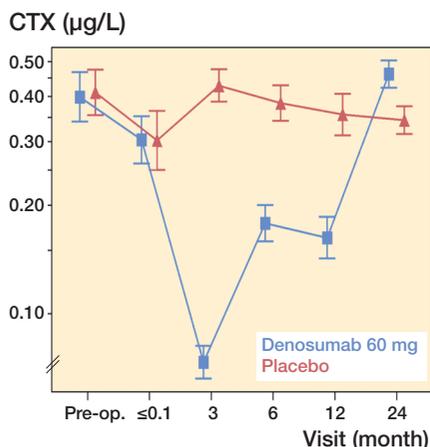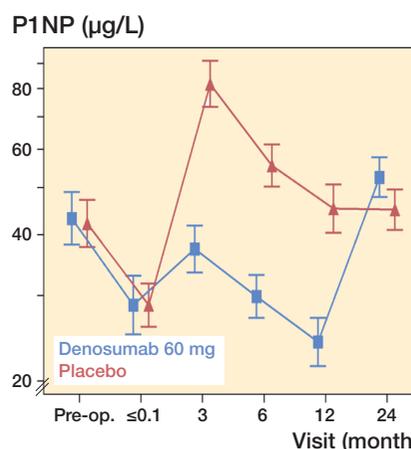Figure 6. P1NP. Y-axis is truncated for better visualization. For visits pre-randomization, descriptive geometric means with confidence intervals are given. For visits post-randomization, model-based, geometric means with confidence intervals are shown. The drug was administered 1–3 days postoperatively.

Table 1. Study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
1	Male or female patients 35–65 years of age with unilateral OAH requiring a THA and an unaffected contralateral hip.	On or has previously had bone-specific treatment (e.g., bisphosphonates, raloxifene, parathyroid hormone, strontium ranelate) in the past 5 years
2	Bodyweight ≤ 110 kg or body mass index (BMI) ≤ 35	Patients on systemic corticosteroid for > 3 months should not be regarded as eligible
3	Living in Uppsala County	Patients with diagnosed malignant disease in the past 5 years or known to have metastasis from malignant disease should not be considered eligible
4	Eligible patients should have been given oral information, a written patient information leaflet and signed an informed consent form	Patients with compromised general conditions and an ASA score of > 31 should not be regarded as eligible
5		Patients with known drug or alcohol abuse or regarded as socially dysfunctional, as judged by the investigators, should not be viewed as eligible
6		Pregnant women or women planning for pregnancy or fertile women (premenopausal) without contraceptives should not be regarded as eligible
7		Patients exposed to large irradiation doses, as judged by the investigators, should not be considered as eligible
8		Enrolled in either another drug study, in another device study, or in another study of an approved drug within 30 days before Visit 1 of the current study should not be regarded as eligible
9		Any condition or laboratory findings that, in the opinion of the investigators, render the patient unsuitable for inclusion (e.g., claustrophobia)

All patients gave oral and written consent to participate.

Table 3. Baseline (preoperative) characteristics in the F-PET subgroup. Values are mean (SD) or median (IQR) unless otherwise specified

Characteristic	Denosumab (n = 16)	Placebo (n = 16)
Age	58 (5)	59 (4)
Male, n (%)	8 (50)	5 (31)
Body mass index	26 (4)	26 (4)
Kellgren–Lawrence grading		
unaffected hip	1 (0–1)	1 (0–1)
affected hip	3 (3–4)	3 (3–4)
Harris Hip Score	60 (57–65)	48 (41–58)
EQ-VAS, median (IQR)	60 (40–66)	40 (24–60)
CTX (μg/L)	0.39 (0.14)	0.48 (0.22)
P1NP (μg/L)	41 (12)	46 (17)
Z-score [a]		
total hip (unaffected hip)	0.26 (1.07)	0.74 (0.73)
total hip (affected hip)	0.02 (1.04)	0.32 (1.08)
L1–L4	0.48 (1.03)	0.79 (0.90)

[a] Age- and sex-matched and weight-adjusted comparison with a White/Caucasian US reference population. None of the patients were osteoporotic according to the criteria of the World Health Association.

Table 4. Periprosthetic BMD, pBMD, ROI

pBMD region Visit	Treatment group	n	Geometric mean change from baseline (CI)	Geometric mean (CI)	Estimated geometric mean ratio (CI)	p-value
ROI 1						
1–3 days	Denosumab 60 mg	32		3.79 (3.51–4.08)		
	Placebo	32		3.92 (3.66–4.18)		
3 months	Denosumab 60 mg	32	1.07 (1.03–1.12)	4.12 (3.97–4.27)	1.10 (1.05–1.16)	0.0003
	Placebo	32	0.97 (0.93–1.00)	3.73 (3.60–3.87)		
6 months	Denosumab 60 mg	32	1.08 (1.04–1.11)	4.17 (4.03–4.31)	1.14 (1.08–1.19)	< 0.0001
	Placebo	31	0.94 (0.91–0.98)	3.67 (3.54–3.80)		
12 months	Denosumab 60 mg	31	1.10 (1.06–1.14)	4.24 (4.07–4.42)	1.17 (1.10–1.24)	< 0.0001
	Placebo	31	0.93 (0.88–0.98)	3.62 (3.47–3.77)		
24 months	Denosumab 60 mg	32	0.99 (0.95–1.03)	3.81 (3.64–3.98)	1.06 (1.00–1.14)	0.06
	Placebo	30	0.92 (0.87–0.97)	3.58 (3.41–3.75)		
ROI 2						
1–3 days	Denosumab 60 mg	32		2.89 (2.68–3.12)		
	Placebo	32		2.96 (2.73–3.21)		
3 months	Denosumab 60 mg	32	1.09 (1.05–1.13)	3.19 (3.09–3.30)	1.12 (1.07–1.18)	< 0.0001
	Placebo	32	0.97 (0.94–1.00)	2.85 (2.75–2.94)		
6 months	Denosumab 60 mg	32	1.10 (1.06–1.15)	3.24 (3.12–3.36)	1.16 (1.10–1.22)	< 0.0001
	Placebo	31	0.95 (0.91–0.98)	2.80 (2.70–2.91)		
12 months	Denosumab 60 mg	31	1.11 (1.07–1.14)	3.26 (3.15–3.38)	1.19 (1.13–1.25)	< 0.0001
	Placebo	31	0.93 (0.89–0.97)	2.75 (2.65–2.85)		
24 months	Denosumab 60 mg	32	1.01 (0.96–1.06)	2.96 (2.83–3.09)	1.09 (1.02–1.16)	0.008
	Placebo	30	0.92 (0.87–0.96)	2.71 (2.59–2.84)		
ROI 3						
1–3 days	Denosumab 60 mg	32		2.85 (2.61–3.12)		
	Placebo	29		2.71 (2.47–2.97)		
3 months	Denosumab 60 mg	32	1.11 (1.07–1.14)	3.09 (2.99–3.20)	1.09 (1.04–1.14)	0.0006
	Placebo	29	1.02 (0.98–1.06)	2.84 (2.74–2.94)		
6 months	Denosumab 60 mg	32	1.09 (1.05–1.13)	3.05 (2.92–3.18)	1.12 (1.06–1.20)	0.0005
	Placebo	28	0.98 (0.92–1.03)	2.71 (2.59–2.84)		
12 months	Denosumab 60 mg	32	1.08 (1.04–1.13)	3.03 (2.89–3.16)	1.10 (1.03–1.17)	0.006
	Placebo	28	0.99 (0.94–1.05)	2.76 (2.63–2.89)		
24 months	Denosumab 60 mg	32	1.00 (0.96–1.05)	2.80 (2.68–2.94)	1.02 (0.95–1.09)	0.6
	Placebo	28	0.99 (0.94–1.04)	2.76 (2.62–2.89)		
ROI 4						
1–3 days	Denosumab 60 mg	32		1.46 (1.18–1.80)		
	Placebo	32		1.37 (1.13–1.67)		
3 months	Denosumab 60 mg	32	1.16 (1.07–1.26)	1.65 (1.52–1.78)	1.13 (1.01–1.26)	0.04
	Placebo	32	1.03 (0.95–1.12)	1.46 (1.35–1.58)		
6 months	Denosumab 60 mg	32	1.18 (1.09–1.26)	1.69 (1.56–1.82)	1.11 (0.99–1.24)	0.07
	Placebo	31	1.07 (0.97–1.17)	1.52 (1.41–1.65)		
12 months	Denosumab 60 mg	32	1.17 (1.08–1.28)	1.68 (1.55–1.83)	1.13 (1.00–1.27)	0.05
	Placebo	31	1.05 (0.96–1.14)	1.49 (1.37–1.62)		
24 months	Denosumab 60 mg	32	1.13 (1.03–1.24)	1.65 (1.52–1.79)	1.03 (0.91–1.16)	0.6
	Placebo	30	1.10 (1.02–1.19)	1.60 (1.47–1.74)		
ROI 5						
1–3 days	Denosumab 60 mg	32		1.92 (1.74–2.12)		
	Placebo	32		1.77 (1.59–1.96)		
3 months	Denosumab 60 mg	32	1.05 (1.01–1.09)	1.93 (1.85–2.02)	1.05 (0.99–1.11)	0.1
	Placebo	32	1.01 (0.96–1.06)	1.84 (1.77–1.92)		
6 months	Denosumab 60 mg	32	1.04 (1.02–1.07)	1.95 (1.88–2.02)	0.99 (0.94–1.04)	0.6
	Placebo	31	1.07 (1.02–1.13)	1.97 (1.90–2.05)		
12 months	Denosumab 60 mg	32	1.08 (1.05–1.12)	2.02 (1.93–2.10)	1.01 (0.95–1.07)	0.9
	Placebo	31	1.09 (1.03–1.15)	2.01 (1.92–2.09)		
24 months	Denosumab 60 mg	32	1.08 (1.03–1.13)	2.01 (1.93–2.10)	0.96 (0.90–1.01)	0.1
	Placebo	30	1.15 (1.09–1.21)	2.11 (2.02–2.20)		
Sum of ROI 1–5						
1–3 days	Denosumab 60 mg	32		13.2 (12.4–14.2)		
	Placebo	29		13.1 (12.2–14.0)		
3 months	Denosumab 60 mg	32	1.09 (1.07–1.11)	14.4 (14.1–14.6)	1.10 (1.07–1.13)	< 0.0001
	Placebo	29	0.99 (0.97–1.02)	13.1 (12.8–13.3)		
6 months	Denosumab 60 mg	32	1.09 (1.07–1.11)	14.4 (14.1–14.8)	1.11 (1.07–1.15)	< 0.0001
	Placebo	28	0.98 (0.95–1.01)	13.0 (12.7–13.3)		
12 months	Denosumab 60 mg	31	1.10 (1.08–1.12)	14.6 (14.2–14.9)	1.12 (1.08–1.16)	< 0.0001
	Placebo	28	0.98 (0.95–1.01)	13.0 (12.7–13.4)		
24 months	Denosumab 60 mg	32	1.02 (1.00–1.05)	13.6 (13.2–14.0)	1.05 (1.00–1.09)	0.03
	Placebo	28	0.98 (0.95–1.01)	13.0 (12.6–13.4)		

Table 5. Periprosthetic SUV, pSUV, ROI

pSUV region Visit	Treatment group	n	Geometric mean change from baseline (CI)	Geometric mean (CI)	Estimated geometric mean ratio (CI)	p-value
ROI 1						
Pre-op.	Denosumab 60 mg	16		4.87 (4.03–5.90)		
	Placebo	16		5.07 (3.46–7.44)		
3 months	Denosumab 60 mg	16	0.83 (0.71–0.98)	4.07 (3.52–4.70)	0.93 (0.75–1.14)	0.5
	Placebo	16	0.89 (0.70–1.13)	4.39 (3.78–5.10)		
6 months	Denosumab 60 mg	16	0.74 (0.60–0.91)	3.66 (3.16–4.24)	0.79 (0.64–0.98)	0.04
	Placebo	15	0.81 (0.62–1.07)	4.63 (3.95–5.42)		
ROI 2						
Pre-op.	Denosumab 60 mg	16		6.06 (4.69–7.83)		
	Placebo	16		7.57 (5.24–10.9)		
3 months	Denosumab 60 mg	16	0.62 (0.51–0.76)	3.92 (3.36–4.58)	0.85 (0.68–1.07)	0.2
	Placebo	16	0.66 (0.50–0.87)	4.60 (3.91–5.40)		
6 months	Denosumab 60 mg	16	0.58 (0.42–0.79)	3.48 (3.02–4.01)	0.67 (0.54–0.83)	0.0007
	Placebo	15	0.62 (0.47–0.82)	5.20 (4.46–6.05)		
ROI 3						
Pre-op.	Denosumab 60 mg	16		5.64 (4.75–6.71)		
	Placebo	16		5.79 (4.01–8.35)		
3 months	Denosumab 60 mg	16	0.40 (0.33–0.48)	2.24 (1.85–2.70)	0.80 (0.61–1.04)	0.09
	Placebo	16	0.50 (0.40–0.63)	2.81 (2.31–3.41)		
6 months	Denosumab 60 mg	16	0.38 (0.31–0.47)	2.13 (1.86–2.45)	0.73 (0.60–0.90)	0.004
	Placebo	15	0.45 (0.35–0.57)	2.91 (2.51–3.37)		
ROI 4						
Pre-op.	Denosumab 60 mg	16		3.90 (3.09–4.92)		
	Placebo	16		4.11 (2.80–6.03)		
3 months	Denosumab 60 mg	16	0.38 (0.27–0.55)	1.51 (1.07–2.11)	0.73 (0.45–1.19)	0.2
	Placebo	16	0.51 (0.34–0.76)	2.07 (1.46–2.94)		
6 months	Denosumab 60 mg	16	0.41 (0.28–0.59)	1.58 (1.21–2.04)	0.66 (0.45–0.97)	0.04
	Placebo	15	0.51 (0.34–0.76)	2.38 (1.80–3.15)		
ROI 5						
Pre-op.	Denosumab 60 mg	16		3.46 (2.59–4.63)		
	Placebo	16		4.22 (2.65–6.70)		
3 months	Denosumab 60 mg	16	0.55 (0.43–0.72)	1.98 (1.53–2.55)	0.79 (0.55–1.15)	0.2
	Placebo	16	0.62 (0.39–0.98)	2.49 (1.91–3.24)		
6 months	Denosumab 60 mg	16	0.49 (0.36–0.66)	1.80 (1.39–2.34)	0.81 (0.55–1.20)	0.3
	Placebo	15	0.49 (0.33–0.73)	2.22 (1.68–2.93)		
Sum of ROI 1–5						
Pre-op.	Denosumab 60 mg	16		24.8 (20.8–29.5)		
	Placebo	16		27.7 (19.3–39.9)		
3 months	Denosumab 60 mg	16	0.56 (0.47–0.65)	14.1 (12.0–16.6)	0.85 (0.67–1.07)	0.2
	Placebo	16	0.63 (0.49–0.82)	16.7 (14.0–19.7)		
6 months	Denosumab 60 mg	16	0.52 (0.41–0.64)	12.9 (11.1–15.0)	0.73 (0.58–0.92)	0.009
	Placebo	15	0.57 (0.44–0.74)	17.7 (15.0–20.8)		

Table 6. Harris Hip Score

Visit	Treatment group	n	Median	Median change from baseline	p-value [a]	p-value [b]
1–3 days	Denosumab 60 mg	32	58.0			
	Placebo	32	51.0			
3 months	Denosumab 60 mg	32	81.0	22.5	< 0.0001	0.1
	Placebo	32	86.0	33.0	< 0.0001	
6 months	Denosumab 60 mg	32	87.0	32.0	< 0.0001	0.07
	Placebo	32	92.0	38.0	< 0.0001	
12 months	Denosumab 60 mg	32	93.5	36.0	< 0.0001	0.01
	Placebo	31	100	42.0	< 0.0001	
24 months	Denosumab 60 mg	32	97.0	38.0	< 0.0001	0.2
	Placebo	31	100	42.0	< 0.0001	

[a] Change from baseline.
[b] Treatment difference

Table 7. Summary of adverse events (AE) and serious adverse events (SAE)

Number of	Denosumab	Placebo	Total
patients reporting any AE	23	20	43
AEs reported	39	49	88
patients reporting any SAE	2	4	6
SAEs	2	7	9
patients reporting any AE possibly related to study treatment	2	4	6
possibly related AEs	2	5	7
patients reporting any AE with maximal intensity "Severe"	0	3	3
patients reporting any AE with maximal intensity "Moderate"	9	10	19
patients reporting any AE with maximal intensity "Mild"	17	14	31