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Etidronate does not suppress periprosthetic bone loss following cemented hip arthroplasty

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Abstract Periprosthetic bone loss after arthroplasty may threaten prosthesis survival. The current study investigated the effect of etidronate therapy on periprosthetic, contralateral hip, and spine bone mineral density (BMD) in a one-year, prospective, randomized, double-blind study on 46 patients after cemented hip arthroplasty. BMD was measured with dual-energy X-ray absorptiometry (DXA). There were no significant differences between mean BMD measurements of the etidronate and placebo groups, with

the exception of the mean percent change in the spine at six months and 12 months and in Gruen zone 3 at six months; in all three cases, the etidronate group had significantly greater mean values. These findings suggest that cyclic etidronate therapy has no significant effect in suppressing periprosthetic bone loss following cemented hip arthroplasty.

Résumé La perte osseuse périprothétique après arthroplastie peut mettre en danger la survie de la prothèse. Nous avons étudié l'effet de l'etidronate sur la densité minérale (DM) de l'os en zone périprothétique, au niveau de la hanche opposée et du rachis. L'étude à un an, prospective, randomisée et en double-aveugle a inclue 46 malades après arthroplastie de la hanche cimentée. La DM était mesurée par absorptiométrie biphotonique (DXA). En général, il n'y avait pas de différence significative entre la DM moyenne du groupe étidronate et du groupe placebo. Les seules exceptions étaient les changements en pourcentage sur le rachis après 6 et 12 mois et en Zone 3 de Gruen après 6 mois; dans tous ces cas, le groupe étidronate avait des valeurs moyennes significativement plus grandes. Ces résultats indiquent que la thérapie cyclique par étidronate n'a pas d'effet significatif pour enrayer la perte osseuse périprothétique après arthroplastie cimentée de la hanche.

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Introduction

One of the primary factors affecting the longevity of an endoprosthesis is the quality of the periprosthetic bone over time following implantation. If the bone stock is maintained, the implant is much more likely to survive relative to an implant that is surrounded by diminishing bone stock. Early periprosthetic bone loss may exceed 30% of the bone mass and often appears in the first three to six months following hip replacement [9, 14, 19]. Periprosthetic bone loss after total hip arthroplasty (THA) can be caused by several factors such as stress shielding and aseptic loosening [12]. The consequence of such bone loss has resulted in complications such as implant destabilization and periprosthetic bony fracture [3, 10].

Etidronate, a synthetic analogue of pyrophosphate, was the first clinically available bisphosphonate. Etidronate binds tightly to hydroxyapatite crystals in the mineralized bone matrix and since it is resistant to pyrophosphatase degradation, etidronate decreases normal and abnormal bone resorption. The anti-resorbing effect is cell mediated, partly by a direct action on the osteoclasts and partly through the osteoblasts, which produce an inhibitor of osteoclastic recruitment [5]. Etidronate has been used in the treatment of Paget's disease, heterotopic ossification, and malignant hypercalcaemia [4]. In patients with postmenopausal osteoporosis, etidronate safely increases bone mineral density (BMD) and decreases the incidence of vertebral fractures [2].

There are few reports on the effect of bisphosphonate on the proximal femoral BMD after non-cemented and cemented THA [11, 20, 24]. Yamaguchi and Masuhara reported that cyclic etidronate therapy significantly reduced periprosthetic BMD loss after non-cemented THA [25]. However, to our knowledge, the effects of etidronate on postoperative bone loss after cemented hip arthroplasty have not been reported. The current study evaluates the effect of cyclic etidronate therapy on the acute phase of periprosthetic bone loss after hip arthroplasty.

Materials and methods

Study design and population

Forty-six patients were evaluated in this prospective study. The criteria for inclusion were primary unilateral cemented hip arthroplasty and no perioperative complications. Patients with primary or secondary osteoarthritis were treated with a cemented THA using an S-shaped, anatomically adapted, femoral stem (SP II, Waldemar Link GmbH, Hamburg, Germany) while patients with a fractured femoral neck were treated with bipolar partial hip arthroplasty with a straight femoral stem (CL Trauma, Lima-Lto s.p.a, Udine, Italy). Both stems were inserted with bone cement (Palacos R, Schering-Plough International Inc., Kenilworth, NJ, USA). Exclusion criteria included any history of disorders known to affect bone or mineral metabolism, seropositive or seronegative arthritis, women of child-bearing potential, active gastrointestinal disease, and renal impairment (serum creatinine level $>130 \mu\text{mol/l}$). Patients were also excluded if they had taken pharmacological doses of oestrogen, progestin, androgen, calcitonin, glucocorticoid therapy, dietary supplementation of calcium or vitamin D within the preceding 12 months, or had ever taken a bisphosphonate or fluoride. All patients provided written informed consent before inclusion, and the study was approved by the National Medical Ethics Committee at Ministry of Health and was performed according to the ethical principles stated in the Declaration of Helsinki. Patients were assigned to either a placebo or etidronate group using a computer-generated, randomization routine. The preparation of placebo (microcrystalline cellulose) or etidronate (Pleostat, Krka d.d., Novo mesto, Slovenia) was

supplied in identical tablets blinded to patients and observers. In both groups, the tablets were given in a two-week cycle followed by 12 weeks of calcium supplementation of 260 mg/day (CaC-500 Sandoz, Krka d.d., Novo mesto, Slovenia). In that manner, patients of the etidronate group received 400 mg/day etidronate during the 14-day cycle.

BMD measurements

BMD scans were performed at one week (baseline), six weeks, three months, six months, and 12 months post-operatively using dual energy X-ray absorptiometry (DXA) (QDR-1,000 plus; Hologic Inc., Waltham, MA, USA). In the implanted femur, BMD was measured at each of the seven Gruen zones in the proximal femur as well as the total proximal femur [6]. In the contralateral femur, BMD was measured in the neck, trochanter, intertrochanter, Ward's triangle, and total proximal femur. BMD of the lumbar spine also was measured at the same time points. The coefficient of variation of the DXA machine was 0.34%. Computer software (prosthetic hip and metal software version 6; Hologic Inc., Waltham, MA, USA) was used to measure periprosthetic BMD in the seven Gruen zones.

Statistical analysis

Initial skewness tests indicated that the data were skewed and, therefore, nonparametric analyses were performed on all data. Mean values of the demographics, serum markers, BMD, and baseline-normalized BMD values were compared between the etidronate and placebo groups at each time point using a Mann-Whitney *U* test with a level of significance of 0.05. For all temporal measurements including BMD and normalized BMD, mean values were compared across each time point within a given group (etidronate or placebo) using a Friedman test with a level of significance of 0.05. The Wilcoxon signed rank post hoc test was used for all significant Friedman outcomes. The proportion of men and women and the proportion of straight and S-shaped femoral implants were compared between the two groups using a chi-square test with a level of significance of 0.05. All statistical analyses were performed using SPSS software (version 11.0; SPSS Inc., Chicago, IL, USA).

Results

Sixty-one patients who were initially eligible for the trial, agreed to participate, and were randomized. Of these, six patients had only baseline DXA scans performed and did not want to participate further because of slight gastrointestinal symptoms or for personal reasons not related to the drug intake. Eight patients were excluded because they missed DXA scans at either the six-month or 12-month time point, or both. One patient died of heart attack. Of the 15 patients who did not complete the study, seven were from

Table 1 Baseline characteristics of patients included in result analysis

General	Placebo (n=20) ^a	Etidronate (n=26) ^a	<i>P</i> value
Age (years)	70±7	70±6	0.9912 ^b
No. of men (=no. of hips)	5	6	1.0000 ^c
No. of women (=no. of hips)	15	20	
Weight (kg)	73.5±8.0	72.3±13.1	0.7064 ^b
Body mass index (kg/m ²)	26.9±3.8	27.4±4.8	0.5277 ^b
Straight stem	7	8	1.0000 ^c
S-shaped anatomical stem	13	18	

^aPlus-minus values are mean±standard deviations (SD)^bAs determined with the Mann-Whitney *U* test^cAs determined with the chi-squared test

the placebo group and eight were from the etidronate group. Therefore, 46 patients completed the study. There were no significant differences between baseline characteristics (Table 1) and the initial BMD (Table 2) of the placebo and etidronate groups.

BMD Measurements

Precision error of the calculations by DXA was as 1.7% in zone 1, 2.6% in zone 2, 4.8% in zone 3, 2.0% in zone 4, 3.2% in zone 5, 3.3% in zone 6, and 3.4% in zone 7. Postoperative BMD ratios around femoral stems and of the contralateral hip and spine are shown in Table 3. In the implanted femur, there were no significant differences be-

tween the mean BMD measurements of the etidronate and placebo groups at any time point with the exception of the mean percent change in Gruen zone 3 at six months. Within the etidronate group, there were significant temporal mean BMD decreases identified in the total proximal femur as well as in Gruen zones 2, 3, 6, and 7; the greatest decrease was 11.1% found in zone 2 at 12 months. Within the placebo group, there were significant temporal mean BMD decreases identified in the total proximal femur as well as in Gruen zones 1, 2, 3, 4, 6, and 7; the greatest decrease was 16.4% found in zone 7 at 12 months.

Within the contralateral femur, there were no significant differences between the mean BMD measurements of the etidronate and placebo groups at any time point. Within the etidronate group and placebo groups, there were no significant temporal BMD changes. Within the lumbar spine, there was a significant difference in the mean percent BMD change between the etidronate and placebo groups at six months and 12 months; the etidronate group had significantly greater mean BMD levels at both time points. Also within the lumbar spine, there was a significant temporal increase in the mean BMD of the etidronate group.

Discussion

DXA has been shown to be an accurate and precise tool for the assessment of periprosthetic BMD and is capable of assessing bony changes before they are evident on plain radiographs [1]. Periprosthetic bone loss following implantation of a femoral stem is a vexing problem, and the importance of monitoring the periprosthetic bone quality over time is paramount [8]. Trevisan, Bigoni, and colleagues reported decreased bone density in the greater trochanter, lateral cortex, stem tip, medial cortex, and calcar in 21 postmenopausal women after insertion of custom cement-

Table 2 Initial average bone mineral density (BMD) at 1 week after operation

Operated Hip	Placebo (n=20) ^a	Etidronate (n=26) ^a	<i>P</i> value ^b
Total periprosthetic area	1.221±0.172	1.188±0.187	0.6103
Zone 1	0.773±0.162	0.731±0.173	0.6181
Zone 2	1.413±0.268	1.429±0.258	0.8074
Zone 3	1.553±0.210	1.533±0.224	0.7648
Zone 4	1.725±0.332	1.671±0.346	0.4714
Zone 5	1.548±0.272	1.561±0.258	0.8855
Zone 6	1.271±0.233	1.190±0.226	0.2825
Zone 7	1.137±0.232	1.048±0.311	0.3875
Contralateral Hip	Placebo (n=19) ^a	Etidronate (n=24) ^a	<i>P</i> value ^b
Total Hip	0.838±0.111	0.853±0.202	0.7505
Femoral Neck	0.727±0.128	0.708±0.159	0.7505
Greater Trochanter	0.617±0.090	0.635±0.161	0.7783
Intertrochanteric Region	0.970±0.130	0.997±0.237	0.5572
Ward's Triangle	0.513±0.159	0.475±0.151	0.6248
Spine	Placebo (n=20) ^a	Etidronate (n=25) ^a	<i>P</i> value ^b
L1–L4	0.944±0.144	0.906±0.218	0.4648

^aPlus-minus values are mean±standard deviation (SD)^bAs determined with the Mann-Whitney *U* test

Table 3 Comparison of postoperative bone mineral density (BMD) ratios around femoral stems, of the contralateral hip, and of the spine

Region	Group	1 week ^a	6 weeks ^a	3 months ^a	6 months ^a	12 months ^a	P-value**
Femoral Stems							
Total	Placebo	100±0 ^{1,2,3,4}	98.1±13.9 ^{1,5}	95.5±12.6 ^{2,5}	95.2±13.8 ³	95.0±15.3 ⁴	0.0004
	Etidronate	100±0	97.5±7.5	96.6±9.1	95.5±7.3	94.6±7.2	0.0345
	P value*	N/A	0.5031	0.1288	0.1661	0.2538	
Zone 1	Placebo	100±0 ⁶	100.4±14.0 ⁷	99.1±14.1	95.9±14.0	95.5±16.9 ^{6,7}	0.0413
	Etidronate	100±0 ^{33,34,35,36}	101.1±14.7 ³³	103.9±31.8 ³⁴	101.3±31.2 ³⁵	99.3±20.6 ³⁶	0.1614
	P value*	N/A	0.6612	0.9818	0.7480	0.5423	
Zone 2	Placebo	100±0 ^{8,9,10}	98.8±21.2 ^{11,12,13}	94.9±18.2 ^{8,11}	92.4±21.1 ^{9,12}	92.8±20.4 ^{10,13}	0.0003
	Etidronate	100±0 ^{37,38,39}	96.0±9.1 ^{40,41}	93.5±13.4 ³⁷	91.5±12.5 ^{38,40}	88.9±13.2 ^{39,41}	0.0007
	P value*	N/A	0.9031	0.3204	0.6657	0.7564	
Zone 3	Placebo	100±0 ^{14,15,16}	97.0±13.2 ^{17,18}	94.1±12.3 ^{14,17}	91.6±14.1 ^{b,15,18}	92.9±13.7 ¹⁶	0.0010
	Etidronate	100±0 ^{42,43,44}	98.7±12.1 ^{45,46}	95.7±9.2 ^{42,45}	95.8±11.7 ^{b,43}	92.0±10.2 ^{44,46}	0.0003
	P value*	N/A	0.7516	0.3317	0.0438	0.4250	
Zone 4	Placebo	100±0 ¹⁹	100.3±16.7 ²⁰	96.3±17.7 ^{19,20}	98.6±16.7	98.3±16.9	0.0103
	Etidronate	100±0	95.9±7.0	96.1±8.4	98.4±15.7	97.8±14.2	0.3404
	P value*	N/A	0.5507	0.4510	0.5350	0.2631	
Zone 5	Placebo	100±0	103.2±14.8	102.4±14.2	97.8±11.2	101.2±10.7	0.5010
	Etidronate	100±0	97.2±8.6	96.6±8.6	96.0±9.5	96.6±12.1	0.3154
	P value*	N/A	0.2143	0.2779	0.6900	0.6576	
Zone 6	Placebo	100±0 ^{21,22,23}	101.0±8.4 ^{24,25,26}	94.0±10.5 ^{21,24}	93.9±13.3 ^{22,25}	91.0±15.3 ^{23,26}	0.0055
	Etidronate	100±0 ^{47,48}	100.8±10.7 ^{49,50}	95.1±15.5 ^{47,49}	92.0±13.6 ^{48,50}	94.9±15.5	0.0004
	P value*	N/A	0.6091	0.6978	0.3407	0.5645	
Zone 7	Placebo	100±0 ^{27,28,29}	97.5±14.4 ^{30,31,32}	85.9±10.7 ^{27,30}	85.9±17.8 ^{28,31}	83.4±18.8 ^{29,32}	<0.0001
	Etidronate	100±0 ^{51,52}	95.8±15.2 ⁵³	94.6±33.4 ⁵¹	89.5±24.1 ^{52,53}	94.2±33.3	0.0043
	P value*	N/A	0.7424	0.6560	0.7396	0.3241	
Contralateral hip							
Total hip	Placebo	100±0	101.3±3.0	101.3±3.6	100.4±5.4	99.7±5.8	0.3725
	Etidronate	100±0	99.5±4.1	99.7±3.9	100.1±4.0	100.1±4.1	0.9409
	P value*	N/A	0.1167	0.2606	0.5409	0.8389	
Femoral neck	Placebo	100±0	99.2±5.2	100.5±5.3	98.1±5.6	98.9±6.8	0.7255
	Etidronate	100±0	99.5±5.2	99.8±5.1	100.0±5.6	100.2±6.7	0.5205
	P value*	N/A	0.8038	0.9415	0.4411	0.4307	
Greater trochanter	Placebo	100±0	100.7±3.8	100.2±6.3	99.8±5.6	98.7±8.9	0.3825
	Etidronate	100±0	98.7±6.2	99.9±4.8	100.2±4.6	100.0±4.7	0.8458
	P value*	N/A	0.5652	0.9902	0.4557	0.6749	
Intertrochanteric region	Placebo	100±0	101.5±4.2	101.0±4.0	101.0±5.0	100.1±6.5	0.9868
	Etidronate	100±0	100.3±3.5	100.1±4.9	100.6±4.1	100.7±4.8	0.5032
	P value*	N/A	0.6102	0.6598	0.9027	0.7507	
Ward's triangle	Placebo	100±0	101.6±17.5	104.5±16.5	97.9±15.7	99.0±13.3	0.8781
	Etidronate	100±0	103.7±20.4	101.8±15.2	107.2±15.7	102.7±16.4	0.8458
	P value*	N/A	0.8548	0.6422	0.0564	0.3470	
Spine							
L1–L4	Placebo	100±0	98.9±3.5	99.0±3.7	99.4±3.8 ^b	99.3±3.4 ^c	0.4819
	Etidronate	100±0 ¹	100.5±2.8 ²	100.3±2.7 ³	101.5±4.4 ^{b,4}	103.4±3.6 ^{c,1,2,3,4}	<0.0001
	P value*	N/A	0.0758	0.2260	0.0230	0.0014	

^aPlus–minus values are mean±standard deviation (SD)*Comparisons between groups for a given time point were made using the Mann-Whitney *U* test (*P*<0.05). Significant differences are denoted by alphabetic superscripts b and c

**Comparisons between time points within a given group were made using the Friedman test (0.05) and a Wilcoxon signed rank post hoc test when appropriate. Significant differences are denoted by common numeric superscripts

less femoral components fully coated with hydroxyapatite; the greatest loss was observed in the calcar region after six months where it exceeded 50% [17]. DXA has been

shown to be a satisfactory tool for evaluating different types of cemented stems, where periprosthetic BMD was most precisely measured without exclusion of cement [23].

Venesmaa and Kroger found reduction of periprosthetic BMD ranging from 5% to 18% during the first three months after cemented THA, but from one to five years, only minor changes were measured [21]. Changes were identified in most of the Gruen zones but were most marked in the proximal femur [21]. These reports of early BMD reduction were the basis of the current study. The current study focused on the effect of etidronate on periprosthetic BMD following cemented THA and hypothesized that patients treated with etidronate would demonstrate a significant reduction of bone loss compared with patients in the placebo group.

Several studies have reported on the effect of bisphosphonate on periprosthetic BMD following total hip arthroplasty. The effect of a single-dose infusion of pamidronate, a newer potent aminobisphosphonate [15], on early periprosthetic BMD changes and biochemical markers of bone turnover was studied in a 26-week, prospective, randomized, double-blinded study of 47 patients who underwent THA with a cemented femoral implant [24]. The authors reported a significant reduction in bone loss compared with placebo for both the proximal femur and the pelvis. Pamidronate therapy was associated with suppression of all biochemical markers of bone turnover compared with placebo, with the exception of urinary free deoxypyridinoline, a marker of bone resorption. The maximum efficacy of pamidronate was seen at week 12, when patients in the pamidronate group lost 1.1% of net femur BMD, including approximately 2.5% in Gruen zone 7, compared with the placebo group, which lost 4% of net femur BMD, including approximately 10% in Gruen zone 7. Fourteen patients in their study had a normal contralateral hip and underwent measurement of BMD of the femoral neck at baseline and at week 26; no significant changes were found between the groups. The results of the current study also indicate that the greatest decrease was in the proximal zones, including the calcar, in both groups. As in the study of Wilkinson and Stockley [24], our study demonstrated that there were no significant differences between the mean BMD levels of the two groups in the contralateral femur at any time. On the other hand, Harris and Watts reported that cyclic etidronate increases BMD levels of the femoral neck, greater trochanter, and Ward's triangle over three years of treatment in postmenopausal women [7].

In contrast to the femoral BMD findings, the current study demonstrated that the mean lumbar spine BMD level of the etidronate group was significantly increased at 12 months and significantly greater than that of the placebo group at six and 12 months. This finding is similar to that of Cranney and Guyatt, who reported that etidronate increased spinal BMD levels over time [2]. Several additional studies have demonstrated that etidronate therapy is beneficial in the treatment of osteoporosis of the spine [16, 22]. Yamaguchi and Masuhara reported the effects of cyclic etidronate therapy on postoperative BMD

loss after cementless THA in a randomized prospective study of 52 patients [25]. The postoperative decreases of BMD in the etidronate group were significantly lower in zones 1 and 7 at six months and in zones 1, 2, 6, and 7 at 12 months. In the current study, there were no significant differences between mean BMD levels of the etidronate and placebo groups at any time, with the exception of the marginal ($P<0.0438$) significant difference in zone 3 at six months. In addition, BMD levels decreased by up to 11.1% in the etidronate group and 16.6% in the placebo group 12 months following implantation.

Other biphosphonates have shown promise in decreasing the rate of bone loss similar to the findings of Wilkinson and Stockley described above. Alendronate has been shown to demonstrate a ten-fold increase in anti-resorptive properties compared with etidronate and has been reported to increase bone density and reduce the fracture risk in the spine and hip in postmenopausal women [13, 18]. Two additional studies have investigated the effect of alendronate on periprosthetic bone loss [11, 20]. The Finnish group of Venesmaa and Kroger reported 13 patients who underwent cementless primary THA and were followed up for six months [20]. Daily alendronate intake significantly suppressed the reduction of BMD in the proximal and total periprosthetic areas. Another study from the French group of Nehme and Maalouf reported 38 patients who underwent cemented primary THA and were followed up for two years [11]. The amount of bone loss was similar to that of the placebo group during the first three months. After this time, however, bone loss in the placebo group increased progressively to 12.7% at 24 months. In the alendronate group, the loss of BMD increased continuously from three months yet at a slower rate than the placebo group, and reached 6.9% bone loss at 24 months. We were not able to demonstrate such an in vivo beneficial effect of etidronate on bone behavior around cemented stems.

In drawing conclusions from the current study, we can conclude that cyclic etidronate therapy does not significantly reduce postoperative periprosthetic bone loss during the first 12 months following cemented THA. Etidronate also seems to have no beneficial effect on BMD loss in the contralateral hip. Although unlikely, studies with a longer follow-up may find that etidronate has an effect that begins after 12 months. The most significant finding was the actual increase in lumbar spine BMD following etidronate therapy. With the introduction of newer, more effective bisphosphonates, the use of etidronate therapy to reduce the amount of periprosthetic bone loss in cemented THA patients is not recommended.

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