Preventing Loss of Femoral Periprosthetic Bone Mineral Density in Cementless Total Hip Arthroplasty Using a Tapered Wedge Stem in Patients With Osteoporosis Treated With Denosumab: a Retrospective, Cohort Study

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Research Article

Keywords: Bone mineral density (BMD), total hip arthroplasty (THA), surgery, femoral periprosthetic

Posted Date: July 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-736895/v1

Abstract

Background*:* Bone mineral density (BMD) of the proximal femur around the stem decreases due to stress shielding after cementless total hip arthroplasty (THA). When severe stress shielding occurs, the risk of periprosthetic femoral fractures increases, and this bone loss can also increase the difficulty of future revision THA. Denosumab is known to improve the quality and strength of cortical bone in the proximal femurs of patients with osteoporosis. The purpose of this study was to investigate whether denosumab prevents loss of proximal femoral periprosthetic BMD in cementless THA using a tapered wedge stem in patients with osteoporosis.

Methods*:* Sixty-three consecutive patients who had undergone unilateral primary THA using a tapered wedge stem were included in this retrospective study. Twenty-four patients who received denosumab for osteoporosis were the denosumab group, and the 39 without denosumab were the control group. At 2 weeks, 6 months, and 12 months after THA, bone turnover markers and femoral periprosthetic BMD were measured.

Results*:* BMD in zone 1 was significantly increased from baseline at both 6 and 12 months after THA in the denosumab group and significantly decreased in the control group. BMD in zone 7 was significantly decreased compared to baseline at both 6 and 12 months after THA in the control group, but not in the denosumab group. The use of denosumab for THA patients with osteoporosis was independently related to preventing loss of periprosthetic BMD of the femur at 12 months after surgery in zones 1 and 7 on multivariate analysis.

Conclusions*:* Denosumab significantly increased proximal femoral periprosthetic BMD in zone 1 and prevented loss of BMD in zone 7 in patients with osteoporosis after cementless THA using a tapered wedge stem at both 6 and 12 months after surgery.

Introduction

The proportion of elderly people is increasing globally. The prevalence of degenerative or traumatic hip disorders requiring surgical intervention is higher in the elderly population, and it is assumed that the number of older patients who choose to undergo total hip arthroplasty (THA) to improve their quality of life will increase [1, 2]. Though THA is one of the most successful surgeries, it has several problems. The bone mineral density (BMD) of the proximal femur around the stem decreases due to stress shielding after cementless THA [3, 4]. It has been reported that female patients with low systemic BMD and high bone resorption marker levels show greater periprosthetic proximal femoral bone loss [5]. When severe stress shielding occurs, the risk of periprosthetic femoral fractures increases [6–8]. Furthermore, this bone loss can also increase the difficulty of future revision THA [7]. Several studies have reported that the loss of BMD in the proximal femur around the stem is reduced by bone antiresorptive therapies [9–13]. However, the preventive effect of bisphosphonates on the loss of BMD around the proximal stem is limited [14]. Denosumab is a fully human monoclonal antibody against RANK ligand (receptor activator

of nuclear factor kappa-B ligand), the key mediator of the formation, activation, and survival of osteoclasts [15]. In the FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) study, denosumab significantly increased dual X-ray absorptiometry (DXA) BMD not only at trabecular bone, but also at cortical bone. This positive effect of denosumab on cortical BMD has not been observed with other antiresorptive therapies for patients with osteoporosis [15]. Therefore, denosumab may be more effective for reducing the loss of femoral BMD around the stem than bisphosphonates. However, there have been few reports of the preventive effect of denosumab on the loss of femoral periprosthetic BMD in cementless THA for patients with osteoporosis. The purpose of this study was to evaluate the effect of denosumab on femoral periprosthetic BMD after cementless THA using a tapered wedge stem in patients with osteoporosis.

Materials And Methods

This retrospective, cohort study was approved by the Ethics Committee of the authors' affiliated institution. Informed consent was obtained from all participants. A total of 66 consecutive patients who had undergone unilateral primary THA using a tapered wedge stem (Anthology, Smith and Nephew, Inc., Memphis, TN, USA, or Accolade II, Stryker Orthopaedics, Mahwah, NJ, USA) by the anterolateral approach in the supine position from May 2016 to February 2020 at one institution were retrospectively reviewed. Of these 66 patients, 27 patients with osteoporosis received denosumab before or after THA. The exclusion criteria included history of previous surgery of the ipsilateral hip, evidence of secondary osteoporosis, rheumatoid arthritis or any other inflammatory arthritis, and treatment with corticosteroids. Three of 27 patients with osteoporosis who received denosumab were excluded because they had rheumatoid arthritis. The denosumab group included 24 patients, with 1 patient who received denosumab a year before THA, and 23 patients who received denosumab from 1 to 3 weeks after THA. The reasons for undergoing THA included osteoarthritis (20 cases) and hip fracture (4 cases) in the denosumab group. All denosumab group patients received 0.75 μg of eldecalcitol daily to prevent hypocalcemia. The 24 patients with osteoporosis who received denosumab were compared to 39 patients who underwent cementless THA without receiving denosumab at the same institution during the same period. The reasons for undergoing THA in the control group included osteoarthritis (36 cases) and osteonecrosis of the femoral head (3 cases).

All 63 participants were assessed for osteoporosis preoperatively or at 2 weeks after THA by measuring BMD of the lumbar spine in the anteroposterior view and determining the presence of a fragility fracture in either the lumbar spine or the proximal femur [16]. All of the patients in the denosumab group and 5 patients in the control group had osteoporosis. In the control group, there were 9 patients who were taking medication for osteoporosis before THA: 4 patients received risedronate, 3 patients received 0.75 μg of eldecalcitol, 1 patient received ibandronate and 0.75 μg of eldecalcitol, and 1 patient received a selective estrogen receptor modulator (SERM). All of the patients in this study underwent DXA (QDR-4500SL, Hologic Inc., Marlborough, MA, USA) to measure femoral periprosthetic BMD 2 weeks, 6 months, and 12 months after THA. BMD measurements around the stem were measured for each of the 7 regions of interest described by Gruen [17] (Fig. 1). BMD of the lumbar spine was also measured in the

anteroposterior side from L2 to L4 by DXA. Bone turnover markers were measured preoperatively for the baseline and then at 6 months and 12 months after surgery. Bone-type alkaline phosphatase (BAP) was measured as a bone formation marker, and tartrate-resistant acid phosphatase-5b (TRACP-5b) was measured as a bone resorption marker. Radiographic evaluation of the hip joint for loosening of the femoral stem was performed. The canal flare index (CFI) according to Noble et al. [18] was also measured preoperatively on the femur of the operative side. The CFI was determined as the width of the femoral canal 20 mm above the mid-trochanteric line divided by the canal width at the isthmus [18].

Statistical analysis

To compare the baseline characteristics of the patients in the 2 groups, the chi-squared test was used for comparisons of categorical variables, whereas Mann-Whitney's U test was used for continuous variables. The mean % changes of BMD around the stem and of bone turnover markers (BAP, TRACP-5b) were evaluated in each of the 2 groups by Friedman's test. Post hoc comparisons were performed using the Bonferroni correction for multiple comparisons. Multivariate analysis was also performed to identify factors related to BMD preservation at the proximal femur in zone 1 and zone 7 at 12 months after THA. All statistical analyses were performed using R software, version 3.6.3 (R Foundation for statistical Computing, Vienna, Australia). Probability values < 0.05 were considered significant.

Results

Baseline demographic and clinical characteristics are shown in Table 1. The mean age at baseline was 73.7 years in the denosumab group and 70.8 years in the control group. The baseline body mass index (BMI) and lumbar spine BMD were significantly lower in the denosumab group than in the control group. There were no significant differences in the type of stem, bone turnover markers, and CFI between the 2 groups.

Table 1
Baseline characteristics of the patients.

	Denosumab (N = 24)	Control (N = 39)	P value
Age (years), mean ± SD	73.7 ± 9.3	70.8 ± 10.3	0.44
Range (years)	58–91	48–86	
Sex (male : female)	1 : 23	4 : 35	0.73
BMI (kg/m^2), mean ± SD	22.0 ± 2.7	25.6 ± 4.3	< 0.01
Type of stem (Anthology : Accolade)	10 : 14	22 : 17	0.29
Osteoporosis (number)	24	5	
Drug for osteoporosis	DSM + Eld 24	RIS 4, Eld 2, IBA + Eld 1, SERM 1	
Lumber Spine BMD (g/cm^2), mean ± SD	0.73 ± 0.14	0.98 ± 0.18	< 0.0001
BAP (μg/l), mean ± SD	15.4 ± 6.5	16.9 ± 5.8	0.44
TRACP-5b (mU/dl), mean ± SD	526 ± 204	566 ± 213	0.78
Canal Flare Index (CFI), mean ± SD	3.42 ± 0.61	3.57 ± 0.69	0.46

BMI: body mass index, BMD: bone mineral density, DSM: denosumab, RIS: risedronate, Eld: eldecalcitol, IBA: ibandronate, SERM: selective estrogen receptor modulator, BAP: bone-type alkaline phosphatase, TRACP-5b: tartrate resistant acid phosphatase-5b

Figure 2 shows the mean % change of BMD around the femoral stem by Gruen's zone. The mean % change of BMD in zone 1 was significantly higher at both 6 and 12 months after THA than at baseline in the denosumab group, but significantly lower in the control group. There was a significant decrease of BMD in zone 7 compared to baseline at both 6 and 12 months in the control group, but not in the denosumab group. Figure 3 shows the mean % change of bone turnover markers. Both the bone formation marker (BAP) and the bone resorption marker (TRACP-5b) were significantly lower 6 and 12 months after surgery than at baseline in the denosumab group. There were no significant differences in bone turnover markers in the control group. On radiographic evaluation of the hip joint, there was no stem loosening in any patients in both the denosumab group and the control group 6 and 12 months after THA. On multivariate analysis, use of denosumab was an independent factor related to change in periprosthetic proximal BMD of the femur in zone 1 (Table 2) and zone 7 (Table 3) at 12 months after THA.

Table 2
Multiple regression analysis for factors affecting %BMD change in Zone1 at 12 months after THA.

	Regression coefficient	95% confident interval	P value	R^2
Model summary			< 0.0001	0.451
Age	0.10	-0.21 to 0.41	0.51	
BMI	0.08	-0.74 to 0.89	0.85	
Lumber BMD	1.34	-17.7 to 20.4	0.89	
use of denosumab	21.6	14.3 to 29.0	< 0.0001	
BMI: body mass index, BMD: bone mineral density				

Table 3
Multiple regression analysis for factors affecting %BMD change in Zone7 at 12 months after THA.

	Regression coefficient	95% confident interval	P value	R^2
Model summary			< 0.0001	0.29
Age	0.01	-0.47 to 0.49	0.97	
BMI	-0.32	-1.59 to 0.94	0.61	
Lumber BMD	9.15	-20.4 to 38.7	0.54	
use of denosumab	25.2	13.8 to 36.5	< 0.0001	
BMI: body mass index, BMD: bone mineral density				

Discussion

The present study demonstrated the preventive effect of denosumab on loss of femoral periprosthetic BMD in zone 1 and zone 7 in cementless THA using a tapered wedge stem in patients with osteoporosis 12 months after surgery. Moreover, BMD in zone 1 was significantly increased from baseline at both 6 and 12 months after THA in the denosumab group. This result was consistent with a previous study using a tapered wedge uncemented stem [19]. Aro et al. showed that denosumab significantly decreased bone loss in the femoral neck (zone 7) and increased periprosthetic BMD in the greater trochanteric region (zone 1) [19]. Nagoya et al. reported that denosumab increased the % change in periprosthetic BMD at zone 7 by an average of 7.3%, but it did not increase at zone 1 in patients with cementless THA using a ZweyMüller-type stem [13]. This discrepancy was considered due to the difference in type of cementless stem between a tapered wedge stem and a ZweyMüller-type stem.

The periprosthetic BMD of the proximal femoral stem was significantly decreased in zone 7 even with the use of bisphosphonates, though bisphosphonates prevented some loss of proximal periprosthetic BMD in zone 1 and zone 7 compared to the control group not given bisphosphonates [9, 11, 20]. In the present study using denosumab, there was no significant decrease of BMD in zone 7 compared to baseline after THA, and denosumab may be more effective in preventing periprosthetic proximal femoral BMD than bisphosphonates. In addition, this study showed that, on multivariate analysis, the use of denosumab was an independent factor related to change in periprosthetic proximal BMD of the femur in zone 1 and zone 7. Poole et al. reported that denosumab significantly increased proximal femoral cortical mass surface density, as well as thickness, in women with osteoporosis [21]. The positive effect of denosumab on cortical bone in the proximal part of the femur is not seen with bisphosphonates. The antiresorptive effect of bisphosphonates is not sufficient in cortical bone, because concentrations of bisphosphonates are lower in cortical bone than in trabecular bone [22, 23]. In contrast, denosumab circulates freely to bone surfaces and into remodeling compartments where it inhibits osteoclastogenesis and can thus inhibit remodeling more rapidly and markedly than alendronate in cortical bone [23]. Since there is greater cortical bone mass than cancellous bone mass in the proximal part of the femur after cementless THA using a tapered wedge stem, use of denosumab, which has a high effect on cortical bone, is considered effective for maintaining periprosthetic BMD. In addition, Zebaze et al. reported that denosumab reduced cortical porosity of the proximal femoral shaft, resulting in increased mineralized matrix volume and improved strength [24]. These effects of denosumab may reduce the risk of periprosthetic femoral fractures after cementless THA.

There are several limitations in this study. First, the present study had a small sample and was retrospective. Further randomized or prospective studies with large sample sizes are needed to investigate the preventive effect of denosumab on the loss of femoral periprosthetic BMD using a tapered wedge stem in patients with osteoporosis. Second, this study had a short-term follow-up period. The BMD in the calcar region continued to decrease faster than would be expected from normal ageing up to 14 years after THA using a tapered uncemented stem [25]. However, it was reported that BMD decreased markedly in the proximal part of the femur during the first operative year, and the bone loss was minimal at only a few percentages per year after the first postoperative year [26]. Thus, it is important to prevent loss of BMD of the proximal femur around the stem within 12 months after THA. Third, some patients in the control group were taking medication for osteoporosis, which may have affected the results of this study. However, denosumab was shown to be effective in preventing loss of BMD in the proximal part of the femoral stem even though some of the patients in the control group may have had a positive effect from the drugs they took for osteoporosis in the present study.

In conclusion, denosumab significantly increased proximal femoral periprosthetic BMD in zone 1 and prevented loss of BMD in zone 7 in patients with osteoporosis after cementless THA using a tapered wedge stem at both 6 and 12 months after surgery. The use of denosumab for THA patients with osteoporosis was an independent factor related to preventing loss of periprosthetic proximal BMD of the femur in zone 1 and zone 7 on multivariate analysis.

Abbreviations

BMD
Bone mineral density
THA
Total hip arthroplasty
RANK ligand
receptor activator of nuclear factor kappa-B ligand
FREEDOM
Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months
DXA
Dual X-ray absorptiometry
DSM
Denosumab
RIS
Risedronate
Eld
Eldecalcitol
IBA
Ibandronate
SERM
Selective estrogen receptor modulator
BAP
Bone-type alkaline phosphatase
TRACP-5b
Tartrate-resistant acid phosphatase-5b
CFI
Canal flare index
BMI
Body mass index

Declarations

Availability of date and materials

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

Acknowledgments

Not applicable.

Funding

Not applicable.

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Contributions

KK, HK, TK, NM and YS contributed to the study conception and design. Date collection and analysis were performed by KK, KO, NS, CS, TK and MC. KK and HK wrote the manuscript. The authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Akita Rosai Hospital. Informed consent was obtained from all participants.

Consent for publication

Written informed consent was obtained from the patients for publication.

Competing interests

The authors declare that they have no competing interests.

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Figures

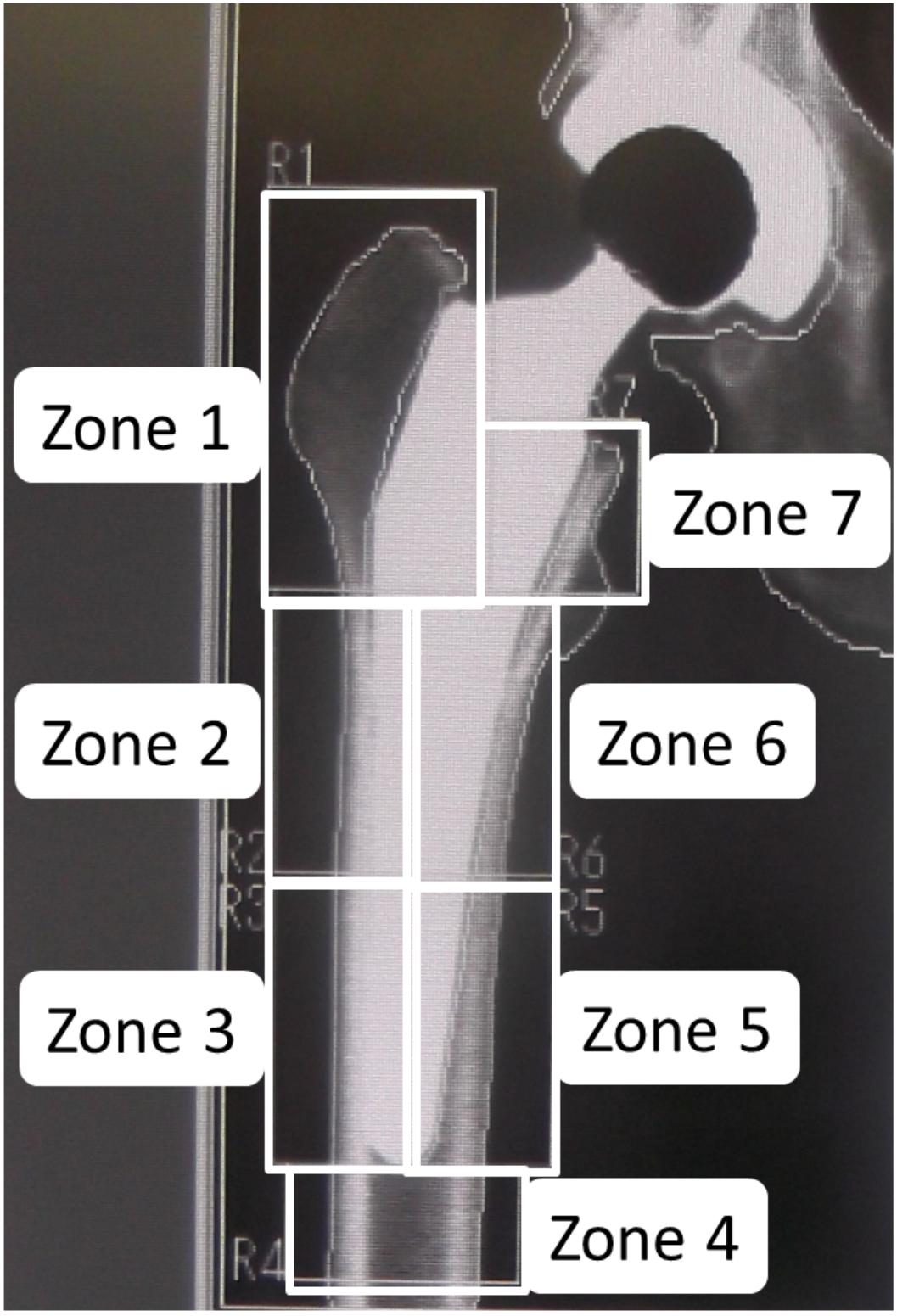

Figure 1

The seven regions of interest according to Gruen`s classification

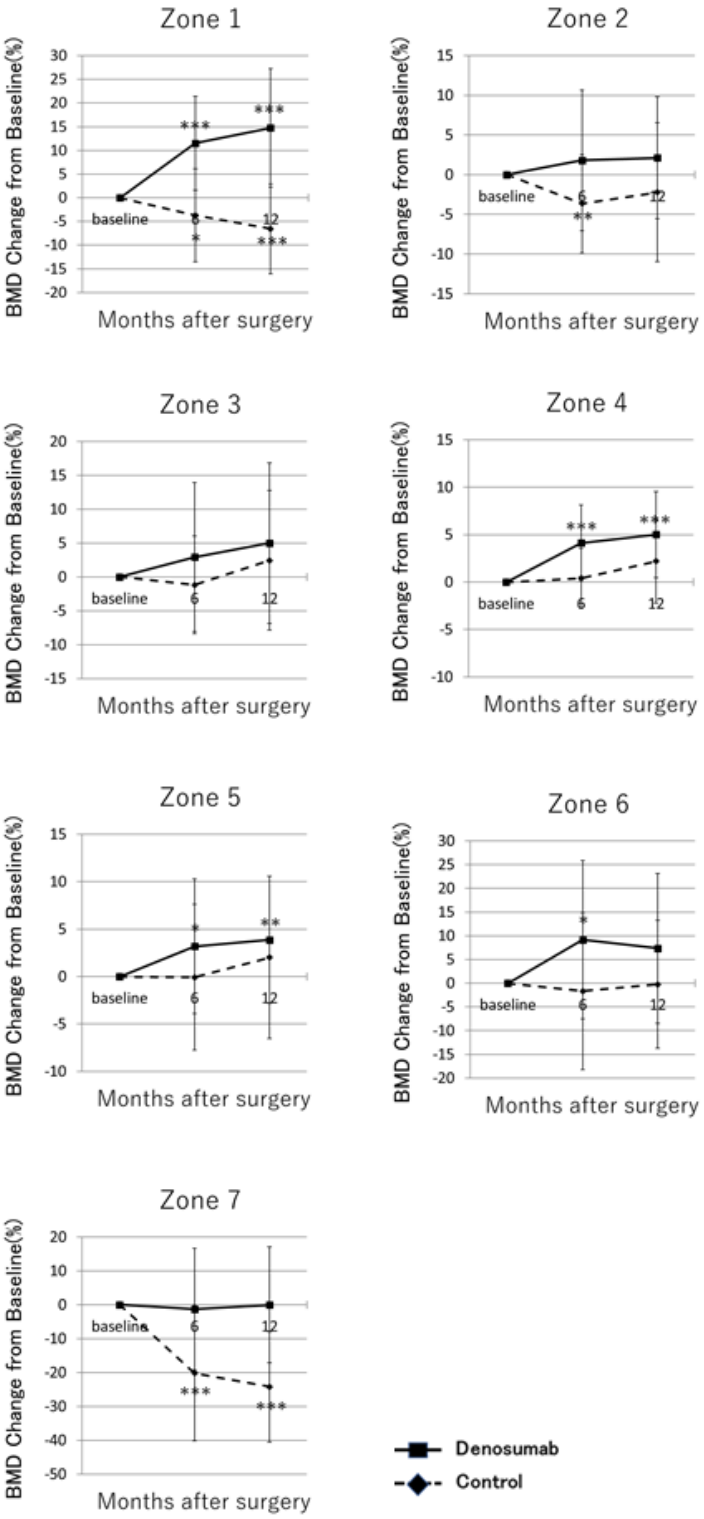

Figure 2

The mean % change of bone mineral density (BMD) around the femoral tapered wedge stem. *p<0.05 vs. baseline, **p<0.01 vs. baseline, ***p<0.001 vs. baseline BMD: bone mineral density

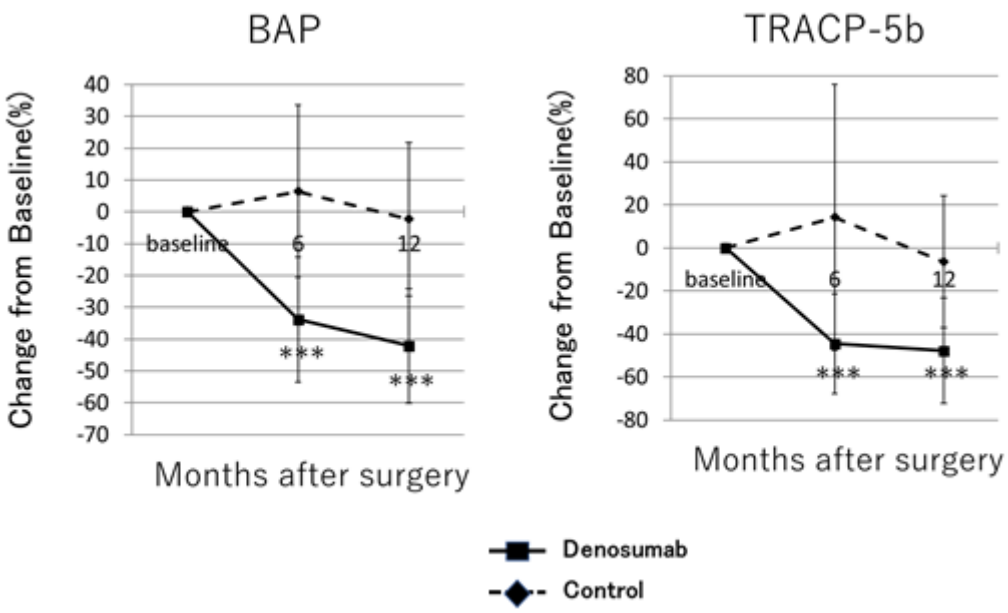

Figure 3

The mean % change of bone turnover makers. BAP: bone-type alkaline phosphatase, TRACP-5b: tartrate resistant acid phosphatase-5b, ***p<0.001 vs. baseline