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ORIGINAL ARTICLE

Effects of zoledronic acid on bone mineral density around prostheses and bone metabolism markers after primary total hip arthroplasty in females with postmenopausal osteoporosis

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Abstract

Introduction To investigate the effect of zoledronic acid on periprosthetic bone mineral density (BMD) and bone metabolism markers after primary total hip arthroplasty in females with postmenopausal osteoporosis.

Methods From November 2015 to April 2016, 40 female patients who met the inclusion criteria were randomized into two groups: a control group (calcium + calcitriol) and a zoledronic acid group (calcium + calcitriol + zoledronic acid). At 1 week and 3, 6, and 12 months after operation, BMD was obtained through dual-energy X-ray absorptiometry (DEXA). At pre-operation and at 3, 6, and 12 months after the operation, levels of bone metabolism markers were obtained by serum examination.

Results Loss of BMD was significantly more pronounced in the control group than in the ZOL group in zones 1, 4, 6, and 7 at 6 months and in zones 1, 2, 4, 6, and 7 at 12 months after the operation. The levels of bone-resorption marker (β-CTX) were significantly lower in the ZOL group than in the control group at 3, 6, and 12 months after operation. The levels of bone-formation marker (TP1NP) performed statistically differences only at 12 months after the operation in these two groups.

Conclusions Receiving an intravenous infusion of 5 mg zoledronic acid after THA can effectively reduce periprosthetic BMD loss and improve bone remodeling in females with postmenopausal osteoporosis.

Summary Zoledronic acid significantly inhibited bone mass loss in zones 1, 2, 4, 6, and 7 after THA and inhibited bone-resorption marker (β-CTX) to improve bone remodeling. Zoledronic acid treatment is potentially important for patients with osteoporosis after THA.

Keywords Bone metabolism markers · Bone mineral density · Postmenopausal osteoporosis · Zoledronic acid

Introduction

Worldwide, osteoporosis causes 8.9 million fractures each year, with one fracture occurring approximately every 3 s [1]. Recently, the number of geriatric hip fractures (the type of osteoporosis-related fracture with the highest fatality rate) has increased sharply, and total hip arthroplasty (THA) has become the conventional treatment. THA can restore hip function and improve patient quality of life [2]. However, bone mineral density (BMD) loss around the prostheses of the proximal femoral bone has been observed [3]. This phenomenon can last for a long time after THA [4]. The loss of BMD may lead to aseptic loosening and periprosthetic fracture, which is a serious problem after THA, and thus cause several negative effects, such as reduced stability, reduced lifetime of the prosthesis, and increased rate of revision [5]. For these reasons, finding a solution to prevent BMD loss and prolong the life span of a prosthesis is a central issue. Bisphosphonate is the first-line drug used in the treatment of osteoporosis. It works by inhibiting bone resorption and has become widely used [6]. Previous studies have shown that bisphosphonate can prevent the loss of bone mineral density [7–9], and a recent study showed that THA patients using bisphosphonate had a lower risk of

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requiring a revision operation than those who did not [10]. Zoledronic acid is a third-generation bisphosphonate, and it has a strong anti-bone-resorption effect, through which it prevents BMD loss around the prostheses, reduces the rate of aseptic loosening and revision, and prolongs the life span of a prosthesis [9]. Zoledronic acid can also affect bone metabolism markers. It works mainly by inhibiting the level of the bone-resorption signals [11].

Postmenopausal females are more likely to suffer osteoporosis, and these patients have lower BMD, which affects initial stability and delays stem osseointegration in cementless total hip arthroplasty [12]. Currently, the number of patients with postmenopausal osteoporosis is increasing rapidly, and the problems they face become more serious after surgery [11]. However, there have been only a few studies of whether bisphosphonate can prevent periprosthetic BMD loss and improve bone remodeling in postmenopausal osteoporosis patients. Here, we investigated the effects of 5 mg zoledronic acid on periprosthetic BMD and bone metabolism markers over the first year after primary THA in postmenopausal osteoporosis patients.

Materials and methods

Patients

This was a randomized single-blind controlled trial, and patients were blinded. Inclusion criteria were as follows: females with postmenopausal osteoporosis (BMD ≤ -2.5) who were willing to undergo primary THA because of a hip disorder, had normal laboratory study results, especially calcium and creatinine levels, and were willing to provide written informed consent. Exclusion criteria were as follows: any previous hip revision, low calcium or high creatinine levels, use of medications affecting bone metabolism, use of cement prosthesis, allergy to bisphosphonates, and any other bone disease. On the basis of these criteria, this study included 40 patients from November 2015 to April 2016 and patients were randomized into control and ZOL groups using a Random Numbers seed of SPSS 22.

Medicine and prosthesis

In the control group, patients received only basic treatment (oral calcium carbonate 1200 mg/day and calcitriol 0.50 μg/day); the ZOL group added an intravenous infusion of 5 mg zoledronic acid at 5–7 days after operation on the basis of the basic treatment. The cementless femoral component (Zimmer, Smith and Nephew), cementless acetabular component (Zimmer, Smith and Nephew), and cross-linked polyethylene liner (Zimmer, Smith and Nephew) were implanted in all patients. All THA procedures used a standard lateral approach performed by one experienced surgeon, and patients were allowed to put their full weight on the limb as soon as possible after operation.

Data collection

The periprosthetic BMD values in all the patients were recorded at 1 week after surgery as baseline by dual-energy x-ray absorptiometry (Lunar Corporation, Madison, WI, USA); subsequently, the periprosthetic BMD levels were obtained at 3, 6, and 12 months after the operation. The periprosthetic zones were evaluated as described by Gruen through the regions of interest (ROI) in the DEXA measurement (Fig. 1). After fasting overnight, morning (08:30–09:30 p.m.) blood samples were obtained from all patients before the operation, which was considered baseline, and subsequent measurements were taken at 3, 6, and 12 months after the operation. Through blood sample analysis, the levels of bone-resorption marker (β-CTX), bone-formation marker (TP1NP), and

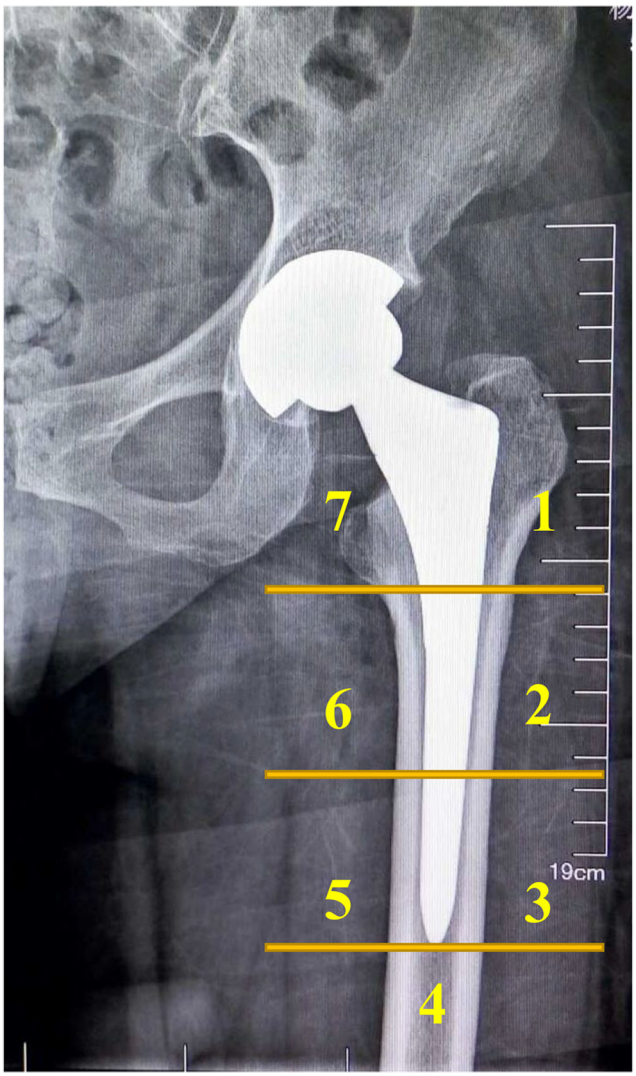

Fig. 1 The length of femoral stem prostheses from proximal to distal is equally divided into three parts. The 2-cm area away from the prosthesis bottom is zone 4, the lateral sides of the prostheses from top to the bottom are zone 1, zone 2, and zone 3, and the medial sides of the prostheses from top to the bottom are zone 5, zone 6, and zone 7

25(OH) D were determined. The related reagents included CTx (ECLIA, Elecsys Crosslaps, Roche), P1NP (ECLIA, Elecsys total P1NP, Roche), and 25(OH) D (CMIA, 25-OH Vitamin D, Abbott). And the double antibody sandwich method was used to measure CTX and TP1NP; the delay immunoassay method was used to measure 25(OH)D. The detail operation step followed the operation instruction of products. In addition, Harris Hip Score (HHS) was recorded for all patients at pre-operation and at 3, 6, and 12 months after the operation.

Statistical analysis

All data were managed through SPSS version 22.0. We used the Fisher exact test to compare categorical variables. Through the normality test of all continuous variables, the independent *t* test was used to analyze the variables followed the normal distribution while the Mann–Whitney *U* test was used to analyze the variables was contrary to the normal distribution. All continuous variables were expressed as mean ± standard error, and the level of significance was 0.05 for all tests.

Results

On account of missing the DEXA examination, 4 patients were excluded in the ZOL group and 3 in the control group. In addition, 1 patient who underwent THA on the other side of her body 3 months after the primary operation was also excluded. Finally, there were data available for 16 patients in the ZOL group and 16 in the control group. Age, body mass index, ambulation time (periods from operation to first-time out-of-bed activity), and left vs right hip were found to have no statistically significant differences ($P > 0.05$) between the ZOL and control groups (Table 1).

In both groups, BMD was reduced from baseline in all Gruen zones at 3, 6, and 12 months (Table 2). However, there was significantly loss of BMD in the control group than in the ZOL group in zone 1 ($P = 0.018$), zone 4 ($P = 0.026$), zone 6 ($P = 0.005$), and zone 7 ($P = 0.010$) at 6 months and in zone 1 ($P = 0.001$), zone 2 ($P = 0.006$), zone 4 ($P = 0.001$), zone 6 ($P = 0.004$), and zone 7 ($P = 0.003$) at 12 months after the operation (Figs. 2 and 3). Comparing all zones, the greatest BMD loss was found in zone 1 and zone 7, and we found statistical differences ($P < 0.05$) between the control group and the ZOL group in zone 1 (− 11.2% vs − 4.4% at 6 months; − 19.4% vs − 8.3% at 12 months) and zone 7 (− 22.7% vs − 16.0% at 6 months; − 27.7% vs − 19.7% at 12 months) (Fig. 4).

Levels of the bone-resorption marker (β-CTX) at 3, 6, and 12 months after operation were obviously decreased in the ZOL group, while levels of β-CTX in the control group were increased at 3 months and then decreased at 6 and 12 months after the operation (Table 3). In the ZOL group, the decrease in β-CTX levels from baseline was much more pronounced than in the control group and the difference was significant at 3 ($P = 0.004$), 6 ($P = 0.001$), and 12 ($P = 0.003$) months (Fig. 5). In both groups, levels of the bone-formation marker (TP1NP) were increased from baseline at 3 months then decreased at 6 and 12 months and we found statistical significance ($P = 0.046$) only at 12 months after operation between the ZOL and control groups (Fig. 6). Levels of the important hormone of bone metabolism (25(OH)D) increased steadily in both groups, and there were no statistically significant differences between these groups at 3 ($P = 0.274$), 6 ($P = 0.476$), and 12 ($P = 0.297$) months after the operation (Fig. 7).

The mean HHS had no significant difference between the ZOL and control groups before the operation ($P = 0.769$). The scores in both groups improved after the operation, but the ZOL group had higher scores than the control group at 6 ($P = 0.046$) and 12 ($P = 0.004$) months after the operation (Table 4).

Discussion

Postoperative periprosthetic BMD loss is a common issue in THA patients. It has been demonstrated to be related to periprosthetic fractures, aseptic loosening, and revision [5]. Intraoperative damage, wear debris-induced inflammatory

Table 1 Baseline characteristics of patients in the ZOL (zoledronic acid) and control groups ($\bar{x} \pm s$)

Group	Age (years)	BMI (kg/m^2)	Ambulation time (days)	Left/right	Case number
Control	74.4 ± 5.7	24.4 ± 4.2	2.5 ± 0.7	8/8	16
ZOL	73.3 ± 6.6	23.9 ± 3.5	2.7 ± 0.6	10/6	16
t value	0.489	0.355	–	–	–
P value	0.629[†]	0.725[†]	0.434[‡]	0.722[#]	–

BMI body mass index

[†] Independent *t* test

[‡] Mann–Whitney *U* test

[#] Fisher's exact test

Table 2 Relative differences in periprosthetic bone mineral density (BMD, g/cm^2) across all Gruen zones in the control and ZOL groups during the first year after surgery (%, $\bar{x} \pm s$)

Gruen zones	Group	Baseline	3 months	6 months	12 months
Zone 1	Control	0.824 ± 0.173	− 6.1 ± 4.3	− 11.2 ± 7.2	− 19.4 ± 6.7
	ZOL	0.827 ± 0.149	− 4.6 ± 6.6	− 4.4 ± 8.3	− 8.3 ± 8.4
	P value	0.969	0.910	0.018	0.001
Zone 2	Control	1.704 ± 0.242	− 5.3 ± 6.2	− 6.4 ± 5.3	− 9.2 ± 5.2
	ZOL	1.731 ± 0.226	− 4.7 ± 5.3	− 3.5 ± 6.0	− 4.3 ± 5.5
	P value	0.678	0.637	0.155	0.006
Zone 3	Control	1.815 ± 0.206	− 4.3 ± 4.5	− 4.8 ± 5.1	− 5.3 ± 5.0
	ZOL	1.909 ± 0.177	− 3.1 ± 5.6	− 3.5 ± 5.0	− 5.0 ± 4.5
	P value	0.177	0.242	0.546	0.881
Zone 4	Control	1.847 ± 0.214	− 2.1 ± 3.5	− 4.2 ± 4.0	− 6.0 ± 4.4
	ZOL	1.774 ± 0.180	− 1.6 ± 3.5	− 1.2 ± 3.3	− 1.5 ± 3.8
	P value	0.300	0.716	0.026	0.001
Zone 5	Control	1.891 ± 0.179	− 3.5 ± 3.3	− 2.9 ± 4.7	− 3.4 ± 4.5
	ZOL	1.963 ± 0.206	− 3.6 ± 3.7	− 2.1 ± 4.4	− 1.9 ± 3.8
	P value	0.169	0.597	0.533	0.097
Zone 6	Control	1.654 ± 0.255	− 7.2 ± 4.4	− 9.2 ± 5.2	− 11.2 ± 5.2
	ZOL	1.700 ± 0.214	− 4.9 ± 4.6	− 4.5 ± 4.0	− 6.1 ± 4.2
	P value	0.580	0.187	0.005	0.004
Zone 7	Control	1.285 ± 0.247	− 16.3 ± 6.0	− 22.7 ± 5.9	− 27.7 ± 6.0
	ZOL	1.207 ± 0.274	− 13.1 ± 7.3	− 16.0 ± 6.2	− 19.7 ± 8.2
	P value	0.409	0.152	0.010	0.003

Data are mean ± standard deviation. *P* values from the independent *t* test (baseline) and Mann–Whitney *U* test (3, 6, and 12 months)

ZOL zoledronic acid

response, and stress shielding are thought to be major mechanisms that contribute to loss of BMD [13]. At present, there is no standard strategy for preventing periprosthetic BMD loss after THA. Several studies have reported bisphosphonates are

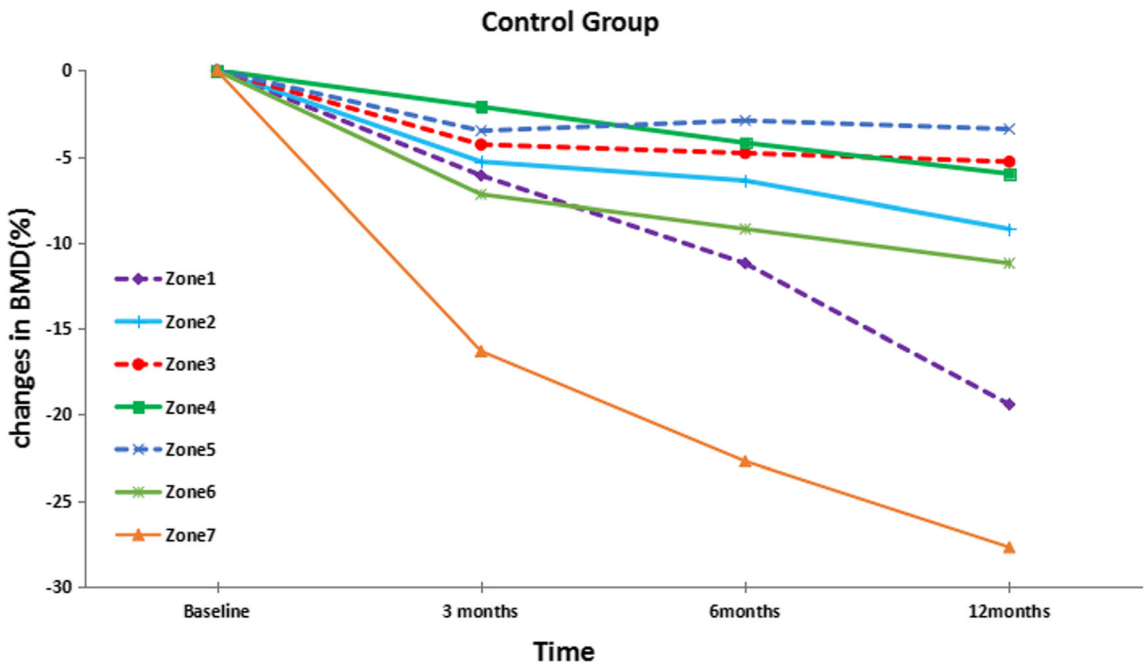

Fig. 2 Relative difference from baseline of periprosthetic BMD in all zones in the control group during the first year after the operation (BMD bone mineral density)

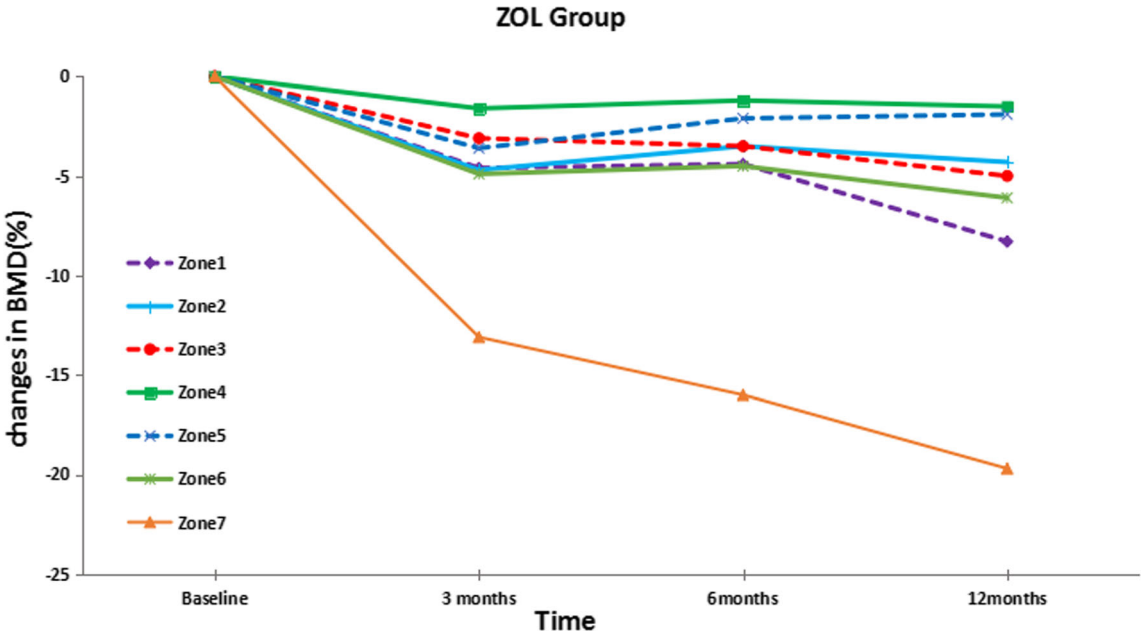

Fig. 3 Relative difference from baseline of periprosthetic BMD in all zones of ZOL group during the first year after the operation (ZOL zoledronic acid)

effective in reducing periprosthetic loss of BMD and decreasing risk of periprosthetic fracture and revision after THA [7–10]. Only a few studies have been performed on the use of oral alendronates and intravenous injection of zoledronic acid to prevent periprosthetic BMD loss, especially in females with postmenopausal osteoporosis [14, 15]. The aim of this randomized study was to investigate the effect of zoledronic acid combined with calcitriol and calcium on periprosthetic BMD loss and bone turnover biomarkers in postmenopausal osteoporosis patients after THA.

Zoledronic acid, as third-generation bisphosphonate [16], its unique nitrogen-containing heterocyclic ring can closely bind to bones, significantly inhibiting the activity of osteoclasts, effectively inhibit bone loss and improve bone mass of patients with osteoporosis. Our study showed that zoledronic acid could effectively inhibit the loss of BMD around the prostheses in zones 1, 4, 6, and 7 at 6 months and in zones 1, 2, 4, 6, and 7 and 12 months after the operation. Previous studies have shown that most loss of BMD occurred early in the postoperative period, and the most prominent efficacy of

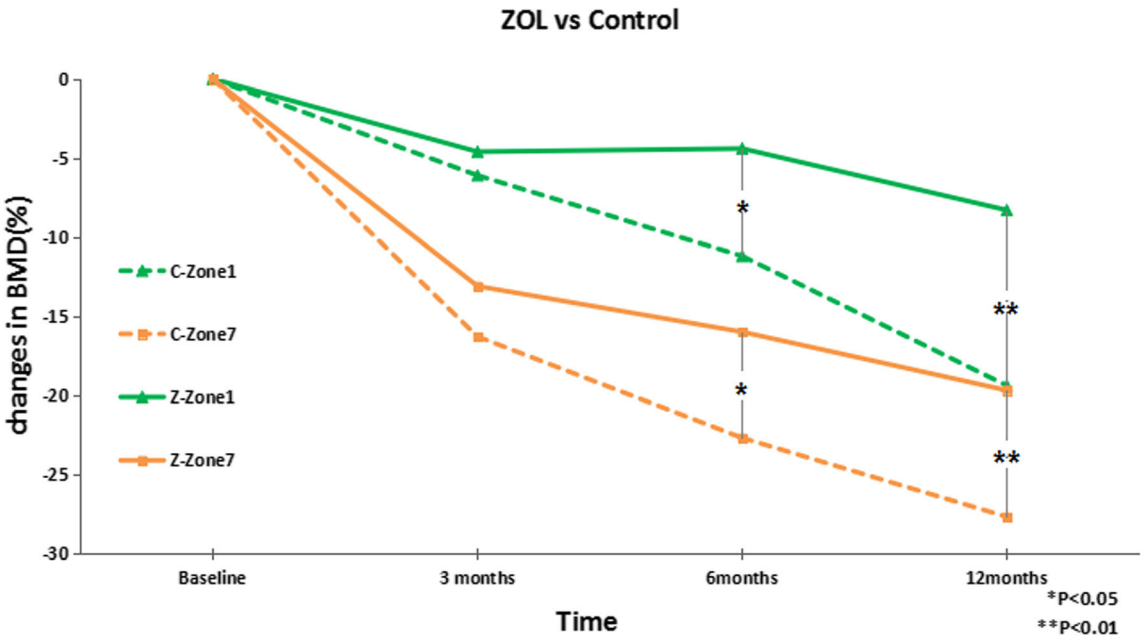

Fig. 4 Relative difference from baseline of periprosthetic BMD in the control and ZOL groups in Gruen zones 1 and 7 (*$P < 0.05$, **$P < 0.01$; C-Zone1, zone 1 in the control group; Z-Zone1, zone 1 in the ZOL group; C-Zone7, zone 7 in the control group; Z-Zone7, zone 7 in the ZOL group)

Table 3 Relative differences in levels of bone metabolism markers (ng/ml) in the control and ZOL groups during the first year after surgery (%, $\bar{x} \pm s$)

Markers	Group	Baseline	3 months	6 months	12 months
CROSSL	Control	0.570 ± 0.318	3.9 ± 48.2	− 2.4 ± 45.4	− 4.3 ± 43.2
	ZOL	0.613 ± 0.293	− 42.9 ± 32.1	− 47.1 ± 30.6	− 49.0 ± 28.0
	P value	0.910	0.004	0.001	0.003
TP1NP	Control	61.65 ± 18.41	49.4 ± 77.4	16.0 ± 67.4	11.4 ± 66.1
	ZOL	72.64 ± 38.94	20.5 ± 71.2	− 3.5 ± 43.3	− 27.6 ± 30.8
	P value	0.319	0.291	0.706	0.046
25(OH)D	Control	13.42 ± 4.65	58.5 ± 59.3	86.7 ± 100.2	127.6 ± 88.3
	ZOL	13.47 ± 3.57	37.6 ± 45.9	65.7 ± 58.3	101.37 ± 44.7
	P value	0.973	0.274	0.476	0.297

Data are mean ± standard deviation. *P* values from the independent *t* test (baseline) and Mann–Whitney *U* test (3, 6, and 12 months)

bisphosphonates took place during the first 3 months and more than 12 months after surgery [14]. Our study showed a protective effect on periprosthetic BMD loss from 6 months to 1 year following surgery. A recent meta-analysis indicated that the bisphosphonate group had a higher BMD ratio in all ROI zones except zone 5 [15]. Scott et al. found that infusion of 5 mg ZOL at 2 weeks and at 1 year following cementless THA reduced periprosthetic BMD loss significantly for Gruen zones 4, 6, and 7 at 6 weeks, 6 months, 1 year, and 2 years and for Gruen zone 1 at 6 months, 1 year, and 2 years. Our data were basically consistent with their observations. In their study, BMD of zone 1 significantly increased at 1 year for both groups, especially for the ZOL group, while we found periprosthetic BMD was reduced in all Gruen zones in both groups. This difference may be caused by different patient populations. Our patients tended to suffer adverse outcome after THA earlier than other patients.

β-CTX is a good indicator of bone resorption, and many studies have reported that zoledronic acid can reduce the level of β-CTX in serum of senile osteoporosis patients [17]. In our study, zoledronic acid showed a strong suppressive effect on the bone-resorption marker β-CTX at 3 months after operation and this effect lasted 1 year after THA; the difference from the control group was significant at 3, 6, and 12 months after the operation. The change of bone-formation marker TP1NP level also expressed a significant difference ($P = 0.046$) at 12 months after operation between the ZOL and control groups. Kobayashi et al. observed that both P1NP (bone-formation marker) and NTx (bone-resorption marker) were increased after surgery in the control group whose

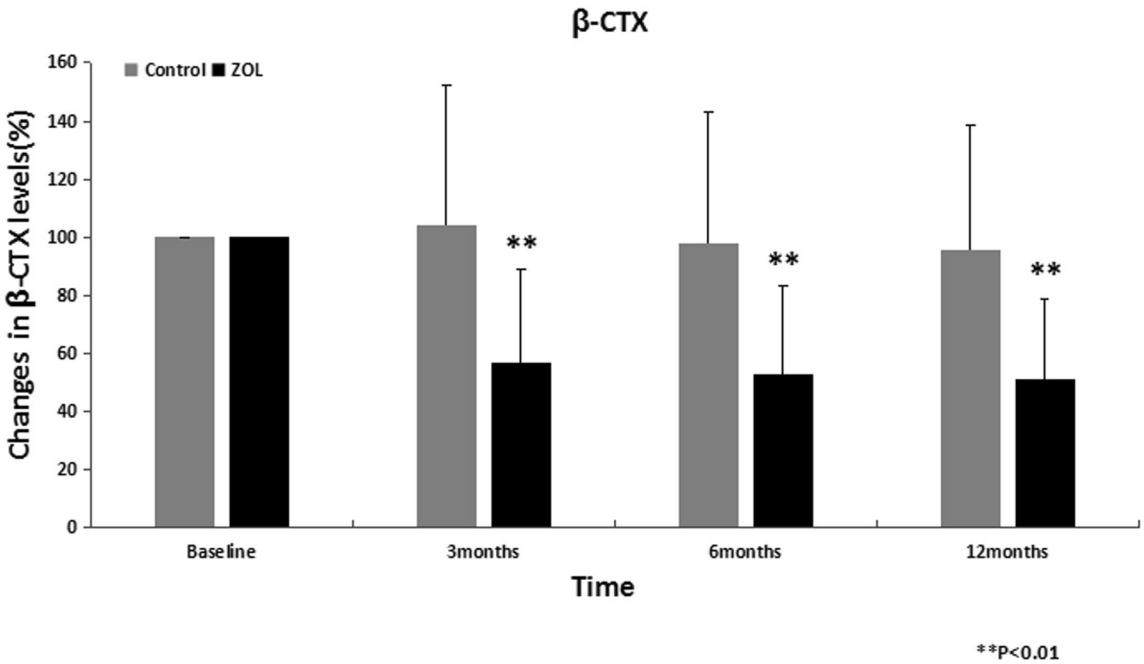

Fig. 5 Relative difference from baseline of bone-resorption marker (β-CTX) in the control and ZOL groups during the first year after the operation (*$P < 0.05$, **$P < 0.01$)

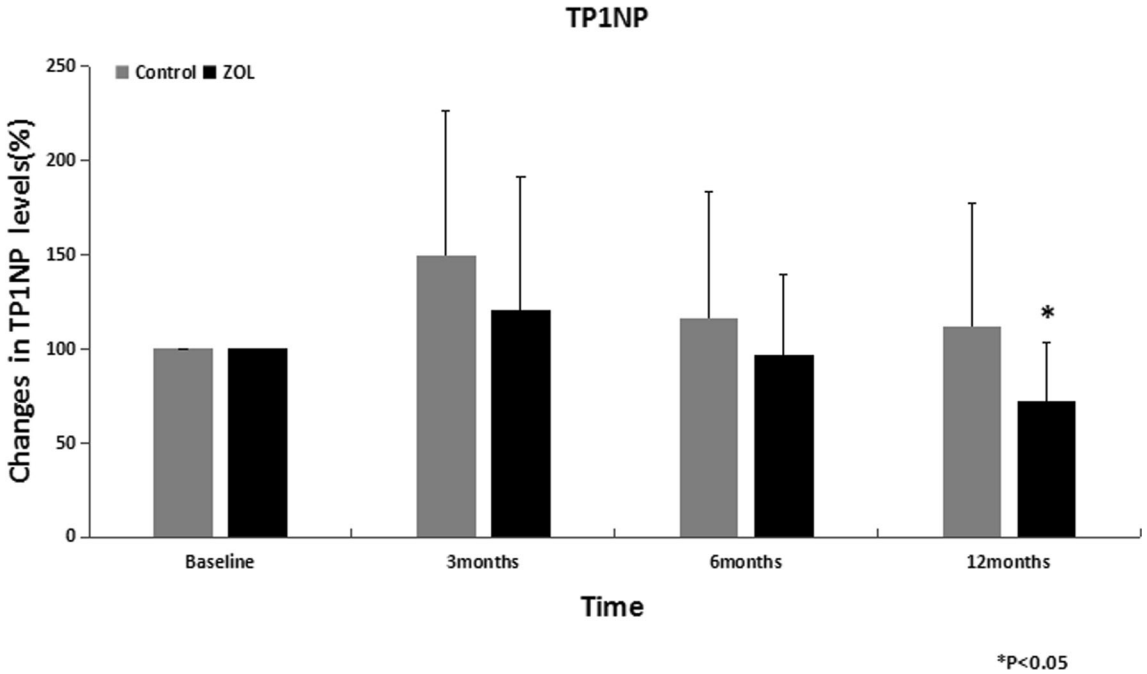

Fig. 6 Relative difference from baseline of bone-formation marker (TP1NP) in the control and ZOL groups during the first year after the operation (*$P < 0.05$, **$P < 0.01$)

patients received no medication, probably due to the stress of surgery [18]. Our study results are consistent with their observations, and we further found levels of TP1NP, like those of β-CTX, decreased at 12 months after surgery in the ZOL group, probably related to the coupling mechanism between osteoblasts and osteoclasts. Some studies show that bone metabolism markers can indicate the effects of treatment at 3 months after the operation while the change in BMD may only work after 1 or 2 years [19]. In our study, the change in bone-resorption marker β-CTX level was significantly earlier than BMD (3 months after the operation vs 6 months). A combination of BMD and bone metabolism markers may indicate the treatment effects of zoledronic acid promptly and help clinicians select suitable treatments.

Vitamin D deficiency is common in patients with postmenopausal osteoporosis [20]. Some studies have shown that vitamin D can increase the response rate and relieve the side effects of bisphosphonates [21]. Calcium (Ca), phosphate (P), and vitamin D are all essential for bone metabolism and the maintenance of the strength and function of the skeleton.

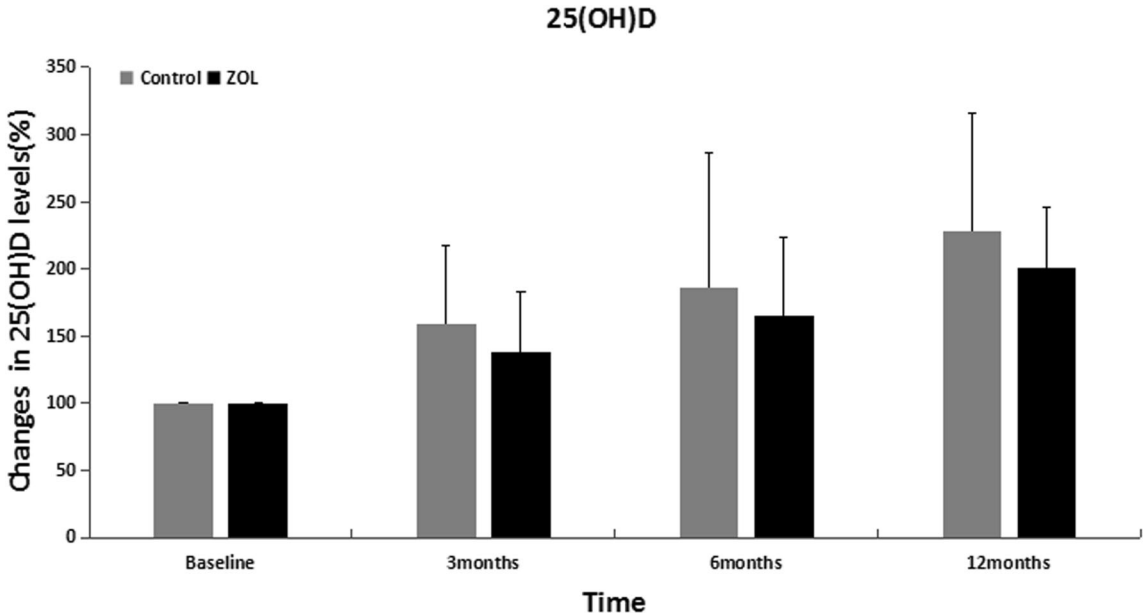

Fig. 7 Relative difference from baseline of 25(OH) D in the control and ZOL groups during the first year after the operation (*$P < 0.05$, **$P < 0.01$)

Table 4 Harris Hip scores in the ZOL and control groups ($\bar{x} \pm s$)

Group	Pre-operation	3 months	6 months	12 months
Control	33.2 ± 14.8	70.7 ± 10.2	75.6 ± 8.9	80.9 ± 7.7
ZOL	34.7 ± 13.3	72.5 ± 10.6	82.0 ± 8.4	89.5 ± 8.0
t value	0.296	0.483	2.083	3.074
P value	0.769	0.633	0.046	0.004

Data are mean ± standard deviation. *P* values from the independent *t* test

The role of vitamin D, in this context, is to participate in the regulation of Ca homeostasis, and the active metabolite of vitamin D (25(OH) D) stimulates calcium absorption from the gut to improve osteogenesis [22]. The level of serum 25(OH) D was found to be commonly deficient in patients with THA, which had adverse effects on osseointegration [23]. In this study, the change in 25(OH) D levels in the ZOL and control groups showed no statistically significant difference ($P > 0.05$), but the levels of 25(OH) D were steadily risen in both groups after calcitriol supplementation, which was beneficial to osseointegration. So our results indicated calcitriol treatment is necessary in postmenopausal osteoporosis patients.

Gerald Friedl et al. showed that zoledronic acid can significantly improve the HHS compared to a control group [24]. In the current study, HHS rapidly increased in both groups compared to pre-operation. Patients treated with zoledronic acid had significantly higher scores than the control group at 6 and 12 months after the operation ($P < 0.05$), and the difference was due to pain and associated restrictions in daily activity. Zoledronic acid has the effect of inhibiting BMD loss, so there are more activities performed in the ZOL group. Even one study showed zoledronic acid to have direct effects on the pathogenesis of bone pain [25].

The worst complication of bisphosphonate treatment is jaw osteonecrosis, but its incidence is low and most cases occur in oncology patients [26]. In our work, we observed no severe adverse event except for two patients developing a mild fever. Long-term studies and more research may be necessary to assess the safety of bisphosphonate for THA patients.

The present study has some limitations. First, a more power sample size was needed to further confirm our conclusion. Second, a longer follow-up period was needed to verity the long-term effects of zoledronic acid treatment after THA, especially whether it can prolong the lifetime of prostheses.

Conclusion

Our research indicates that receiving an intravenous infusion of 5 mg zoledronic acid after THA can effectively prevent periprosthetic BMD loss and improve bone remodeling in postmenopausal osteoporosis patients. The significant differences in bone metabolism markers' change performed at 3 months after the operation, which is earlier than BMD change. Combining BMD and bone metabolism markers' examination was more reasonable than either strategy alone for evaluating the effect of zoledronic acid. Our study indicated that zoledronic acid combined with calcitriol and calcium was an effective treatment protocol to prevent BMD loss. Our conclusions need to be confirmed in larger sample sizes and a longer follow-up period.

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Compliance with ethical standards

Conflicts of interest None.

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